It’s Not What It Looks Like!

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INTRODUCTION

Canine primary pulmonary neoplasia is an uncommon occurrence, but due to an increased average life span, better preventative and awareness, better diagnostics or possibly increased exposure to environmental carcinogens, the incidence of diagnosis has increased in the last decade. (2,3) However, while the occurrence is increasing, the incidence of pulmonary neoplasia in dogs is remarkably lower than that in humans, and accounts for approximately 1.2% of all tumors. (6,7). Adenocarcinoma is the most common histologic type of canine lung tumor, followed by squamous cell carcinoma, chondroma, fibroma, and plasmacytoma. (8) Adenosquamous carcinoma has been reported as an uncommon pulmonary tumor, but research of spontaneous growth of primary pulmonary tumors reported a 13 % occurrence of pulmonary adenosquamous carcinomas. (9) The majority of primary lung tumors are malignant with adenocarcinoma being the most commonly reported in dogs.

HISTORY AND PRESENTATION

A pulmonary mass is more often documented as a metastatic pulmonary tumor rather than a primary pulmonary tumor. A typical presentation for a primary pulmonary neoplasia is a 10-year-old dog with a non-productive cough, though patients may also present with bilateral lameness of the carpi or tarsi due to hypertrophic osteopathy (HO). The median age of diagnosis for primary pulmonary neoplasia varies from 9 to 12 years old with no current sex predilection documented. (5,9) Primary pulmonary neoplasia has been documented more often in Bernese mountain dog, Rottweilers, Boxers and Golden retrievers. (5) Even though most affected dogs originate from an urban region, there is no significant association documented between the surrounding environment and the development of pulmonary neoplasia. Recently, an association

has been identified with increased anthracosis and pulmonary neoplasia development in dogs suggesting an environmental association from polluted air (specifically carbon-pollution). (11)

Clinical presentation of a primary lung tumor varies depending on the location of the tumor, grade of the tumor, rate of the metastasis, or the presence of pulmonary disease. The most common clinical presentations are non-productive cough, dyspnea, lethargy, and weight loss. Other clinical signs that may be seen on presentation are exercise intolerance, lameness, carpi/tarsi bony swelling, tachypnea, wheezing, vomiting or regurgitation, or pyrexia. (4,5). Lameness and bony swellings are most commonly due to the manifestation of a painful periosteal reaction and associated soft tissue swelling of the limbs known as paraneoplastic hypertrophic osteopathy, and less commonly, due to metastatic bony proliferation. Owners have recognized the clinical signs of pHO between 1 day and 6 months prior to diagnosis with the median time period of clinical signs being 3 weeks prior to diagnosis. (12) Even though primary pulmonary tumors are typically malignant, they are commonly an incidental finding on thoracic radiographs in a dog and clinical signs are absent in 25% of patients on presentations.

PATHOPHYSIOLOGY

Most primary lung tumors originate from airway epithelium and are classified as adenocarcinoma, bronchioalveolar carcinoma, or squamous cell carcinoma. (14) However, pulmonary adenocarcinoma has been documented originating from the terminal bronchioles and alveoli as well. (4) Ultrastructural features typical of adenosquamous carcinoma are the growth of both gland-like adenocarcinoma and a layer of differentiated squamous cell carcinoma. (1)

The metastatic process uses the bloodstream, lymphatics, and intrapulmonary components as the highway for its travel in the dog. Primary pulmonary neoplasia will metastasize regionally to the

tracheobronchial lymph nodes, pleurae, pericardium, heart, and the diaphragm. The affected area is not restricted to the thoracic region and can have metastasis to the liver, kidney, spleen and rarely the brain. (4,5) Usually the metastasis has already spread to the regional lymph nodes if the patient is presenting with clinical signs: this is directly correlated with a shorter survival time than pulmonary neoplasia as an incidental finding. (5)

Even though hypertrophic osteopathy associated with pulmonary neoplasia has been well documented in human medicine, the pathogenesis in human and veterinary medicine still remains undetermined. The most common theory is the physiological increase in peripheral blood flow to the distal limbs causes local passive congestion which stimulates proliferation of the periosteum in the localized are of bone. The resultant bony thickening associated with pHO diminishes within two weeks after surgical excision of the tumor and the associated lameness will resolve within the next 3-4 months. (6) This quick resolution has direct association with the tumor, so future studies could lead to correct etiologic identification.

