Computed Tomography of a Cat with Primary Intratracheal Lymphosarcoma Before and After Systemic Chemotherapy

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ABSTRACT
A 12 yr old male neutered domestic shorthair cat presented with worsening tachypnea of 1 mo duration and open mouth breathing. Radiographs revealed tracheal narrowing at the thoracic inlet. Computed tomography (CT) revealed a contrast enhancing 8-cm long fusiform mass within the dorsal tracheal membrane. Tracheobronchoscopy confirmed the presence of the tracheal mass at the thoracic inlet, and lymphoma was diagnosed based on uniformly atypical lymphoid cells on aspirated bronchoalveolar lavage fluid. The cat was treated with combination chemotherapy consisting of cyclophosphamide, vincristine, doxorubicin, and prednisolone. Thoracic radiographs and CT performed 1 mo after completion of the 6 mo chemotherapy protocol revealed resolution of the tracheal mass. The cat remained clinically normal at 21 mo after treatment. (J Am Anim Hosp Assoc 2011; 47:e131–e137. DOI 10.5326/JAAHA-MS-5571)

Introduction
Primary malignant tumors of the trachea are rare in both dogs and cats.1 Primary tracheal tumors can be very difficult to diagnose in practice, often requiring specialized diagnostic equipment such as tracheobronchoscopy and computed tomography (CT). Tumors that have been reported in the feline trachea include lymphosarcoma, adenocarcinoma, squamous cell carcinoma, carcinoidoma, and seromucinous carcinoma.2–9 There are 11 reports of feline tracheal lymphosarcoma in the veterinary literature, making it the most commonly reported tracheal neoplasm.2–7 Notwithstanding, there is no standard treatment of feline tracheal lymphoma. Treatments that have been used include systemic chemotherapy, surgery, and radiation therapy, either alone or in combination.2–6
Combination chemotherapy therapy used for feline lymphoma is frequently some variation of the University of Madison Wisconsin (UMW) protocol.10–12

The largest case series of primary intratracheal lymphoma included four cats.5 The cats ranged in age from 4 to 10 yr old. Two cats were treated with radiation therapy after experiencing adverse events subsequent to chemotherapy and were clinically normal 8 and 17 mo after radiation therapy. A third cat was treated with combination chemotherapy (vincristine, cyclophosphamide, doxorubicin, and prednisone) and was clinically normal 19 mo after starting therapy. The fourth cat was treated with prednisolone and methylprednisolone acetate and was clinically normal for 35 days, at which time the cat became dyspneic and was euthanized. This report describes the clinical presentation, diagnosis (including pre- and posttreatment CT imaging), treatment, and outcome of a cat with intratracheal lymphoma.

Case Report
A 12 yr old male neutered domestic shorthair cat presented to the referring veterinarian with a 1 mo history of tachypnea and intermittent open-mouth breathing that was getting worse. The cat’s left eye had been enucleated 1 yr prior due to trauma, but otherwise the cat had no history of any serious medical problems.
The referring veterinarian submitted a complete blood count (CBC) and serum biochemistry profile to a commercial laboratory, performed in-house feline leukemia virus/feline immunodeficiency virus (FeLV/FIV) serologic testing, and obtained thoracic radiographs. The CBC and biochemistry profile were unremarkable, and the cat was FeLV P27 antigen and FIV antibody negative. The heart and lungs were normal on thoracic radiographs; however, narrowing of the trachea was noted at the thoracic inlet. The cat was treated initially with oral enrofloxacin and albuterol via inhaler. The owners thought that the cat’s breathing improved minimally after albuterol administrations, but the open-mouth breathing did not resolve. The cat was referred to the Boren Veterinary Medical Teaching Hospital at Oklahoma State University (OSU) for further evaluation.

