Case Report

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Multimodal non-surgical treatment of a feline tracheal adenocarcinoma

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Abstract

Case summary A 10-year-old, castrated male domestic shorthair cat presented with a 2–3 month history of weight loss, lethargy and coughing. Thoracic radiographs revealed a soft tissue opacity overlying the dorsal trachea from the first rib to second rib and the ventral aspect of the trachea extending from the second rib to approximately the fourth rib. CT confirmed a mass involving the dorsal, right lateral and ventral aspects of the trachea narrowing the lumen and extending from vertebra C7 through T4. Bronchoscopy revealed a partially circumferential irregular and multilobulated tracheal mass, which was biopsied. The histopathological diagnosis was tracheal adenocarcinoma. The cat was treated with a definitive course of external beam radiation therapy (RT; 3 Gy × 18), cytotoxic chemotherapy, a tyrosine kinase inhibitor and palliative RT. The cat remained asymptomatic for 2 months and the mass remained stable radiographically for 11 months after RT.

Relevance and novel information With multimodal treatment the cat had a survival time of 755 days. Initial treatment included definitive RT, carboplatin and piroxicam, followed by toceranib phosphate and palliative RT when the mass recurred. This case report describes the first documented use of non-surgical treatment and long-term outcome of tracheal adenocarcinoma in a cat. This case report is an indication that prolonged survival can be achieved with multimodal therapy.

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Case description

A 10-year-old, male neutered domestic shorthair cat weighing 4.13 kg was referred to the Auburn University Veterinary Teaching Hospital for evaluation of a suspected tracheal mass observed on thoracic radiographs. Major complaints included a 2–3 month history of weight loss, coughing, lethargy and progressive dyspnea. Recent history included 2–3 days of anorexia with one episode of regurgitation the night prior to presentation. Previous treatment consisting of cefovecin, prednisone and chloramphenicol had been unsuccessful. Testing for feline leukemia virus and feline immunodeficiency virus was negative.

On physical examination at first presentation (day 1) the cat was found to be in poor physical condition. It was tachypneic with increased respiratory effort, with both inspiratory and expiratory stridor noted. A grade II/VI left parasternal systolic heart murmur was auscultated. Other findings included mild dental calculus, pale pink and tacky mucous membranes and flea infestation. The remainder of the physical examination was otherwise within normal limits.

Lymphopenia (775 × 10^3/µl; reference interval [RI] 1500–7000 × 10^3/µl) and eosinophilia (1550 × 10^3/µl; RI 0–750 × 10^3/µl) were detected on complete blood count. These findings were attributed to stress and a flea infestation, respectively. Abnormal biochemical findings included elevated alanine transaminase (184 U/l; RI 26–77 U/l), elevated aspartate aminotransferase (288 U/l; RI 12–45 U/l), elevated creatinine kinase (13,207 U/l; RI

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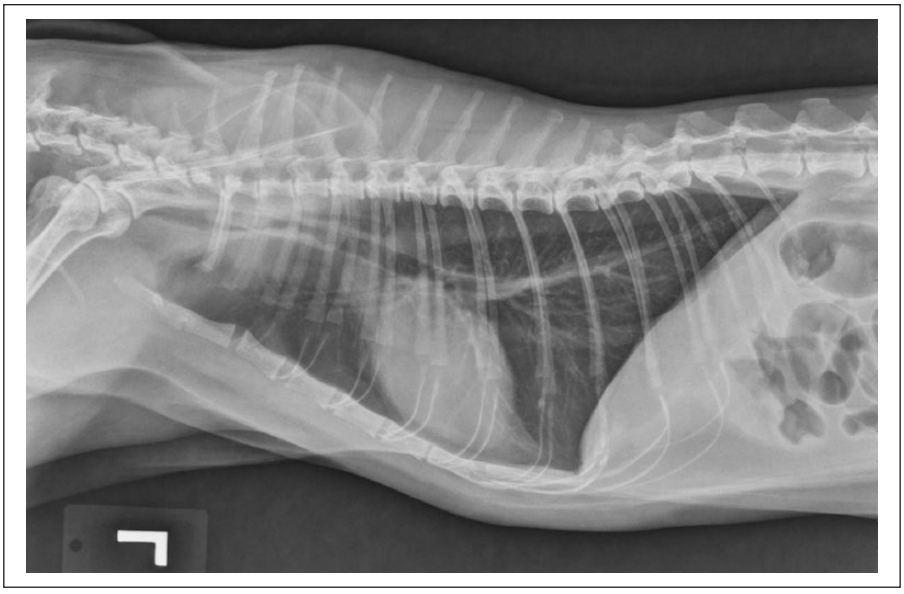