DIFFERENTIAL DIAGNOSES

Most canine patients with a pulmonary adenosquamous carcinoma present clinically for a non-productive cough or respiratory problem which can help localize the search for the diagnosis. However, patients may also present for lameness from bilateral, symmetrical bone thickening of the carpi and tarsi without any concurrent clinical sign. This syndrome has been documented in dogs, as a paraneoplastic disease most commonly associated with a primary or metastatic pulmonary tumor. (6) Hypertrophic osteopathy has also been described in several articles in The Journal of the American Veterinary Medical Association being secondary to extrapulmonary neoplasia, infectious, inflammatory, or parasitic lung disease such as a renal pelvis transitional cell carcinoma, Spirocerca lupi esophageal granuloma, bacterial endocarditis,

or Heartworm disease. (12,16,17,18) Once HO has been identified, diagnostics are warranted to detect a possible pulmonary mass as the primary differential which will narrow the differential list. Once the cause is narrowed down to a pulmonary mass, the rule-out list consist of primary or metastatic neoplasia, pulmonary abscess, parasitic granuloma, or lymphomatoid granulomatosis (19)

DIAGNOSTIC APPROACH/CONSIDERATIONS

Thoracic radiography is the most common diagnostic tool used by clinicians for proper diagnosis of a pulmonary mass. The typical radiographic presentation of primary pulmonary neoplasia of all types is a solitary, well-defined nodule that has reached 3-5 mm for reliable detection. (4) Other mass patterns have been documented such as, multiple nodules, lobar consolidation, or mixed alveolar interstitial patterns. Pulmonary adenocarcinoma is most commonly located in the left caudal lung lobe whereas a pulmonary mass located in the left cranial or right middle lobe is more commonly diagnosed as a histiocytic sarcoma. (14) The location of the pulmonary mass can be suggestive of type of neoplasia but is not definitive. Even though thoracic radiographs identify the pulmonary mass, they are limited in accurately diagnosing pulmonary metastasis and thoracic lymphadenopathy. Pleural effusion is an uncommon occurrence in dogs, but a recent case report on adenocarcinoma was documented presenting with a history of pleural effusion that was identified cytologically as a pyogranulomatous exudate. Post mortem examination revealed a mucinous pulmonary adenocarcinoma. As such, a history of pleural effusion should warrant further investigation for pulmonary neoplasia. A thoracentesis can be performed to further evaluate the effusion fluid cytologically, though this may be insensitive for identifying malignancy.

Computed tomography is another diagnostic tool that is not always available in private practice but can be very effective in diagnosing unforeseen pulmonary metastasis or tracheobronchial lymphadenopathy. Computed tomography has been recognized as being more sensitive than thoracic radiographs due to its ability to identify a mass/nodule at 1 mm in diameter which is significantly smaller than the 3-5 mm seen by thoracic radiographs. (4,5) Magnetic Resonance Imaging can also be used for better identification of the smaller nodules but due to potential of motion artifact it is not commonly selected. Additional uncommonly used diagnostic tools are tracheal wash, bronchoalveolar lavage, and brush cytopathology due to their poor diagnostic capabilities for diagnosing pulmonary neoplasia unless tracheobronchial lymph nodes are involved. (2,3)

Once a pulmonary mass has been identified in the thoracic cavity, the next step for clinicians is to determine a definitive diagnosis, which is done by evaluation of tissue samples or cytological specimens. Fine needle aspirate (FNA) of the mass, the most common diagnostic technique used by clinicians, can be performed via a blind stick technique, ultrasound-, CT-, or fluoroscopy-guided. Accurate identification of a pulmonary mass by FNA occurs 82% of the time when an ultrasound guided technique is used. (5) Considering a diagnosis of a pulmonary mass has a greater than 50% chance of being malignant, the purulent and necrotic center can be very unhelpful when trying to provide a definitive diagnosis.