On physical examination at OSU, there was an increased inspiratory effort (extrathoracic obstructed airway breathing pattern) with inspiratory wheezes bilaterally on thoracic auscultation. The cat had severe periodontal disease, but the remainder of the physical examination was normal. A CBC revealed only a moderate lymphopenia (582 lymphocytes/μL; reference range, 1,200–1,800/μL), and the serum biochemistry profile was normal. Thoracic radiographs revealed normal heart and lungs, but the narrowing of the trachea at the thoracic inlet initially described by the referring veterinarian remained (Figure 1). An esophagram was performed to determine whether the apparent narrowing of the trachea was an artifact due to superimposition of the esophagus. The esophagram confirmed that the trachea was narrowed at the thoracic inlet and that the esophagus was dorsal and widely separated by at least 0.4 cm from the trachea in that region (Figure 2).

The cat was admitted into the hospital’s intensive care unit (ICU) for observation of its respiratory rate and effort. The cat was administered one puff of albuterol via inhaler q 12 hr. Multiple slice CT and video tracheobronchoscopy were performed under general anesthesia on the second day of hospitalization. Contrast agent was iohexal. CT was performed from the fourth cervical vertebra to the fifth thoracic vertebra. The mass extended from the fourth cervical vertebra to the second thoracic vertebra. CT revealed a contrast enhancing 8 cm long fusiform mass in the dorsal trachea at the thoracic inlet, displacing the dorsal membrane ventrally and causing tracheal stenosis (Figures 3A, B and 4) with dorsal displacement of the esophagus. Ventral displacement of the dorsal longitudinal ligament of the trachea causing tracheal stenosis was confirmed by tracheobronchoscopy (using a 3.8 mm flexible bronchoscope), and a Grade III/IV tracheal collapse (>75% reduction in the tracheal lumen diameter) was visualized at the thoracic inlet (Figure 5). A bronchoalveolar lavage was performed. On cytologic examination, the aspirated fluid contained moderate numbers of uniformly atypical lymphoid cells that were large with a single large nucleus. Some of the atypical lymphoid cells contained prominent nucleoli. Low numbers of bacterial rods were seen associated with a few squamous epithelial cells. The cytologic diagnosis was lymphoma with some oropharyngeal contamination.

A combination chemotherapy protocol (prednisolone, vincristine, cyclophosphamide, and doxorubicin) or radiation therapy was recommended, but the owners declined. The cat was discharged with albuterol via inhaler q 12 hr, butorphanol (0.25 mg/kg per os [PO] q 8–12 hr), prednisolone (2 mg/kg PO q 24 hr), and famotidine (0.5 mg/kg PO q 12 hr).

The cat returned to OSU 6 days after discharge in respiratory distress (open-mouth breathing with increased inspiratory effort.
and tachypnea) and the owners elected to pursue chemotherapy. The cat was placed in an oxygen cage in the ICU and the CBC and serum biochemistry profile were repeated before initiating chemotherapy. A mild mature neutrophilia (9,918 neutrophils/μL; reference range, 2,500–8,500/μL), mild lymphopenia (1,026 lymphocytes/μL; reference range, 1,200–8,000/μL), and slightly increased albumin (4.1 g/dL; reference range, 2.5–3.9 g/dL) were noted, consistent with stress and mild dehydration. The UMW 6 mo feline lymphoma protocol was selected and induction using L-asparaginase† (400 U/kg subcutaneously), vincristine‡ (0.5 mg/m² IV), and prednisolone (2 mg/kg PO q 24 hr × 7 days) was initiated.10–12 Within 24 hr of the first treatment, the cat was breathing normally and was removed from the oxygen cage.

For the duration of the chemotherapy protocol, a CBC was performed before each treatment and renal values (blood urea nitrogen [BUN], creatinine, urine specific gravity) were obtained.

**FIGURE 3** A: Pretreatment precontrast computed tomography (CT) axial image at the level of the sixth cervical vertebra demonstrating narrowing of the trachea (arrow). B: Pretreatment postcontrast CT axial images at the level of the sixth cervical vertebra. A contrast enhancing fusiform mass (arrow) in the dorsal tracheal wall causing narrowing of the trachea was noted.

