

Bella's Ray's Pulmonary Dismay

Megan W. Kuenast
Mississippi State University
College of Veterinary Medicine
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Advisor:
Sarah Castaldo, DVM

Introduction:

Primary pulmonary neoplasia is not as common in canines as it is in humans. Of the cases that are properly diagnosed, primary pulmonary neoplasia is estimated to be only 1% of all cases of canine neoplasia, which is even less common than metastatic neoplasia.^{3,5} Adenocarcinoma is the most common type of canine lung tumor.¹² The prevalence of canine lung tumors in necropsy studies ranged from 0.5 to 9 percent, and clinically, the incidence in one study reported 4-17 cases per 100,000 dogs.¹² The typical signalment of dogs with primary lung tumors are those over the age of 10-years-old, with no sex predisposition. Boxers, Doberman Pinschers, Australia Shepherds, Irish Setters, and Bernese Mountain Dogs tend to have a slightly higher predilection than other breeds.^{5,15} Around 25% of dogs with a pulmonary neoplasia are asymptomatic upon diagnosis, and their diagnosis is often made incidentally for an unrelated problem.⁵ The most common clinical signs for a primary pulmonary neoplasia can include a nonproductive cough, hemoptysis, fever, lethargy, exercise intolerance, weight loss, dysphagia, anorexia, and lameness, especially if bone or skeletal muscle metastasis occurs or if hypertrophic osteopathy develops.⁵

Primary pulmonary adenocarcinoma can be found in many different species of animals, such as in human, canine, feline, bovine and ovine species.¹⁵ In sheep, pulmonary adenocarcinoma is a contagious lung cancer caused by a retrovirus that induces oncogenic transformation of alveolar and bronchiolar secretory epithelial cells.⁶ Pulmonary neoplasia in cattle are rare, but the majority of tumors diagnosed appear to be adenocarcinoma.¹⁴ Cats with primary pulmonary neoplasia tend to have a more rapid progression of disease and higher rate of metastasis than seen in the dog, with metastasis to the digits being unique to cats.¹⁵

Adenocarcinoma has been found to be one of the most common primary tumors in the gastrointestinal tract of dogs, as well as a primary tumor in the apocrine gland of the anal sac,

and it accounts for 17% of all perianal tumors.^{1,6} Primary adenocarcinoma in the lungs has been reported to metastasize to tracheobronchial lymph nodes, tissues of the thorax, spleen, heart, pericardium, kidneys, bone, skeletal muscles, as well as the central nervous system, but have lower rates of metastasis than other neoplasia, such as squamous cell and anaplastic carcinomas.^{3,15} A case reported in a 10 year old dog had metastasis to the uvea, brain and adrenal glands.³ Primary pulmonary adenocarcinoma, if seen as a focal mass, is frequently found in the right caudal lung lobe; however, it has more commonly been reported as multifocal growths, and it is often found in more than one lung lobe.¹⁵

Classification of primary lung tumors as well as the diagnosis is made based on the histological pattern and assessment of the tumor.^{5,12} In humans, dogs, and cats, adenocarcinoma is the most common type of histologic lung cancer.^{5,14} Adenocarcinoma is a malignant epithelial tumor, and most tumors are thought to arise from terminal bronchiolar alveolar regions, with bronchogenic derivation being rare. They are also characterized by their glandular structures containing secretory products, with mucus being the most common secretion.¹⁵ Histological classification of primary pulmonary adenocarcinoma, according to the World Health Organization, can be broken down into four subtypes including: acinar, papillary, solid with mucin production, and bronchioloalveolar carcinoma, with mixed patterns also seen.^{2,15} On histopathology in low grade adenocarcinoma, there are glandular spaces lined by cuboidal to columnar cells in a single layer, or pseudostratified appearance with uniform nuclei.¹⁵ High grade consists of irregular glandular spaces with cellular pleomorphism, atypical nuclei, and a high mitotic count.¹⁵

History and presentation:

Bella, an approximately 10-year-old, female-spayed, German Shepherd, presented to MSU-CVM Oncology Service, on September 25th, 2019, for evaluation of an intrathoracic mass that was seen incidentally on radiographs from her referring veterinarian. Bella originally presented to her primary veterinarian on August 9th, 2019, for a re-check of her previously diagnosed UTI and crystalluria, as well as a new complaint of right forelimb lameness. Her veterinarian prescribed Dasquin Advanced and carprofen. On September 19th, 2019, Bella returned to her primary veterinarian due to the unresolving right front lameness, with new symptoms of pain at the right shoulder and left elbow. Radiographs were taken and showed osteoarthritis in both elbows and an incidental mass. Three view thoracic radiographs were then taken, localizing the mass to the region of the right cranial lung lobe. Additionally, Bella was noted to have a history of environmental allergies, which have previously caused her to have ocular discharge and an intermittent, productive cough; however, it has been successfully managed on chlorpheniramine.