TREATMENT AND MANAGEMENT OPTIONS

Upon identification and diagnosis of a pulmonary adenosquamous carcinoma, surgical excision via partial or complete lobectomy with complete margins is the treatment of choice. Each case of pulmonary adenocarcinoma differs in location, size, and rate of metastasis, therefore the correct surgical approach is key in effectively treating the patient. A right or left

lateral thoracotomy is the most preferred surgical approach by surgeons. With this approach, good visualization can be achieved, as well as adequate access for lung lobectomy and mass removal. A median sternotomy can be performed when bilateral primary or metastatic tumors are present; however, post-operative pain and complications can be more substantial when compared to a lateral thoracotomy. Thoracoscopy, a minimally invasive approach that involves small incisions in the intercostal space for placement of surgical instruments, is gaining popularity. However, it requires more advanced technical skill level and surgical equipment to perform. One recent study focused on thoracoscopic lung lobectomy for primary lung tumors, ending with the recommendation that thoracoscopic-assisted lung lobectomy is most appropriate for small, peripheral pulmonary tumors. (5) A more prolonged post-operative recovery is the expected outcome of any thoracic surgery, therefore the resulting average of 1 day spent in critical care following thoracoscopic lobectomy may increase the practice of this procedure. (20)

Once the approach has been decided, the next step is the removal of the pulmonary mass via a partial or complete lung lobectomy. The continuous overlapping suture method is one technique used to properly seal intrapulmonary vessels for adequate resection of the lesion but applies a significant increase in surgical time when compared to the stapling technique. The more commonly used lobectomy technique is surgical staples which decrease the surgical time and incidence of intra-operative complications. These two techniques described are both effective in removing the pulmonary adenosquamous carcinoma, thus surgeon preference and experience may ultimately dictate technique. Pulmonary adenosquamous carcinoma has the ability to compromise all lobes of one side of the thorax, and it has been reported that dogs can survive with 50% loss of lung volume with death occurring when 75 % of lung volume is lost. Considering the left lung lobes only make up 42 % of the overall lung volume, a

pneumonectomy is performed on the left side with less expected complications. Following a pneumonectomy, the contralateral lung attempts to regenerate the lost lung volume with a hyperplastic response increasing the lost intrapulmonary components. There have been secondary changes noted such as right ventricular hypertrophy and increased pulmonary resistance, which decrease the survival time of the procedure if the patient does not have a healthy heart prior to surgery. In addition to lung lobectomy, it is recommended that the surgeon identify and biopsy the tracheobronchial lymph nodes for any involvement with the primary tumor as metastasis to regional lymph nodes as part of staging for prognosis after surgery. If the tracheobronchial lymph nodes are enlarged upon palpation, complete resection is recommended to prevent further metastasis in the body. (5)

Treatment for pulmonary neoplasia is also possible by use of adjunctive chemotherapy to reduce the size of the tumor, halt further growth, and prevent metastasis. It has been recognized in the literature that human and canine pulmonary genomics show similarity but the chemotherapeutic treatment research of the canine pulmonary neoplasia has been limited in regards to effective responses when compared to human research. One of the most recent studies of chemotherapy in pulmonary tumors is targeted around the effects of vinorelbine, a semisynthetic derivative of the vinca alkaloids that acts at disrupting the mitotic spindle apparatus. The remarkable aspect of vinorelbine in humans is the 300-fold greater concentration in the lungs than in the plasma, but this has not been fully documented in dogs. A 2015 JAVMA article reported that in 15 dogs the chemotherapeutic effect of vinorelbine was not significant following surgical excision of the primary pulmonary tumor with or without administration of the drug whereas, 3 of 18 dogs who did not undergo surgery but received vinorelbine administration had a partial response. (21) An older study also addressing the efficacy of

vinorelbine treating primary pulmonary neoplasia reported a very similar finding as 2 of 16 dogs had a partial response to the drug. (22) In both of these studies, the hematological effects were monitored with the most common identified as neutropenia and myelosuppression. Due to the partial response along with monitoring for the well documented adverse effects, vinorelbine may be an option for adjunct chemotherapy in dogs with primary pulmonary carcinomas.

Other reported treatment options are radiofrequency ablation and a tumour-derived chaperone-rich cell lysate (CRCL) vaccine, but due to the lack of continued research published these two option are experimental at best.

EXPECTED OUTCOME AND PROGNOSIS

When an owner is told their dog has been diagnosed with a pulmonary adenosquamous carcinoma, multiple questions run through their head such as the how bad they are affected, how to treat, and how long do they have to live, with or without treatment. To properly answer those questions, one must correctly stage the tumor using TNM staging method, with the most significant prognostic indicator being lymph node involvement. The alphanumeric code describes the size original tumor (T), the regional lymph node involvement (N), and distant metastasis (M) to effectively stage the primary pulmonary neoplasia. The tumor stage has been correlated to actual number median survival days with T1 at 790 days, T2 at 196 days, and T3 tumors at 81 days. (3) The single, well differentiated primary pulmonary tumor located at the periphery of the lobe have a disease free interval of 493 days and median survival time (MST) of 790 days whereas, compared to a dog with moderate to poor differentiation of the tumor has a MST of 251 and 5 days, respectively. (3,5) Regional lymph node involvement has been documented numerous times as a negative prognostic indicator with a significantly shorter MST when compared to a solitary neoplasm with no local lymph node invasion. A dog presenting