Figure 1 Thoracic radiographs at initial presentation (day 1) showing an irregularly narrowed tracheal lumen from the level of vertebra C7 through T4. There was soft tissue opacity overlying the dorsal trachea from the first rib to the second rib and a curvilinear irregularly margined soft tissue opacity on the ventral aspect of the trachea extending from the second rib to the fourth rib

100–250 U/l), hypocalcemia (9.0 mg/dl; RI 9.5–11.6 mg/dl), hypophosphatemia (3.1 mg/dl; RI 4.3–5.9 mg/dl) and hypochloremia (107 mEq/l; RI 114–120 mEq/l).

Urinalysis revealed a mild decrease in urine concentration (urine specific gravity 1.023). Urine sediment examination showed 100–200 red blood cells per high power field, rare white blood cells and few fat droplets. The hematuria was attributed to sample collection by cystocentesis.

Thoracic radiographs revealed an irregularly narrowed tracheal lumen from the level of vertebra C7 through T4. There was soft tissue opacity overlying the dorsal trachea from the first rib to the second rib and a curvilinear irregularly margined soft tissue opacity on the ventral aspect of the trachea extending from the second rib to the fourth rib (Figure 1).

An echocardiogram revealed mild mitral valve regurgitation. Cardiac chamber and wall dimensions and systolic function were within normal limits.

A CT scan, esophagoscopy and bronchoscopy were performed. The cat was sedated with midazolam (0.2 mg/kg IV) and oxymorphone (0.05 mg/kg IV), and induced with propofol (6 mg/kg IV). General anesthesia was maintained with isoflurane via an endotracheal tube during the CT scan and with intermittent propofol (1.2 mg/kg IV) boluses during bronchoscopy and esophagoscopy. CT of the cervical and thoracic trachea confirmed narrowing of the trachea at C6 through T1 due to a soft tissue mass in the dorsal aspect of the lumen and flattening of the ventral aspect of the canal on the right side (Figure 2).

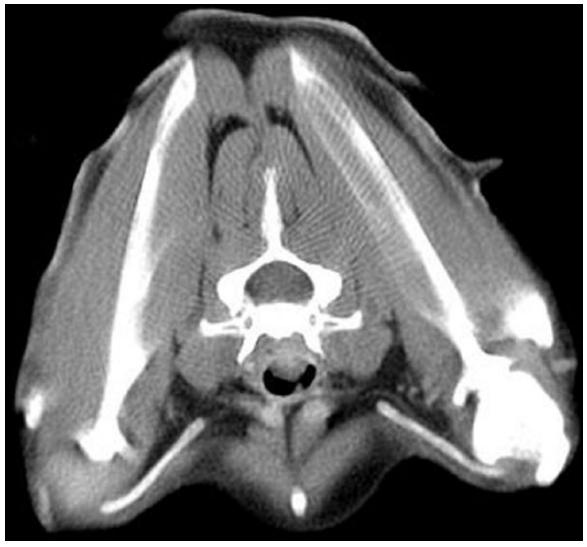

Figure 2 CT scan at initial presentation (day 2) showing narrowing of the trachea due to a soft tissue mass in the dorsal aspect of the lumen and flattening of the ventral aspect of the canal on the right side

No abnormalities were noted during the esophagoscopy procedure. On bronchoscopic examination, an irregular and multilobulated intraluminal tracheal mass was observed with partial obstruction distal to thoracic inlet. The mass was present on the dorsal and ventral aspects of the tracheal lumen, appearing to be partially circumferential (Figure 3). This irregularity of the