**FIGURE 4** Pretreatment postcontrast CT reconstruction demonstrating the mass in the dorsal tracheal wall. The arrows in the figure indicate the cranial and caudal borders of the intratracheal mass.

**FIGURE 5** Pretreatment tracheobronchoscopy revealing the dorsal tracheal mass narrowing the tracheal lumen. The tracheal mucosa was hyperemic.
before each treatment with doxorubicin. The cat remained persistently lymphopenic throughout the protocol and, on three occasions, treatment was delayed for several days due to a mild neutropenia. Other side effects noted during the treatment protocol included decreased appetite, vomiting, diarrhea, lethargy, and loss of whiskers and guard hairs. The cat was only hospitalized once overnight during the feline lymphoma treatment protocol for hypersalivating and vomiting before chemotherapy administration. The CBC, serum biochemistry profile, and urinalysis performed during the single hospitalization did not reveal any serious abnormalities. All patient values on the CBC and serum biochemistry were within the reference ranges for the laboratory. Urinalysis revealed a small (+2) amount of blood. Urine culture was negative for bacterial growth. The owners did not observe hematuria at home and subsequent urinalyses were negative for blood.

The cat was administered isotonic replacement IV fluids overnight in the ICU. In the morning the cat was clinically stable and premedicated with dolasetron, 0.6 mg/kg IV 30 min before chemotherapy. No further vomiting occurred; however, the cat did continue to hypersalivate before each chemotherapy treatment.

One month after completion of chemotherapy, thoracic radiographs, tracheal CT, and dental prophylaxis were performed under general anesthesia. Thoracic radiographs were unremarkable (Figure 6), and the trachea appeared normal on CT (Figures 7A, B). Twenty-one months after completion of the 6 mo combination chemotherapy protocol, the cat had no respiratory abnormalities and remained clinically normal.

Discussion

Lymphoma is a common mesenchymal neoplasm of cats. In FeLV-negative cats, the gastrointestinal system is the most commonly affected site. Other sites include the mediastinum, (especially in younger FeLV serologically positive cats), lymph nodes, kidneys, nose, eyes, and central nervous system. Lymphoma of the respiratory system (i.e., trachea, bronchi, or lungs) appears to be rare, with lymphoma being the most commonly reported tracheal tumor. In the cat described in this report, thoracic radiographs did not reveal any abnormalities in the lungs. Although a CT examination of the lungs is more sensitive for detecting small masses, it was not performed in this case and concurrent pulmonary involvement could not be ruled out.

FIGURE 6  Lateral cervical radiograph at the completion of the 25 wk chemotherapy protocol demonstrating a normal trachea.

FIGURE 7  A: Posttreatment precontrast CT axial image at the level of the sixth cervical vertebra. No mass lesion was noted. B: Posttreatment postcontrast CT axial image at the level of the sixth cervical vertebra. No mass lesion was noted.
(CT was only performed to image the trachea at the level of the thoracic inlet). The atypical lymphoid cells noted in the bronchoalveolar lavage fluid were assumed to have been exfoliated from the tracheal tumor rather than bronchial airways. Staging of lymphoma was also not performed in this case due to owner constraints and the severity of the cat's condition at the time of the second presentation. The cat had no other clinical abnormalities on physical examination, CBC, biochemical profile, or urinalysis that suggested involvement of other organ systems. Most primary tracheal tumors in cats appear radiographically as solitary distinct intratracheal masses. Stenosis of the airway or narrowing of the trachea can also be observed. In one study of cats with laryngeal, laryngotracheal, and tracheal masses, there was a statistically significant correlation with the presence of a soft tissue opacity in the larynx or trachea and a diagnosis of neoplasia. In some cases of lymphoma of the respiratory system, thoracic radiographs might not reveal any abnormalities. In the cat described in this report, a distinct mass was not obvious on the digital radiographs. Rather, only a narrowing of the trachea at the thoracic inlet was obvious. For most types of lymphoma an ultrasound guided aspirate is very appropriate for diagnosis. However, due to the location of the tracheal mass (dorsal tracheal membrane), this cat would have had to be heavily sedated or under general anesthesia to obtain an ultrasound guided aspirate. The risk of puncture or laceration of vital structures in the area around the trachea, as well as the risk of pneumomediastinum, made obtaining a sample of the mass via endoscopy more appropriate. Due to the difficulties in imaging near the trachea, and the fact that most general practitioners would likely lack experience in that area, an ultrasound guided aspirate of a tracheal mass is a procedure that would likely only be done by a specialist (radiologist).

