Nasal Adenocarcinoma in a 12 year old Mixed Breed Dog

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Summary:

A 12 year old female spayed mixed breed dog was treated at the Cornell University Hospital for Animals for a nasal carcinoma. Due to advanced local disease including invasion of the orbit, cribriform plate, and hard palate, a course of palliative radiation therapy was pursued. The patient experienced acute radiation side effects, necessitating additional hospitalization. The patient returned regularly for follow-up appointments, and eight months after her last radiation treatment, the patient passed away.

Case History:

A 12 year old female spayed mixed breed dog was presented to the Cornell University Hospital for Animals' Oncology service on February 23rd, 2011, for evaluation of a mass in the left nasal cavity. The patient had initially been seen by her referring veterinarian approximately four months prior to presentation for episodes of coughing. Skull radiographs taken at that visit revealed only a slight increase in soft tissue opacity in the region of the left nasal cavity, with no bony lysis appreciated. A course of ciprofloxacin was started to treat a possible bacterial infection within the nasal cavity. The patient continued to cough despite antimicrobial therapy. On repeat skull radiographs taken a week prior to presentation, bony lysis was appreciated in the area of the left nasal cavity. An endoscopic exam performed by the referring veterinarian revealed a mass within the left nasal passageway. Two small biopsies were taken endoscopically and submitted for histopathology, the results of which were pending at the time of presentation. The patient was referred to Cornell for further evaluation and discussion of treatment options.

Clinical Findings:

On initial presentation, the patient was bright, alert, and responsive. She was overconditioned, with a Body Condition Score of 6/9. She was eucardic and normothermic, and was tachypneic without increased respiratory effort. A 2.5 cm x 2.1 cm x 2.7 cm firm, non-ulcerated soft tissue mass was present extending from the medial canthus of the left eye rostrally. Serous ocular discharge was present from the left eye, and this eye was unable to be retropulsed. The right eye was normal. Left sided mucopurulent nasal discharge was present, with decreased airflow from this nostril. The patient's breathing was stertorous, and she sneezed often during the exam. On oral exam, the hard palate was displaced ventrally in the caudal aspect of the mouth, more so on the left side. No peripheral lymphadenopathy was present, and a neurologic exam did not reveal any abnormalities. The patient had a history of diabetes mellitus, for which she was being treated by her referring veterinarian. The patient also had an incidental soft tissue mass on the dorsal aspect of her head, measuring 0.8 cm x 0.5 cm. This mass had been present for many years and had not changed in size, according to the owner. No other abnormalities were appreciated on physical exam.

Problem List and Differential Diagnoses:

Problems from the history included the four month history of coughing, the nasal mass observed endoscopically and the bony lysis appreciated on radiographs from the referring veterinarian, as well as the history of diabetes mellitus. Problems from the clinical findings included the firm soft tissue mass extending from the left eye, the ventral displacement of the hard palate, the ocular discharge and absent retropulsion of the left eye, the left sided nasal discharge, stertorous breathing, sneezing, and the soft tissue mass on the dorsal aspect of the head.

The top differential for the nasal mass was neoplasia within the nasal cavity. This would explain the historical findings including presence of the mass and the bony lysis on radiographs. Neoplasia would also explain the clinical findings of the discreet mass, the facial deformities, ocular abnormalities, nasal discharge, stertorous breathing, and sneezing.

Within the category of neoplasia, the top neoplastic process was nasal carcinoma, with the most likely type being adenocarcinoma, followed by squamous cell carcinoma and undifferentiated carcinoma. Nasal sarcoma was the next most likely neoplastic process. The most likely type within this category was chondrosarcoma, followed by fibrosarcoma, osteosarcoma, and undifferentiated sarcoma. Less likely were rare tumors of the nasosinal region, including round cell tumors such as lymphoma and transmissible venereal tumors, hemangiosarcoma, neuroendocrine carcinoma, a nerve sheath tumor, fibrous histiocytoma, rhabdomyosarcoma, and leiomyosarcoma. Non-neoplastic differentials for the mass within the nasal cavity included a cyst, hematoma, abscess, granuloma, or foreign body, although these were further down the list of differentials.

Differentials for coughing included secondary side effects related to the nasal mass, infectious/inflammatory causes, or a foreign body. It was thought that the most likely reason for coughing was in relation to extension of the mass into the pharyngeal region causing irritation, or due to irritation from nasal discharge, caused by the mass, being aspirated or swallowed.