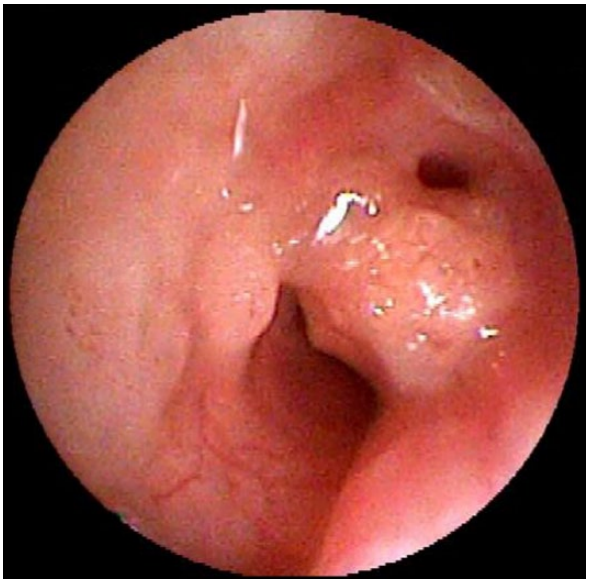

Figure 3 Bronchoscopy image (day 2) showing an irregular and multilobulated intraluminal tracheal mass

mucosal surface extended distally past the tracheal bifurcation. Biopsies and impression cytology of the mass were taken. The cat was given dexamethasone sodium phosphate 2.4 mg (2 mg/kg of prednisone equivalent, intravenously) following biopsies, owing to the concern of further inflammation causing complete occlusion of the tracheal lumen.

Cytologic analysis of an impression smear of the mass showed moderate mixed cell inflammation with moderate cellular atypia. Histopathologic evaluation of the tracheal biopsies revealed multiple glandular structures lined by several layers of cuboidal neoplastic cells. The glands were supported by moderate amounts of fibrovascular stroma and multifocally had central accumulations of basophilic, foamy material. The neoplastic cells had moderate amounts of eosinophilic, vacuolated cytoplasm and large, oval nuclei with finely stippled chromatin and 1–2 prominent nucleoli. There was marked anisocytosis, anisokaryosis and cellular and nuclear pleomorphism with no mitotic figures seen. There were scattered neutrophils throughout the neoplasm. These findings led to a diagnosis of tracheal adenocarcinoma.

Antibiotics (doxycycline 10 mg/kg PO q12h for 7 days), corticosteroids (prednisolone, 2 mg/kg PO q12h) and acepromazine (0.05 mg/kg PO q8–12h as needed for anxiety associated with respiratory difficulty) were prescribed. Because of the location and size of the mass, surgery was not a feasible option for treatment. The owners elected to pursue a definitive course of radiation therapy (RT) followed by chemotherapy. A CT repeated on day 6 for RT planning showed no obvious changes in the tracheal mass.

A computerized, conformal RT plan was prepared, based on the CT images. The prescription was 18 daily (Monday–Friday, day 11–36) 3 Gy fractions of 6 MV x-rays delivered with a clinical linear accelerator for a total dose of 54 Gy to the 97% isodose line with a maximum isodose of 105.7%. The dose was delivered through equally weighted parallel opposed lateral portals. The field extended from C4 to T5 and was approximately 3.4 $\times$ 9.0 cm contoured slightly to the curve of the trachea including a 0.5 cm planning target volume (PTV).

For RT the cat was sedated daily for treatment with an intramuscular sedative combining dexmeditomidine (0.05 mg/kg IM) and butorphanol (0.4 mg/kg IM). Reversal with atipamezole hydrochloride (0.5 mg/kg IM) was administered after completion of the procedure. Prednisolone (1 mg/kg PO q12h) was continued through the first 4 days of irradiation. Beginning on day 5 of irradiation, methylprednisolone acetate (5.5 mg/kg SC) was given every 3 weeks.