To determine the underlying cause for the tracheal narrowing, CT was used. There have been no previous reports of CT to evaluate feline tracheal lymphoma. In human medicine, CT is considered superior to thoracic radiographs in detecting abnormalities in the trachea and bronchi. One study reported sensitivity of 66% for thoracic radiographs in detecting tracheal and bronchial disease and sensitivity of 91–97% for CT. In that study, CT was not able to reliably differentiate malignant from benign lesions in humans. Based on the findings in the case described herein and the demonstrated increased sensitivity of CT in human medicine for detecting tracheal lesions, CT should be considered in veterinary patients with signs of inspiratory dyspnea with nonspecific changes on thoracic radiographs.

A metabolic cause for the episode of hypersalivation and vomiting before chemotherapy and hypersalivation before subsequent chemotherapy treatments could not be found in this cat. The cat hypersalivated upon restraint for catheter placement and when the chemotherapy technician was present (the same technician administered the majority of the chemotherapy treatments). These episodes resemble a condition called anticipatory nausea and vomiting (ANV) that occurs in 25–30% of human chemotherapy patients. There are no published reports of ANV in cats. ANV is characterized by nausea and vomiting before chemotherapy administration and is believed to be a conditioned response. Risk of ANV increases as the number of chemotherapy treatments increases.

Human patients that exhibit nausea and vomiting after chemotherapy are at an increased risk of developing ANV. The cat in this report did not have any reported postchemotherapy vomiting; however, the owners reported that after some treatments (especially vincristine), the cat’s appetite was decreased for 1–3 days. It is possible that the cat experienced a mild to moderate degree of nausea after chemotherapy, and this conditioned him to respond to elements associated with chemotherapy administration, such as restraint for catheter placement and the presence of the chemotherapy technician.

<table>
<thead>
<tr>
<th>Signalement</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>7 yr old male Siamese</td>
<td>Surgery, prednisone, cyclophosphamide, doxorubicin</td>
<td>Complete clinical remission at 8 mo</td>
</tr>
<tr>
<td>4 yr old male castrated DSH</td>
<td>Prednisone, cyclophosphamide, vincristine, doxorubicin</td>
<td>Complete clinical remission at 19 mo</td>
</tr>
<tr>
<td>11 yr old male castrated DSH</td>
<td>Prednisone, vincristine (1 dose), radiation therapy</td>
<td>Complete clinical remission at 17 mo</td>
</tr>
<tr>
<td>13 yr old male castrated DSH</td>
<td>Prednisone, cyclophosphamide vincristine (discontinued due to myelosuppression), radiation therapy</td>
<td>Developed several skin nodules diagnosed as lymphoma. At 8 mo after radiation therapy, no respiratory signs noted.</td>
</tr>
<tr>
<td>13 yr old male castrated DSH (present report)</td>
<td>Prednisolone, cyclophosphamide, vincristine, doxorubicin</td>
<td>Complete clinical remission at 15 mo</td>
</tr>
</tbody>
</table>

