Furby's Ferocious Sneezing Fits

A Case Report of Feline Nasal Lymphoma

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Class of 2020

Clinicopathologic Conference

January 31, 2020

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Introduction

Lymphosarcoma or lymphoma is a malignant neoplasm of hematopoietic origin, or more specifically of lymphocytes. Lymphoma is one of the most common malignancies diagnosed in feline patients, accounting for up to 30% of all feline neoplasms.[1] Unlike lymphoma in the canine patient, feline lymphoma generally manifests locoregionally, with the most common site being alimentary followed less commonly by mediastinal, nasal, and other sites.[1] There are a variety of both known and suspected influencing factors in the development of lymphoma in cats, including concurrent retrovirus infection (feline leukemia [FeLV] and feline immunodeficiency virus [FIV]), genetic factors, environmental (i.e. tobacco smoke), chronic inflammation, and immunosuppression.[1] The age of affected cats has historically followed a bimodal distribution, particularly since mediastinal lymphoma has a stronger association with younger, retrovirus positive patients.[2]

Nasal lymphoma is considered a rare manifestation of feline lymphoma, but it is the most common primary feline nasal tumor.[3,4,5] These cases tend to be seen in older (median age: 8 - 11 years), retrovirus negative cats, with the Siamese breed and males being overrepresented.[1,4,5] In the majority of cases, nasal lymphoma tends to remain a localized disease in that it does not spread beyond the nasal cavity/sinuses. However, in about 20% of cases, involvement of distant lymphoid tissue has been documented at the time of necropsy.[6] The most common presenting signs localize to upper respiratory disease, including: nasal discharge, sneezing, upper respiratory noise (stertor, stridor, wheezing), and increased respiratory effort.[1,4] The median duration of clinical signs reported prior to diagnosis is approximately 2 months.[1] Since nasal lymphoma has a relatively low rate of systemic involvement, treatment employs methods of local disease control, as with radiation therapy, and can be curative.[1,7]

History and Presentation

Furby, an approximately 9-year-old neutered male domestic longhair feline, first presented to the MSU-CVM Internal Medicine Department on June 24, 2019 for suspected nasal neoplasia. Approximately 1 month before presentation to MSU-CVM, Furby demonstrated intermittent loud respiratory sounds and sneezing, as well as nasal discharge that varied in viscosity and color. In addition, Furby's appetite had been progressively decreasing since his onset of respiratory signs. Furby's last documented normal respiratory status (sounds, discharge, etc.) coincided with a dental prophylaxis on May 19, 2019. Ten days later, on May 29th, Furby presented to his primary veterinarian again for inspiratory stertor and unilateral yellow mucoid discharge from the right nostril. At this visit, skull radiographs were performed and revealed a soft tissue/fluid opacity in the right nasal cavity. Furby received an injection of dexamethasone SP and Convenia (cefovecin sodium) from his primary veterinarian which reportedly improved the consistency of Furby's nasal discharge. Relevant historical medical information includes a positive FIV status via ELISA Snap Test and a Grade II/VI parasternal heart murmur, both diagnosed in November 2017.

On presentation to MSU-CVM, Furby was bright, alert, and responsive. His vital parameters were within normal limits (T 102.1, P 180, R 28), and he was evaluated at a body condition score of 4/9 (weight: 4.40kg). The only abnormalities noted on physical examination were bilateral serous nasal discharge, consistent inspiratory stertor with mildly increased respiratory effort, and an unkempt/dull hair coat. There was no apparent facial deformity, hard palate softening, nor peripheral lymphadenopathy appreciated on physical exam. In addition, no heart murmur was appreciated on cardiothoracic auscultation at MSU-CVM.

Diagnostic Approach

Several initial diagnostics were performed to determine the underlying etiology for his respiratory signs. A minimum database (CBC, chemistry panel, and urinalysis) revealed the following abnormalities: moderate eosinophilia, mild increase in both total protein and globulins, a large amount of bilirubinuria. In preparation for nasal biopsies, a coagulation panel was performed and yielded normal results. Thoracic radiographs only showed mild signs of chronic bronchitis, an expected variant for his age. Due to historic concern for a heart murmur, an echocardiogram was performed to ensure appropriate cardiac function prior to sedation and general anesthesia for future diagnostics and therapies; no abnormalities were noted. Diagnostics then proceeded to a computed tomography (CT) study of the head/skull with contrast under general anesthesia. The CT interpretation described a multitude of changes in the nasal cavities including: moderate amounts of fluid and soft tissue attenuating material bilaterally, disorganization to absent nasal turbinates bilaterally, some extension of fluid attenuating material into the right sphenopalatine and frontal sinuses as well as bilaterally in the maxillary recesses, punctate lysis of the right lacrimal and ethmoid bones, and lysis of the right ventral aspect of the cribriform plate. Most changes observed on CT were noted to be more severe on the right side; additionally, enlarged medial retropharyngeal lymph nodes were noted bilaterally. Rhinoscopy was not performed due to concern regarding the integrity of the cribriform plate, so instead blind nasal biopsies were performed bilaterally and submitted for both impression smear cytology slides and histopathology. Samples for both a cryptococcal antigen screening and feline herpesvirus PCR were submitted and later returned as negative. The cytology slides returned with evidence of severe suppurative inflammation and of large immature lymphocytes bilaterally; significant lymphoid proliferation was reported on the slide from the right nostril.