Upon presentation to MSU-CVM, Bella was bright and alert. She weighed 27kg and had a body condition score of 5/9. She had normal vital parameters, with a temperature of 101.9 degrees Fahrenheit, a heart rate of 60 beats per minute, and a respiratory rate of 60 breaths per minute. On pulmonary auscultation, normal bronchovesicular sounds were heard, and no crackles or wheezes were appreciated. On cardiac auscultation, no obvious murmurs or arrhythmias were heard. Her mucous membranes were pink and moist, with a capillary refill time of less than 2 seconds. She had bilateral ocular discharge, and a small raised nodule was appreciated on the left side of her nose. Mild crepitus was appreciated in her elbows, shoulders,

and stifles bilaterally. The remainder of her physical exam was unremarkable. Full rectal and neurological exams were not performed.

Diagnostic approach:

After a thorough physical exam was completed, a minimum database, including a CBC, Serum Chemistry, and Urinalysis, were performed. The CBC showed a moderate lymphopenia (572g/dl). The Chemistry showed a mild hypophosphatemia (2.1 mg/dl) and a mild hypomagnesemia (1.6 mg/dl). On urinalysis Bella had a specific gravity of 1.022 with 2+ proteinuria and blood in her urine.

Next, an ultrasound guided fine needle aspirate of the thoracic mass was performed under sedation. Four slides were examined, revealing large dense streaks of amorphous necrotic debris, cholesterol crystals, a moderate number of erythrocytes, a low number of eosinophils, and an increased number of neutrophils. Epithelial cells were also found that were characterized by round to oval shaped indistinct nuclei centrally located with a granular chromatin pattern. The most likely diagnosis at this time was an epithelial neoplasm, with marked necrosis and mild suppurative inflammation, but a biopsy with histopathology was recommended for a definitive diagnosis.

At that time, in order to further diagnose Bella's pulmonary mass and check for metastasis, a computer tomography (CT) with contrast was then performed, focusing on Bella's thorax and abdomen. CT is more sensitive than radiography in detection of pulmonary nodules and it is the modality of choice for oncologists desiring to stage dogs with malignant neoplasia.⁹ CT can evaluate tumors in more detail to determine the treatment plan and prognostic factors such as tumor size, lymph node involvement, and pulmonary or distant metastasis.⁸ In Bella's right dorsal cranial lung lobe, an ovoid, smoothly margined, heterogenous soft tissue dense

mass measuring 7 x 4.4 x 6.6 cm was found. This mass was causing a mediastinal shift to the left, and subsequently creating a mild, left- sided displacement of the intrathoracic esophagus and trachea. The pulmonary parenchyma surrounding the mass contained a non-contrast enhancing, soft tissue dense area. In the abdomen, the liver and spleen were enlarged with rounded margins. The spleen contained multiple heterogenous contrast enhancing, soft tissue dense nodules, measuring 1.1 cm at its largest diameter.

In preparation for surgery, Bella was blood typed and found to be DEA 1.1 negative. An MDR-1 test was sent off due to the potential for chemotherapy treatment. Bella's presumptive diagnosis was a primary pulmonary neoplasm, but a granuloma could not be ruled out at this time.

Pathophysiology:

The pathophysiology of canine primary pulmonary adenocarcinoma is still not completely known, but much of what is described is derived from human classifications and studies. Lung tumors of epithelial origin can arise from many progenitor cells, including basal and secretory cells in the large airways, and non-ciliated secretory cells and type II pneumocytes in the terminal bronchioles.¹⁵ In humans, carcinomas usually arise from the larger airways and adenocarcinomas from the distal airways, with tumors in the distal airways being more commonly seen in non-smokers.¹⁵ Various molecular alterations have been recorded in human lung cancer, including modifications in growth factor expression, mutations in oncogenes, chromosomal deletions and mutations, and altered expression of tumor suppressor genes.¹⁵

The molecular classifications of pulmonary neoplasia can be an important factor in determining the type of chemotherapy treatment used for patients. The epidermal growth factor receptor (EGFR) is part of the receptor tyrosine kinase family, which is a group of

transmembrane proteins involved in cell-to-cell transduction, and overexpression is thought to have a proliferative advantage to neoplastic cells by triggering tumor development and progression.¹³ A study of 37 dogs with primary lung cancer found that 28 tumors (76%) expressed an epidermal growth factor receptor, which was determined by immunohistochemistry, and 68% of the tumors found to have the EGFR overexpression were adenocarcinomas.^{13,15} In humans, other alterations have included changes in the EGFR encoded by c-erbB1, ras gene family, loss of the short arm of chromosome 3, loss or altered retinoblastoma tumor suppressor gene, or missense mutations in the p53 tumor suppression gene.¹⁵ Mutations in k-ras occurred in approximately 30% of human adenocarcinomas and in a study with colony-raised beagles exposed to PuO₂ (plutonium IV oxide), mutations in k-ras were seen in approximately 19% of the lung tumors.¹⁵