The soft tissue mass on the dorsal aspect of the head was not the patient’s primary problem, and was not related to the clinical signs with which the patient presented. The mass was considered to be most likely benign, as the owner stated that it had been present for a long time period and had not changed in size. Differential diagnoses for this mass included a sebaceous gland tumor, cutaneous cyst, fibroma, granuloma, and lipoma. Further diagnostic work-up of this mass was not pursued.

Diagnostic Tests:

Routine staging was performed, including a complete blood count (CBC), chemistry panel, urinalysis, and imaging with thoracic radiography, abdominal ultrasonography, and computed tomography (CT) of the head. The only abnormality noted on CBC was a monocytosis (2.4 thou/µL, ref 0.1 – 1.3). Common causes of this finding include inflammation and glucocorticoids (i.e. a stress leukogram), both of which could have attributed to the monocytosis seen in the patient. Abnormalities noted on the chemistry panel included hypoglycemia (56 mg/dL; ref 63 – 118) and a mild hypoalbuminemia (3.0 g/dL; ref 3.1 – 4.2). The hypoglycemia was a result of insulin administration that morning without the patient having eaten. The patient did not display any clinical signs related to this finding. The hypoalbuminemia was very mild. This finding could have been a result of decreased production due to an acute phase reactant response from the inflammation associated with the mass, or this value may have been a normal finding in this patient. The urinalysis was a voided sample, and had a urine specific gravity (USG) of 1.019, indicating that the patient was adequately hydrated. This value was not very concentrated, but was above the accepted range for isosthenuria (1.008-1.012), indicating that the patient did have the ability to concentrate urine. There were no other significant findings in all three diagnostic tests.

Three view thoracic radiographs were obtained to evaluate for presence of metastasis within the lungs. These radiographs were clinically normal. As treatment of the nasal mass would be a significant financial commitment for the owner, an abdominal ultrasound was performed to rule out concurrent disease that may have changed the decision to pursue therapy. Results of the ultrasound revealed mild, diffuse hepatomegaly and at least two, less than 1.2 cm in diameter, hyperechoic liver nodules that did not bulge the liver margins. The hepatomegaly was considered consistent with vacuolar hepatopathy secondary to diabetes mellitus. The hepatic nodules were ruled likely benign, due to extramedullary hematopoesis or nodular hyperplasia, but metastatic neoplasia could not be ruled out based on ultrasonography alone. The remainder of the ultrasound was unremarkable.

CT of the head with contrast was performed the following day in order to assess the extent of local disease and allow for accurate planning of radiation therapy. The left nasal cavity was filled with heterogeneously contrast-enhancing, soft-tissue attenuating tissue extending through the hard palate, cribriform plate, nasal bone, and maxillary bone, into the oral cavity, left retro-orbital space, and cranial cavity. The mass crossed midline, invaded the infraorbital foramen, and completely occluded the nasopharynx. The left frontal sinus was completely filled with fluid-attenuating material. Also of note was periosteal new bone formation symmetrically along both tympanic bullae and the basioccipital bone.

Under the same anesthetic event, surgical biopsies of the nasal mass and lymph node aspirates of both mandibular lymph nodes were performed. As biopsies of the mass obtained endoscopically by the referring veterinarian were non-diagnostic, punch biopsies of the mass were obtained to determine the nature of the mass. This was performed in a sterile fashion using a punch biopsy instrument. Biopsies were taken through the epidermis and dermis covering the mass, into the mass itself. Samples were taken from different areas of the mass, including the center of the mass, as viewed externally, as well as the periphery. Multiple biopsy samples were submitted for histopathology. Results of histopathology confirmed the diagnosis of neoplasia, specifically carcinoma. Further differentiation was not possible due to small size of the tissue fragments. The aspirates from both mandibular lymph nodes were submitted for cytology, and were determined to be reactive lymph nodes with no neoplastic cells present in the samples provided.

Upon recovery from general anesthesia, the patient became markedly hypoxic and anxious, necessitating sedation and reintubation for maintenance of a patent airway. Reasons hypothesized for this complication include introduction of inflammation and hemorrhage due to biopsy sample collection, as well as the patient's compromised mental status post-anesthesia making it difficult for her to attempt open-mouth breathing versus breathing through her nose. After consultation with the owner, a tracheostomy tube was placed. As the patient would be induced under general anesthesia and recovered daily for radiation therapy treatments, there was concern that she would have further difficult recoveries. Therefore, the tracheostomy tube was left in place for the duration of her stay in the hospital. This required a second CT for radiation planning to accommodate the tracheostomy tube into the radiation positioning.