Furby was discharged the day of his nasal biopsies with buprenorphine for pain control and monitoring instructions for worsening respiratory signs until the nasal biopsy results returned.

At the time of first discharge, the top differential diagnoses for Furby's signs and diagnostic results included neoplasia (i.e. lymphoma, nasal adenocarcinoma, squamous cell carcinoma) and fungal infection (as with *Cryptococcus neoformans*). The presence of bony lysis on Furby's CT resulted in significantly lesser consideration given to severe bacterial rhinitis/sinusitis, nasal foreign body, and other inflammatory rhinitis (allergic, lymphocytic-plasmocytic) as the primary disease process. Other conditions such as trauma, congenital conditions (cleft palate, ciliary dyskinesia, stenosis), and dental disease were readily eliminated from the differential list based on Furby's history, signalment, and/or physical exam findings.

Furby's nasal biopsies returned with the diagnoses of early nasal lymphoma with mild epitheliotropism and secondary chronic suppurative rhinitis. The biopsy report described large numbers of large lymphoblasts with prominent nucleoli, variable cytoplasm cell volume, and 5+ mitotic figures. A mixed population of inflammatory cells, including neutrophils, small lymphocytes, and macrophages were also described and attributed to secondary rhinitis.

Based on the biopsy results, Furby presented again to MSU-CVM on July 8th for additional staging diagnostics to identify any possible systemic involvement and to discuss appropriate treatment options with his owner. The only changes noted on Furby's signs and physical exam from June include progressive inappetence, 0.4 kg weight loss, and a change in nasal discharge character to more mucoid and green-colored bilaterally. Staging diagnostics included abdominal radiographs and ultrasound with fine needle aspirates of the liver and spleen. Abdominal radiographs showed mild hepatosplenomegaly. Abdominal ultrasound revealed enlargement of the gastric, pancreaticoduodenal, and right colic lymph nodes; other incidental

ultrasonographic findings include gallbladder sludge, cystolithiasis, and urinary bladder debris. Ultrasound-guided fine needle aspirates of the liver and spleen were obtained under sedation; the enlarged abdominal lymph nodes were not accessible for aspiration. Neither cytology of the liver nor spleen displayed evidence of metastatic neoplasia, though mild changes consistent with hepatic lipidosis were noted due to Furby's poor appetite. Given lack of definitive evidence of additional tissue involvement, Furby's nasal lymphoma was classified as stage 2b, defined as a single extra-nodal tumor with regional lymph node involvement.[1]

Pathophysiology / Disease Overview

Lymphoma is described as a malignant neoplasia of proliferative lymphoid tissue. As with other types of neoplasia, the inciting cause of the transformation of normal cells into a malignant variant is largely unknown and attributed to a variety of influencing factors. In general, retroviral infections have a well-documented association with lymphoma, where FeLV infection is associated with a 60 fold increased risk and FIV infection is associated with a 6 fold increased risk of lymphoma development compared to seronegative cats.[2] Additional factors considered relevant in nasal lymphoma cases include chronic exposure to tobacco smoke, chronic inflammation (i.e. feline herpesvirus recrudescence, environmental irritants) and immunosuppression (including FIV infection).[1,2] A study conducted by Santagostino et al. identified expression of FeLV antigens p27 and gp70 in approximately 54% of their nasal lymphoma cases despite seronegativity, implying an effect despite infection clearance.[4] Chronic persistent rhinitis has been implicated in promoting an expansion of B-lymphocytes populations in mucosa-associated lymphoid tissues and correlates with the predominant nasal lymphoma phenotypic distribution of B-cell tumors in up to 85% of cases.[4] When multiorgan involvement is

identified, some of the sites reported include additional lymph nodes, spleen, renal parenchyma, myocardium, and CNS involvement via erosion through the cribriform plate.[4]