RT was associated with minimal acute adverse effects. The cat was anorexic following the first two fractions of RT but began eating after being prescribed mirtazipine (1 mg/kg PO q72h). It was also moderately dehydrated following the first three fractions of radiation. The cat received subcutaneous fluids and recovered sufficiently to undergo anesthesia for RT the next day. This episode is unlikely to have resulted from irradiation. No other adverse events occurred throughout the cat's treatment.

Marked improvement in inspiratory and expiratory stridor was noted after four fractions of radiation. The cat had a pronounced inspiratory and expiratory strider on day 1 of RT; however, stridor was no longer present after the first week of treatment.

Chemotherapy with carboplatin was started (on day 39) at 180 mg/m^2 intravenously every 3 weeks for six treatments. Maropitant citrate (1 mg/kg SC) was given prior to carboplatin administration. Following the first dose of chemotherapy, the cat was sedated with dexmeditomidine (0.04 mg/kg IM) with reversal via atipamezole hydrochloride (0.4 mg/kg IM) for subsequent carboplatin doses, owing to fractious behavior. Severe halitosis was noted prior to administration of the third dose of carboplatin (day 81); thus, cefovecin (8 mg/kg SC) was given in the event that the halitosis was due to a secondary bacterial infection in the cat's trachea due to necrosis of the adenocarcinoma. No significant bone marrow or gastrointestinal toxicity was noted during chemotherapy; however, the cat was persistently lymphopenic and eosinophilic, which was attributed to the stress of hospitalization and a flea infestation, respectively. Although flea prevention had been previously prescribed, the cat remained flea infested owing to poor owner compliance secondarily to large numbers of cats within their multi-cat household.

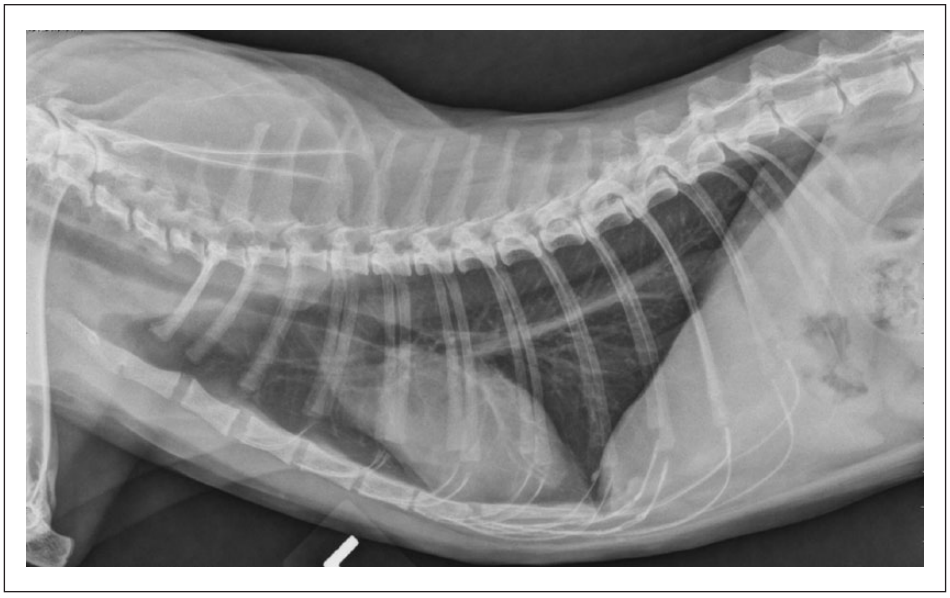

Figure 4 Thoracic radiographs following definitive radiation therapy (day 81) showing radiographic improvement of intraluminal tracheal mass

Piroxicam (0.3 mg/kg PO q24h) was also administered for approximately 10 months (day 81 to day 302) beginning at the time of the third carboplatin dose for its anti-inflammatory effects to address suspected tracheitis secondarily to the intratracheal mass, acute effects of RT as well as its possible antitumor effects.

Approximately 2 months after completion of RT (day 102), an occasional cough (once to twice weekly) was noted by the owners.