The risk factors that predispose and influence the occurrence of primary lung neoplasia in dogs are largely unknown. In a study of 35 dogs with known primary lung neoplasia, it was found that black, dusty material in macrophages of the lung parenchyma, known as anthracosis, indicated exposure to air pollution and may be associated to an increased risk of lung cancer in dogs.¹³ Particulate matter in the lungs has been linked to pulmonary neoplasia, due to their effect on suppression of DNA repair, enhancing replication errors, and inducing reactive oxygen species causing proliferation, apoptosis, and inflammation of cells.¹³ Reactive oxygen species are known to activate the EGFR causing overexpression and increased gene copy numbers.¹³

Treatment and management:

When performing surgery for the removal of a solitary lung tumor, an intercostal thoracotomy is the customary approach.¹² This approach will allow better exposure to the lung for lobectomy and the local lymph nodes. If exploration of the thoracic cavity is warranted, a

median sternotomy is preferred.¹⁰ A total lung lobectomy is usually performed, unless the tumor getting excised is located at the periphery of the lung lobe.¹⁰ Complications for a thoracotomy can include hemorrhage, pneumothorax, lung lobe torsion, pyothorax, infection, coagulopathy, and subcutaneous emphysema.¹² Another common complication is the development of pulmonary congestion due to impaired gas exchange of the dependent lung because the animal is in lateral recumbency.¹⁰ It is important to maintain good ventilation and avoid fluid overloading these patients during this procedure, in order to avoid congestion.

Bella was transferred to the surgery service on the morning of September 26th, 2019, for an intercostal thoracotomy and right cranial lung lobectomy. The night before surgery she was maintained on LRS fluids, Trazodone, and Cerenia. The day of surgery, Bella was placed in left lateral recumbency, and her surgical site was clipped and prepped with a 4% chlorhexidine solution. She was then given intravenous cefazolin pre-operatively and every 90 minutes intra-operatively for her prophylactic antibiotic treatment. A 10 cm skin incision was made on the right lateral thorax, at the 4th intercostal space, between the 4th and 5th ribs. The subcutaneous tissues were bluntly dissected with Metzenbaum scissors, and then the latissimus dorsi was elevated to increase exposure. Next, the serratus ventralis thoracis and the external and internal intercostal muscles were transected with sharp dissection and electrocautery. The parietal pleura was then bluntly perforated, and the thoracic cavity was entered. Finochietto rib retractors were used to open the thoracic cavity and visualize the mass in the right cranial lung lobe. The right cranial lung lobe, which included the mass, was then excised carefully using the blunt dissection technique described previously, and a scalpel blade. A Satinsky clamp was then placed at the hilus of the lung, around the cranial and middle mainstem bronchi. Following this, a TA 30 stapler was placed distal to the clamp and fired, and the lobes were transected distal to the stapler

with a scalpel blade. The thoracic cavity was then lavaged with sterile saline. A 14-gauge Mila thoracostomy tube was placed into the thoracic cavity and 2-0 Dexon sutures were placed and tied using a purse string and finger trap pattern to close the thoracic cavity. The ribs were opposed using 0 PDS in a simple interrupted pattern. Sutures were preplaced circumferentially around each rib using caution not to perforate pulmonary parenchyma. Once all sutures were placed, the middle suture was tied first making sure not to overtighten. The muscles were opposed using 2-0 PDS in a simple interrupted pattern. The subcutaneous tissues were closed using 2-0 PDS in a simple continuous pattern and the skin was closed using medical grade wide skin staples. The chest was evacuated until negative pressure was achieved. It is important to keep the thoracostomy tube open during closure of the thoracic cavity to avoid a tension pneumothorax and to evacuate the air from the pleural space following closure.¹⁰ Lastly, the surgical site was covered with telfa pads and suresite bandages, then Bella was moved to recovery. Bella recovered from anesthesia uneventfully. Post-operatively, Bella was maintained on LRS fluids, a fentanyl CRI, and trazodone. Her thoracostomy tube was aspirated for fluid and air every 12 hours. Her fentanyl CRI was stopped on September 27th, 2019, the day after her surgery. She was then started on Tylenol 4 and her thoracostomy tube was pulled.