Disease Treatment and Prognosis

When nasal lymphoma is confined to the nasal passage, radiation therapy (RT) is considered the treatment of choice with reported complete response rates of 75 to 95% of cases.[1] Though not clinically practical, Dah-Renn et al reviewed cases of feline nasal lymphoma to determine predictors of higher RT responses. The study concluded that tumors expressing high levels of Ki-67 and apoptotic factors were more radiosensitive and thus carried a more favorable prognosis.[7] To achieve complete response, a definitive radiation protocol has outlined as a radiation dose of at least 32 Gray (Gy or units of radiation).[1] In cats with systemic involvement, cases of tumor recurrence, or cases in which RT is not accessible, chemotherapy is recommended as the next treatment option. The preferred chemotherapy for nasal lymphoma follows a CHOP protocol containing doxorubicin, vincristine, cyclophosphamide, and prednisolone for up to 25 weeks.[1] In cats with known renal insufficiency, doxorubicin is excluded (COP protocol) because of its known nephrotoxicity; however, doing so is associated with shorter disease-free intervals.[1]

Positive prognostic indicators for feline nasal lymphoma include epitheliotropism, high tumor radiosensitivity, and the use of a definitive RT protocol.[4,7] Anemia and lysis of the cribriform plate are known negative prognostic indicators.[4,7] For cats with localized disease treated with a definitive RT, the reported prognosis is good, with a median survival time of 1.5 to 3 years.[1,7] Patients with incomplete responses to RT are expected to have a median survival time closer to 4.5 months.[1] When chemotherapy alone is used and achieves complete remission, median survival time is approximately 2 years.[1]

Case Outcome

On July 15, 2019, Furby started definitive radiation therapy; he boarded in the MSU-CVM hospital for the duration of radiation therapy. Furby received a total of 34 Gy (units of radiation), divided into 17 fractions of 2 Gy. These fractions were delivered over a 3.5-week period under heavy sedation with 20mcg of dexmedetomidine, 0.8mg of butorphanol, and 1 to 2mg of alfaxalone. All sedation drugs were given intravenously via catheter, and Furby was reversed with 0.04mL of atipamezole intramuscularly following the completion of each fraction. Furby's nasal discharge and stertor improved rapidly and were considered resolved after approximately 4 fractions. Furby's appetite remained decreased during the first two weeks of RT, so he received capromorelin (Entyce) orally once daily until his appetite was considered resolved (around July 30th). Furby did not exhibit any acute side effects of radiation therapy during treatment. On August 9th, Furby was discharged with monitoring instructions for both worsening respiratory signs and changes in appetite. At the time of discharge, Furby was considered to be in clinical remission.

Two weeks following the completion of radiation therapy, on August 22nd, Furby returned for re-staging and a discussion of chemotherapy benefits. No additional concerns or recurrence of clinical signs were reported. Many of the same staging diagnostics were repeated for re-staging. The most notable change on bloodwork was a moderate, non-regenerative anemia defined by a 22.6% hematocrit and 0.2% reticulocyte percentage (June 2019: 43.5% hematocrit). There was no evidence of nodular metastasis on thoracic radiographs. Unfortunately, abdominal ultrasound revealed a mottled appearance to the spleen and larger abdominal lymph nodes compared to measurements taken in June 2019. Splenic cytology was poorly diagnostic, though no overt signs of lymphoma were reported. Given the spleen's appearance and progressive

abdominal lymphadenopathy, administration of chemotherapy (following a CHOP protocol) was recommended. On August 22nd Furby received 1.5 mg/m^2 of vincristine intravenously in the left medial saphenous vein, uneventfully. Furby was discharged with prednisolone and both metronidazole and ondansetron for management of potential gastrointestinal side effects. Furby's owner was advised to have a CBC performed at Furby's primary veterinarian in seven days to check his neutrophil count/nadir prior to administration of cyclophosphamide (continuing the CHOP protocol). To investigate an underlying cause of Furby's anemia, a PCR panel for Mycoplasma spp. was submitted and returned with negative results.

In the couple of weeks following his vincristine administration, Furby's owner reported a marked decline in his energy level and elected to not pursue additional chemotherapy due to quality of life and chemotherapy side effect concerns. Despite stopping chemotherapy, Furby's owner reported on January 21, 2020 that he seems to have made a full recovery with a normal energy level, resolved anemia, and no recurrence of respiratory signs.

Conclusion

Nasal lymphoma, though a rare manifestation of feline lymphoma, is the most common upper respiratory tract tumor diagnosed in feline patients. Cases generally present with upper respiratory tract signs such as nasal discharge and sneezing, though may also be accompanied by non-specific signs like inappetence, lethargy, and weight loss. Diagnosis relies on CT evaluation of tumor invasion and sampling the affected tissue via cytology or more ideally, nasal biopsy. Treatment more commonly involves the use of definitive radiation protocols with the intent of achieving a favorable prognosis compared to other manifestations of feline lymphoma, particularly in cases of disease confined to the nasal cavities/sinuses.

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