Thoracic radiographs were repeated every 3 months throughout treatment. The first recheck thoracic radiograph was performed 45 days following completion of RT (day 81), which revealed partial remission of the tracheal adenocarcinoma and no evidence of pulmonary metastatic disease (Figure 4). The mass remained stable with no significant growth or metastatic lung disease noted during subsequent radiograph rechecks (days 81–309).

Ten months after definitive RT (day 315), the cat was reported to be coughing more frequently (3–4 times weekly). Each coughing episode lasted about 10–15 s and consisted of a string of about 15 dry, non-productive coughs. The episodes never resulted in respiratory distress. Thoracic radiographs revealed a static thorax with no radiographic evidence of cardiopulmonary disease and a static appearance to the trachea with persistent narrowing and proliferation noted along the ventral border of the trachea at the level of the thoracic inlet. At that time, the cat was prescribed hydrocodone (0.25 mg/kg PO q24h) and doxycycline (5 mg/kg PO q12h) for presumptive inflammatory airway disease. Differentials included RT side effects (tracheal stricture formation), infectious (bacterial, parasitic or fungal), inflammation (bronchitis or asthma) or neoplasia.

The cat presented on day 383 for a work-up of its insidious chronic coughing. Thoracic radiographs were performed and revealed mild progressive disease of the tracheal adenocarcinoma with the previously noted irregularity of the mucosal surface of the tracheal wall at the level of the thoracic inlet, and a few small convex lucencies extending into the lumen from the ventral and dorsal wall. The cat was sedated with midazolam (0.1 mg/kg IV), butorphanol (0.2 mg/kg IV) and dexmeditomidine (0.002 mg/kg IV) and induced with propofol (6 mg/kg IV) and a second bronchoscopic examination was performed. General anesthesia was maintained with intermittent propofol (1.75 mg/kg IV) boluses. Abnormal findings included several multifocal, raised, nodular lesions noted throughout the trachea with the most affected area being the beginning of the intrathoracic trachea (Figure 5). Several solitary lesions were also noted more distally within the mainstem bronchi of the right lung. Biopsies were obtained and mild hemorrhage was noted. Dexamethasone (0.7 mg/kg IV q24h for two doses) was administered for treatment of inflammation and irritation following the procedure. Cytologic analysis of impressions smears of the tracheal biopsy was consistent with carcinoma with marked suppurative inflammation. Histopathological evaluation led to the diagnosis of recurrence of tracheal adenocarcinoma. At this time, piroxicam was discontinued and the cat was prescribed prednisolone (1mg/kg PO q24h) and sucralfate (0.5 tablet, PO q12h for 5 days) along with the previously prescribed doxycycline and hydrocodone.

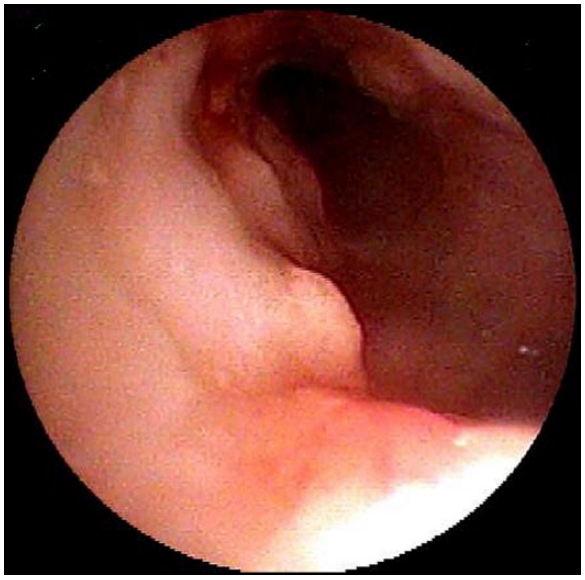

Figure 5 Second bronchoscopic examination performed after definitive radiation therapy (day 383) for work-up of insidious coughing showed several multifocal, raised, nodular lesions noted throughout the trachea