In the days to follow, based on histopathology, Bella's pulmonary tumor was diagnosed to be primary pulmonary adenocarcinoma. The mass was encapsulated, expansive, locally infiltrative, and multilobulated, composed of cuboidal to columnar shaped epithelial cells. There were eosinophilic collagenous stromal septae and inflammatory cells throughout, as well as, areas of eosinophilic necrotic debris and cholesterol clefts. The neoplastic epithelium extended to the surrounding pulmonary stroma. The individual epithelial cells were composed of an eosinophilic cytoplasm, with a single oval nucleus and chromatin, with an average of 6-10

mitotic figures per high power field. The mass appeared to be completely excised, and the tumor had a mixed pattern, consisting of papillary, solid, and acinar components.

Several studies have documented the effects of chemotherapy and radiation therapy for neoplasia in dogs. In one study, 42 dogs with adenocarcinoma had a longer time until disease progression when receiving Toceranib Phosphate as a chemotherapy agent, which is a multitarget tyrosine kinase inhibitor along with surgery, compared to 50 dogs treated with surgery alone.¹⁶ In another study, 37 dogs with carcinomas that were treated with a combination therapy of Gemcitabine (thymidylate synthetase inhibitor) and Carboplatin (alkalizing agent) had a response rate of 13%.⁴ Preoperative radiotherapy may also be useful in dogs for solitary lung adenocarcinomas that cannot undergo immediate surgery, or in dogs that have tumors that are very large and reduction is optimal before undergoing surgery.⁷ Tumor size was reduced and growth was suppressed within months following radiotherapy with a median of 56 days.⁷ In dogs that undergo a lung lobectomy via thoracotomy or thoracoscopy for solitary lung tumors, the average survival time ranges from 4-46 months, with a mean of 13 months.⁷

Case outcome:

Bella was discharged from MSU-CVM on September 28th, 2019, with Tylenol 4 and carprofen, for pain control and inflammation. Bella's owners were instructed to keep Bella on strict cage rest for the next two weeks to ensure her incision would heal properly. On October 17th, 2019, Bella returned to MSU-CVM to have a consult with the oncology service and get her incision checked by the surgery service. Her incision was healing appropriately, so Bella was cleared for bathing and released from complete activity restriction. Bella returned on November 20th, 2019, to get her first chemotherapy treatment with Carboplatin and to re-check her thoracic radiographs for any signs of metastasis. Bella had no respiratory or other clinical signs, except

for mild lethargy. At the time of presentation, a few days prior, it was noted that she had just finished a course of cephalexin for a urinary tract infection. A CBC, Serum Chemistry, Urinalysis and Urine Culture and Sensitivity were performed. The CBC showed a moderate lymphopenia and there was no growth after 48 hours on urine culture. There were no signs of metastasis on her radiographs, and she was prescribed Ondansetron as an anti-emetic to prevent vomiting from her chemotherapy. Metronidazole was also prescribed and to be given as needed. On December 11th, 2019, Bella received her second dose of Carboplatin. Another CBC was performed showing a mild leukopenia, mild lymphopenia, and mild eosinopenia, as well as, a small animal renal profile showing no abnormalities. Clavamox was prescribed prophylactically due to an expected drop in her white blood cell count around this time of her chemotherapy treatment. Ondansetron and metronidazole were also prescribed again and to be given as needed. On January 2nd, 2019, Bella returned for her third dose of Carboplatin. Her owner reported that she had some episodes of vomiting and diarrhea since her last visit. Thoracic radiographs, a small animal renal profile and a CBC were performed. Her renal profile showed a mild anion gap, her CBC showed a very mild lymphopenia and mild eosinopenia, and her thoracic radiographs showed no signs of metastasis. On January 23rd, 2020, Bella returned for her fourth dose of Carboplatin. Her renal profile was normal, and her CBC showed a mild leukopenia, neutropenia, lymphopenia and eosinopenia. Later that evening Bella presented to the MSU-CVM emergency service for abdominal pain and bloat. On presentation she was laterally recumbent and dull. She had pale and tacky mucous membranes, a prolonged to absent CRT, weak and thready pulses, and low blood pressures. On abdominal FAST scan she had a large gas filled structure in the cranial to middle abdomen and a ping auscultated in the left abdomen. During her initial triage and catheter placement she stopped breathing. Cardiopulmonary resuscitation (CPR)

was then performed. She was intubated and intratracheal doses of atropine and epinephrine were given alternating every 2 minutes. CPR was performed for 14 minutes until it was stopped with her owner's permission. A necropsy was not performed on Bella, but her presumptive cause of death was a suspected gastric dilatation and volvulus.

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