The cases that are listed in this table are feline tracheal lymphosarcoma cases that received chemotherapy as part of their treatment regimen. Cases that did not receive treatment or were treated with surgery alone were excluded from the table. DSH, domestic shorthair.
5-Hydroxytryptamine (5-HT) receptor antagonists, benzodiazepines, and behavior modification have all been used in human patients to control ANV; however, no single treatment has been completely successful at eradicating this condition. Dolasetran⁶⁸, a 5-HT receptor antagonist, was administered to this cat before chemotherapy administration and prevented vomiting but not hypersalivation. The addition of a benzodiazepine may have been beneficial in this case.¹⁷,¹⁸

The importance of the addition of l-asparaginase to this cat’s chemotherapy protocol could be construed as controversial but was included as part of the modified UMW chemotherapy protocol for feline lymphoma.¹² L-asparaginase is a bacteria-derived enzyme that hydrolyzes the amino acid asparagine. Neoplastic lymphoid cells do not have asparagine synthetase and are euthanized quickly due to decreased protein synthesis. In contrast, most non-neoplastic mammalian cells contain asparagine synthetase and can replace depleted asparagine stores posttreatment. This is the reason that l-asparaginase is only minimally myelosuppressive and has relatively few side effects. It has been suggested that l-asparaginase may not be as toxic to neoplastic lymphoid cells in cats as in dogs due to cats’ higher dietary protein requirements, rate of hepatic protein metabolism, and transamination. In one study, l-asparaginase resulted in decreased plasma asparagine concentrations; however, the duration of decrease was shorter than the decreased plasma asparagine concentrations measured in the dog.¹⁹

In this report, the cat’s clinical signs improved dramatically over a short period of time (within 24 hr) after administration of l-asparaginase; however, vincristine and prednisolone were administered concurrently so the effectiveness of l-asparaginase alone cannot be determined. In the authors’ opinion, the use of l-asparaginase in combination with prednisolone and vincristine at the time of the first treatment had no adverse clinical effects and might have been helpful in initially reducing the tumor size and relieving tracheal obstruction.

CT performed 1 mo after completion of chemotherapy revealed complete resolution of the tracheal mass and presumably the lymphoma. Previous case reports of cats treated with combination chemotherapy indicated that survival times could be prolonged to 8 and 19 mo.⁵⁶ Based on these previous cases of intratracheal lymphoma, treatment with combination chemotherapy or radiation therapy could result in long-term remission and could even be curative in cats (Table 1). The cat described in this report appeared to support this possibility. Further, combination chemotherapy might be a more accessible treatment option for owners due to the limited availability of radiation therapy.

Conclusion
In conclusion, CT should be considered an appropriate and often necessary diagnostic modality in cats with inspiratory dyspnea, especially if thoracic radiographs fail to demonstrate any obvious or conclusive abnormalities. Combination chemotherapy appears effective in inducing remission in cats with tracheal lymphosarcoma with reported remission duration ranging from 8 to 21 mo in published case reports of cats with tracheal lymphosarcoma treated with combination chemotherapy.

FOOTNOTES
a SNAP FIV/FeLV Combo Test; IDEXX Laboratories, Inc, Westbrook, ME
b Baytril; Bayer Corporation, Shawnee Mission, KS
c Albuterol via inhaler; Armstrong, West Roxbury, MA
d LightSpeed; General Electric, Fairfield, CT
e Tracheobronchoscopy; Olympus, Center Valley, PA
f Iohexal (Omnipaque); distributed by GE Healthcare, Fairfield, CT
g Torbutrol, Torbugesic; Fort Dodge, Madison, NJ
h Prednisolone; Butler Animal Health, Dublin, OH
i Famotidine; Bedford Laboratories, Bedford, OH
j l-Asparaginase, ELSPAR; Ovation Pharmaceuticals, Deerfield, IL
k Vincasar; Sican, Inc., Irvine, CA
l Adriamycin; Bedford Laboratories, Bedford, OH
m Normasol-R; Hospira Inc., Lake Forest, IL
n Anzemet; Sanofi-aventis, Bridgewater, NJ

REFERENCES