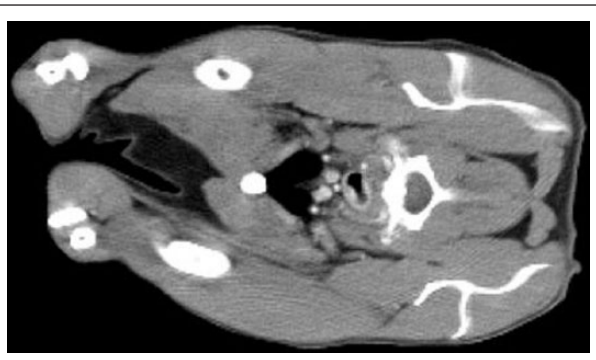

Figure 6 Recheck CT exam 16 months after definitive radiation therapy (day 525), which revealed distortion of the trachea secondarily to an intraluminal tracheal mass

Chemotherapy with toceranib phosphate (2.8 mg/kg PO q48h) was commenced on day 389 and was continued for approximately 4 months. No adverse effects were noted during therapy. The only abnormality noted on complete blood count during therapy was a persistent eosinophilia which was attributed to the cat's flea infestation. Recheck radiographs performed on day 442 revealed static disease.

On day 503, the cat presented for worsening of its cough and occasional labored breathing. At this time a dose of doxorubricin (20 mg/m^2, IV) and cyclophosphamide (100 mg/m^2, PO) was given. Prior to chemotherapy administration the cat was pretreated with maropitant citrate (1 mg/kg SC) and diphenhydramine (2.2 mg/kg SC).

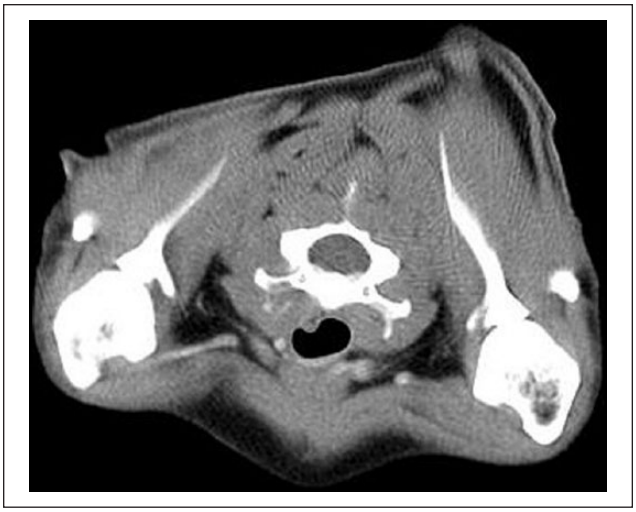

Figure 7 Recheck CT following palliative radiation therapy (day 567). Findings were consistent with a partial response to radiation

Owing to lack of improvement of the cough and persistence of intermittent labored breathing, a third CT was performed on day 525, which revealed distortion of the trachea from the level of C4 and extending to the level of T2. The distortion was marked from C5 to T1 secondarily to the presence of a contrast-enhancing intraluminal mass that covered the inner aspect of the trachea (Figure 6). There was no evidence of local or regional lymphadenomegaly.

The cat received a palliative course of radiation therapy (days 526–538). The prescribed dose of irradiation was six daily 4 Gy fractions of 6 MV x-rays for a total dose of 24 Gy to the 95% isodose 102.7%. A new computerized plan was prepared from the current CT images. The shape and size of the field were essentially the same as in the initial definitive course of irradiation, including the trachea from the level of the vertebra C4 to T5. The dose was delivered through equally weighted parallel opposed lateral portals. No acute adverse radiation side effects were observed.

A fourth CT was repeated on day 567. Findings were consistent with a partial response to RT (Figure 7).

Recheck thoracic radiographs performed on day 607 revealed progression of disease with a slight increase in length of the tracheal mass when compared with the previous radiographs (Figure 8). At this time, the owners reported an occasional cough in the mornings. Physical examination revealed upper airway stertor on auscultation of the cranial trachea on inspiration and expiration. L-Lysine (250 mg/cat, PO q24h) was prescribed for a presumptive upper respiratory tract infection.