Treatment:

The patient was treated with external beam radiation therapy using 6 megavolt (MV) photons. She received 3 gray (Gy)/fraction daily for 10 treatments, for a total dose of 30 Gy of radiation. This was a palliative treatment plan chosen to alleviate side effects caused by the tumor, namely the patient's difficulty breathing. Port films were taken at the beginning of treatment, as well as throughout the treatments on specific days to monitor the treatment area and make any necessary changes in patient positioning. Bolus, a synthetic skin equivalent material, was applied over the treatment field to ensure the appropriate dose of radiation to the tumor. As the patient's left eye was within the treatment field, the eye was prophylactically treated with Puralube ophthalmic ointment four times a day.

The patient's tracheostomy tube required maintenance every six hours. This consisted of suctioning the tube using a vacuum system under light pressure, cleaning the area around the tube using sterile saline, using A&D ointment around the tube site to prevent tissue irritation, and nebulization and coupage. During the first five days of having the tracheostomy tube placed, the patient experienced multiple episodes of complete occlusion of the tube with mucoid secretion, requiring removal and replacement with a new tube during most of these episodes. After the initial five days, the patient did not experience any further such episodes.

The patient's last day of radiation treatment was March 15th, 2011, and she was scheduled to be discharged the following day. On March 16th, the patient became inappetant, febrile, and developed oral mucositis. This necessitated buprenorphine administration for pain control, as well as Unasyn administration for infection prevention. The same day, removal of her tracheostomy tube was attempted. However, the patient again became hypoxic, requiring tracheostomy tube replacement. Hospitalization was continued to provide management of the patient's radiation side effects. On March 18th, further pain control was added to the treatment plan, in the form of an intravenous ketamine and lidocaine constant rate infusion (CRI), as well as oxymorphone administration subcutaneously. Intravenous prednisolone and diphenhydramine were added as well to reduce inflammation within the oral cavity. The patient responded well to this added therapy, appearing slightly more interested in food.

On March 20th, moist desquamation of the skin in the treatment field was noted, as well as continued oral mucositis. On March 23rd, an ophthalmology consultation revealed presence of an indolent ulcer in the left eye, as well as bilateral keratoconjunctivitis sicca (KCS). Medical management for these problems was initiated. Topical atropine ophthalmic preparation was administered in the left eye every other day to reduce pain caused by ciliary muscle spasm associated with the ulcer. Topical terramycin antibiotic ointment was administered in the left eye four times a day to prevent infection of the ulcer. To manage the KCS, 2% cyclosporine drops were administered topically in both eyes twice a day to promote tear formation, and Puralube ophthalmic ointment was applied in both eyes four times a day to maintain hydration.

Throughout the patient's stay in the hospital, her blood glucose levels were measured twice daily due to her history of diabetes mellitus. Insulin administration was not required, as her blood glucose levels remained stable within normal limits.

On March 24^{th}, the patient was improving and was eating well. Her tracheostomy tube was successfully removed, and the following day, March 25^{th}, she was discharged to the care of her owner.

The patient returned for a two week recheck appointment. At that appointment, alopecia of the treatment field was appreciated. The oral mucositis was continuing to resolve, and her oral mucosa was only slightly inflamed. Her indolent ulcer was not healing with the medical management, and a grid keratotomy was performed.

At the two month recheck, the patient was doing well at home, with a normal activity level and appetite, as reported by her owner. Hyperpigmentation of the skin, as well as alopecia, was present in the treatment field. Thoracic radiographs performed at that appointment were clinically normal, with no evidence of tumor metastasis.

Three months post-radiation treatment, tumor regrowth was appreciated on endoscopic exam performed at the referring veterinarian. At the patient's appointment with the Oncology service, carboplatin chemotherapy was initiated on request of the owner to pursue further treatment. The owner was made aware that chemotherapy is generally not effective for nasal tumors.

At the patient's five month recheck appointment, a left sided head tilt was appreciated, as well as leukotrichia in the treatment field. There was no fluorescein stain uptake in the left eye. Carboplatin chemotherapy was continued. At the six month recheck appointment, there was a pronounced left sided head tilt, as well as regrowth of the mass within the oral cavity.