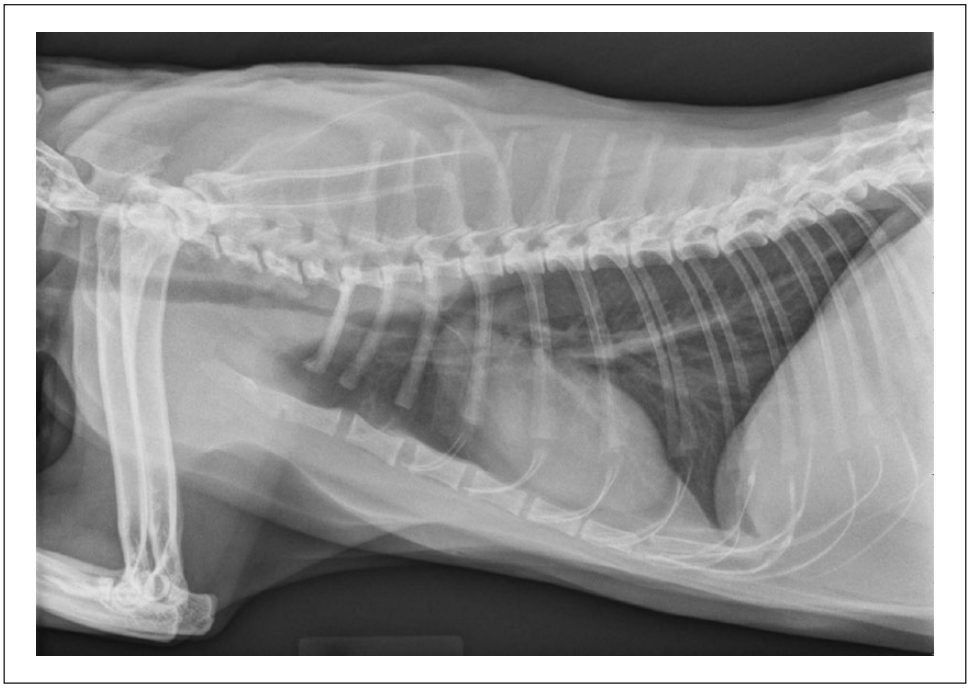

Figure 8 Recheck thoracic radiographs performed on day 607 showing progression of disease with a slight increase in length of the tracheal mass

On day 753, the patient presented in severe respiratory distress. Owing to poor quality of life, humane euthanasia was recommended at this time. The owners elected to bring the cat home at this time and the cat was euthanized by the referring veterinarian 2 days later (day 755).

Discussion

Primary tracheal neoplasia is an uncommon malignancy in cats.[1,2] Several different histologic types of tracheal tumors have been reported in the veterinary literature, with epithelial malignancies being the most common.[3–18] Affected cats are generally middle-aged-to-older cats with a mean age of 9.5 years, with no sex predilection.[3–18] In relation to tracheal adenocarcinoma, Siamese and domestic shorthair cats are reported to be the most commonly affected breeds; however, there are also previous reports of a Persian and domestic longhair with tracheal adenocarcinoma.[3–8]

Clinical signs of affected cats are generally consistent with upper airway obstruction such as dyspnea, stridor, wheezing, exercise intolerance and cough. Other clinical signs may include weight loss, lethargy, intermittent cyanosis and collapse.[1–3,11,15–17]

Survey radiography is the diagnostic procedure of choice as air within the trachea provides a natural contrast medium for visualization of a mass.[2,16,17] Radiographically, most tracheal tumors will appear as a distinct tracheal mass; there is also a previous report of an annular tracheal mass.[17] In one study, a soft tissue opacity within the trachea was found to be a statistically significant indicator of tracheal neoplasia.[17] Other described radiographic abnormalities include overexpansion of the lungs, prominent pulmonary vasculature and flattening of the diaphragm.[15,17] Advanced imaging such as CT or MRI may be useful for further characterization of the mass.[2] The use of bronchoscopy allows direct visualization of the tumor and permits procurement of brush cytology and biopsy samples.[2,19]

Prognosis is generally considered poor; however, there is limited available information regarding the treatment and prognosis of cats affected by tracheal adenocarcinoma. In a previous study of cats with tracheal tumors (of which one cat was affected with tracheal adenocarcinoma), cats with a tube tracheostomy as the sole form of treatment had a median survival time of 3 days (mean 3.3 days, range 1–6 days).[3] For cats not euthanized at diagnosis, surgical excision has historically been the treatment of choice.[4–8] Isolated reports describe cats living for 12–17 months before tumor recurrence after surgical intervention.[4,6] Other case reports describe cats alive at 3 and 12 months postsurgery.[4,8] Although RT and chemotherapy have been used for treatment of other tracheal tumor types, to our knowledge, there are no current reports regarding the efficacy of carboplatin specifically for the treatment of feline adenocarcinoma.

In addition to the RT, this cat also received platinum chemotherapy for treatment of its tracheal adenocarcinoma. There are no current reports regarding the efficacy of carboplatin specifically for the treatment of feline

adenocarcinoma. However, carboplatin has been previously reported to show some efficacy against carcinomas.[20] A phase 1 clinical trial of carboplatin in feline patients affected by various malignancies, including assorted carcinomas, reported that carboplatin at a dose of 240 mg/m^2 was safe and well tolerated in tumor-bearing cats.[20] Preliminary response data from this study found an 11.9% overall response rate after a single dose of carboplatin.[20] However, doses of carboplatin administered in that study were lower than the generally recommended dosing schemes, owing to the phase 1 nature of the trial. To continue, reported response rate assessment only included a single dose of the drug; thus, maximal responses may not have been achieved in patients who received only one treatment. Further studies are necessary to better determine the therapeutic role of carboplatin in cats affected by tracheal adenocarcinoma.

Current research has revealed that overproduction of prostaglandins in association with neoplastic processes is correlated with increased angiogenesis, immune suppression, increased invasion and metastasis, and antiapoptotic mechanisms.[21] Cyclooxygenase (COX) is the enzyme responsible for prostaglandin production. Specifically, COX-2 has been identified as a potential player in oncogenesis.[21] To support this theory, COX-2 overexpression has been identified in a number of different animal cancers.[22] The use of non-steroidal anti-inflammatory drugs (NSAIDs) to inhibit the COX-2 pathway has been proposed as a chemopreventative and chemotherapeutic tool. Studies have shown that the use of COX-2 inhibitors may have advantageous results in veterinary cancer patients, especially in the treatment of canine transitional cell carcinoma.[23] In feline patients, the role of NSAIDs in cancer therapy with regard to efficacy, anti-neoplastic mechanisms and ideal dose remains unknown. However, the long-term use of piroxicam in cats affected with various cancers has been found to be safe and well tolerated.[24]

Toceranib phosphate is a multi-target small molecule inhibitor approved for use in the treatment of canine grade II/III mast cell tumors. It has also shown promise in the treatment of other malignancies.[25] It exerts its effects on neoplastic cells and the tumor microenvironment by targeting multiple cell surface and angiogenic receptors, including vascular endothelial growth factor receptors, platelet-derived growth factor receptor, KIT and Flt3. A recent retrospective study evaluating the toxicity of toceranib phosphate administration in cats revealed that toceranib phosphate was well tolerated in feline patients with a similar toxicity profile in relation to canine patients.[26] In dogs, the biologic response rate for various solid tumors types (including carcinomas) treated with toceranib is reported to be 54–74%.[27] A recent study regarding the use of palladia in the treatment of feline mast cell tumors and various epithelial neoplasms reported an overall biologic response rate of 57.1%.[28] Further studies are necessary to determine the efficacy of toceranib phosphate in the treatment of feline tracheal adenocarcinoma.

Conclusions

In this case report, definitive RT was well tolerated and did not result in any significant acute adverse side effects. RT initially resulted in marked improvement in inspiratory and expiratory stridor. The cat remained asymptomatic for 2 months following RT and radiographically stable for 11 months thereafter. Because RT was followed by carboplatin chemotherapy and piroxicam, it is difficult to discern whether RT alone was responsible for the extended lack of disease progression. With multimodal therapy, the cat had a survival time of 755 days, which is longer than survival times observed in previous reports.

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