At the patient's seven month recheck appointment, the owner reported worsening neurologic signs at home. The patient was bumping into things, was circling, and the owner did not believe that she had vision. On physical exam, a new mass was present within the oral cavity, as well as presence of epistaxis and mucopurulent nasal discharge. The owner was provided with Palladia chemotherapy to administer at home. As the patient was diagnosed with a urinary tract infection at this visit, it was recommended that Palladia not be started until the infection was cleared. The patient passed away in her sleep on November 15th, 2011, 8 months after her last radiation treatment. She had not yet received Palladia therapy at the time of death.

Discussion:

Nasal tumors comprise one percent of all neoplasms in dogs, with 75% being malignant tumors [1]. Approximately 2/3 of nasal tumors in dogs are carcinomas, with the most likely carcinoma being adenocarcinoma [2]. Nasal tumors in general are characterized by progressive local invasion of the surrounding tissues, including the cribriform plate, brain, orbit, and oral cavity. Destruction of bone is present early on in the progression of disease [3]. The metastatic rate is relatively low at diagnosis, 0% - 12%. At the time of death, the metastatic rate for these tumors can range from 40% - 50% [1,3]. These tumors tend to metastasize to the lungs and regional lymph nodes, with other less likely sites being brain, kidney, and bone [1]. Common clinical signs associated with canine nasal tumors include epistaxis, mucopurulent nasal discharge, facial deformity, sneezing, dyspnea, stertorous breathing, exophthalmos, and ocular discharge [4].

Treatment of canine nasal tumors is aimed at controlling local disease. Median survival time (MST) without treatment is 95 days. The prognosis is poorer if epistaxis is present than if absent, with MST being 88 days versus 224 days, respectively [3].

Curative surgery is generally not possible due to bony invasion of the tumor, the location of the tumor, and the advanced stage of disease that many of the canine patients present with at diagnosis [5]. Associated with surgery is a high morbidity rate without a significant extension of life. Many dogs develop some degree of rhinitis or bacterial infection post-surgery, to only gain 3-6 months as reported in the literature [5]. Chemotherapy is usually not effective for macroscopic disease, and provides poor long term tumor control in nasal tumors [4].

Palladia was prescribed for this patient as an alternative treatment when a new tumor was identified within the oral cavity. Palladia (generic name toceranib phosphate) is a small molecule tyrosine kinase inhibitor that is approved in dogs for the treatment of grade II or III, recurrent, cutaneous mast cell tumors (MCT) with or without regional lymph node involvement. Its mechanism of action is through inhibition of the tyrosine kinase (TK) activity of several receptor tyrosine kinases, including VEGFR-2 (vascular endothelial growth factor receptor 2), PDGFR-beta (platelet derived growth factor receptor beta), and Kit (stem cell growth factor receptor), all of which have been shown to be expressed in certain tumor types, including MCT, sarcomas, carcinomas, and melanomas [6]. These kinases are believed to be involved in growth, pathologic angiogenesis, and metastatic processes of the tumor types. Palladia acts as a competitive inhibitor of adenosine triphosphate (ATP) by blocking the ATP binding sites of these kinases, preventing receptor phosphorylation and downstream signal transduction [6]. The use of Palladia in treating canine mast cell tumors has been well documented, but there is not substantial research regarding treatment of other solid tumors using Palladia. A recent as yet unpublished study by London et. al. treated dogs with other tumor types using Palladia to promising results, including 7 patients with nasal carcinoma. Of the 7 patients with nasal carcinoma, only two patients were re-imaged post treatment, making assessment of response difficult. One patient experienced complete remission as evidenced by CT, and the other experienced partial remission as evidenced by CT. Three other patients experienced "clinical benefit", defined in the study as improvement of clinical signs (epistaxis and nasal obstruction). Therefore, 5/7 patients with nasal carcinoma improved in this study, for an overall clinical benefit rate of 71.4% [6]. While promising, the authors identified the need for further investigation of the true utility of Palladia in treatment of solid tumors.

Radiation therapy is the gold standard currently in treating canine nasal tumors. Proliferating cells, be they tumor cells or normal tissue, are typically radiation sensitive. There are two mechanisms by which ionizing radiation leads to cell death. Both mechanisms begin the same way: an x-ray photon ejects an electron from its atom. This photon donates energy to the electron, creating a "fast electron". In direct action, this fast electron directly acts on the DNA to cause DNA damage, leading to cell death [7]. In indirect action, this fast electron instead interacts with a water molecule to create free radicals [7]. These free radicals then go on to act on the DNA, causing damage leading to cell death. Indirect action represents about 2/3 of the damage caused by ionizing radiation [7].

There are two types of radiation treatment schemes commonly discussed: definitive and palliative. In definitive radiation, the goal is to cure or obtain long term control of the tumor, with anticipation that the patient will survive for at least one year [in veterinary medicine]. The total dose of radiation is larger than that of palliative, and is administered over a longer period of time, with small fraction sizes [8]. Palliative radiation has the goal of relieving pain and side effects associated with the tumor, and does not attempt to control the tumor for any length of time. Indications for palliative radiation include inoperable tumors, advanced tumors, a tumor unlikely to respond to chemotherapy, or concurrent disease that does not make definitive radiation or chemotherapy an option [8]. The total dose of radiation is usually smaller than compared to definitive, and is administered in larger individual fractions than typical of definitive radiation [8].

There are side effects associated with both definitive and palliative radiation treatment schemes. Acute side effects are generally more of a concern with definitive radiation. This is due to the daily treatment schedule that allows little time for normal tissue repair between treatments [8]. These side effects occur in renewing tissues. Tissues commonly affected are the mucosa of the oral and nasal cavities and colon, the skin, and some ocular tissues [8]. Late side effects are generally more of a concern with palliative radiation. This is due to build up of damage from radiation within non-renewing tissues [8]. Tissues commonly affected are bone, nerve, and some ocular tissues [8]. Late side effects are not typically encountered often, because the patients receiving palliative care do not tend to live long enough to see late side effects occur.

Radiation therapy for canine nasal tumors is associated with the greatest improvement in survival. Typical definitive treatment plans for nasal tumors, as reported in the literature, generally deliver a total dose of 36-57 Gy, and result in MST ranging from 7-23 months [4,9]. One and two year survival rates range from 37%-60%, and 17%-48%, respectively [4,9]. Typical palliative treatment plans deliver a total dose of 16-40 Gy, with a reported MST in one study by

Gieger et. al. of 146 days. This study had one and two year survival rates of 25% and 9%, respectively [4].

In general, canine nasal tumors carry a poor prognosis due to tumor progression into normal tissue [2]. The majority are malignant neoplasms, and due to the advanced clinical stage at which many patients are diagnosed, treatment is often difficult [2]. The patient in this case report was given a 3 month prognosis, due to the advanced stage of her tumor at the time of diagnosis. As reported, the patient survived 7 months past the diagnosis of nasal carcinoma at Cornell. Although the owner invested a considerable sum of money into the patient's treatment and therapy, he was happy with the outcome and the extra time with which his dog was provided.

Works Cited:

[1] Turek MM, Lana SE. Canine Nasosinal Tumors. In: Withrow and MacEwen's Small Animal Clinical Oncology, 4th ed. 2007. Saunders; St. Louis, MO: 525-535.

[2] Henry CJ, Brewer WG, et al. Survival in dogs with nasal adenocarcinoma: 64 cases (1981-1995). *J Vet Intern Med* 1998;12:436-439.

[3] Rassnick KM, Goldkamp CE, et al. Evaluation of factors associated with survival in dogs with untreated nasal carcinomas: 139 cases (1993-2003). *J Am Vet Med Assoc* 2006;229:401-406.

[4] Gieger T, Rassnick K, et al. Palliation of clinical signs in 48 dogs with nasal carcinomas treated with coarse-fraction radiation therapy. *J Am Anim Hosp Assoc* 2008;44:116-123.

[5] Adams WM, Bjorling DE, 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;227:936-941.

[6] London C, Mathie T, et al. Preliminary evidence for biologic activity of toceranib phosphate (Palladia®) in solid tumours. *Veterinary and Comparitive Oncology* 2011; doi: 10.1111/j.1476-5829.2011.00275.x

[7] McEntee MC. Veterinary radiation therapy: review and current state of the art. *J Am Anim Hosp Assoc* 2006;42:94-109.

[8] LaRue SM, Gillette EL. Radiation Therapy. In: Withrow and MacEwen's Small Animal Clinical Oncology, 4th ed. 2007. Saunders; St. Louis, MO: 193-208.

[9] Buchholz J, Hagen R, et al. 3D conformational radiation therapy for palliative treatment of canine nasal tumors. *Vet Radiol Ultrasound* 2009;50:679-683.