asymptomatically with pulmonary neoplasia as an incidental finding has a longer life expectancy with a MST of 545 days whereas, the clinically symptomatic patient has a significant decrease in MST at 240 days. A patient whose biopsy results in the diagnosis of an adenocarcinoma has a far better prognosis and survival time (19 months) with surgical excision than the neoplasia being a squamous cell carcinoma (8 months). (5) Even though the biological properties of adenosquamous carcinomas show resemblance to adenocarcinomas and are normally diagnosed as adenocarcinomas, it has been reported in humans that the prognosis of adenosquamous carcinomas is significantly poorer than that of adenocarcinomas and squamous cell carcinomas. (10)

CONCLUSION

Primary pulmonary adenosquamous carcinoma typically presents in a dog ranging from 9-12 years old with a non-productive cough. Some cases of primary pulmonary neoplasia have an associated paraneoplastic syndrome known as hypertrophic osteopathy which presents with an onset of lameness over the last 2-3 weeks. The physical exam will identify bilateral, symmetrical periosteal reaction with thickening of the carpi and tarsi with possible injected sclera seen bilaterally while the rest of the physical exam is normal. If a dog presents coughing or has HO, thoracic radiographs should be performed to identify the potential pulmonary neoplasia as the source. Once pulmonary neoplasia is identified, computed tomography is recommended to properly assess the mass and to note the level of metastasis if any. An ultrasound-guided fine needle aspirate of the mass is recommended to help differentiate between primary or metastatic neoplasia because further evaluation of the body is warranted if it diagnosed as a metastatic. Once a diagnosis is attained, surgical excision via lateral thoracotomy or thoracoscopy is recommended as the treatment of choice due to the decreased amount of post-operative

complications and quicker recovery time. During surgery, the tracheobronchial lymph nodes should be biopsied to stage the tumor. If regional lymph nodes are involved, it is the duty of the veterinarian to properly inform the owner of the negative prognostic indication that is linked too. If the biopsy returns with a poor differentiation of the neoplasia and has lymph node involvement, adjunct chemotherapy, such as vinorelbine, is recommended but the owner must also be informed that this drug does not have a high rate of response associated with it. Owners' education of the entire process and expected outcome is crucial in pursuing the treatment of primary pulmonary neoplasia.

REFERENCES:

1. Lee J-H, Lee J-H, Yoon H-Y, Kim N-H, Sur J-H and Jeong S-W. Hypertrophic osteopathy associated with pulmonary adenosquamous carcinoma in a dog. Journal of Veterinary Medical Science 2012; 74: 667–672.
2. Ogilvie GK, Haschek WM, Withrow SJ, et al. Classification of primary lung tumors in dogs: 210 cases (1975-1985). J Am Vet Med Assoc 1989;195(1):106-108
3. McNiel EA, Oglivie GK, Powers BE, Hutchison JM, Salman MD, Withrow SJ. Evaluation of prognostic factors for dogs with primary lung tumors: 67 cases (1985-1992). J Am Vet Med Assoc. 1997:1;211(11):1422-1427.
4. Merck Veterinary Manual website. Neoplasia of the Respiratory System in Small Animals. Available at: www.merckmanuals.com/vet/respiratory_system/respiratory_diseases_of_small_animals/neoplasia_of_the_respiratory_system_in_small_animals. Accessed July 8th, 2016.
5. Kudnig ST, Séguin B. Respiratory tract and thorax, Lung. In: Veterinary Surgical Oncology. Ames: John Wiley & Sons, Ltd. 201
6. Brodey, R. S., and P. H. Craig, 1965: Primary pulmonary neoplasmas in the dog; a review of 29 cases. J. Am. Vet. Med. Assoc. 147, 1628–1643.
7. Ogilvie, G. K., W. M. Haschek, S. J. Withrow, R. C. Richardson,H. J. Harvey, R. A. Henderson, J. D. Fowler, A. M. Norris, J. Tomlinson, D. McCaw, J. S. Klausner, R. W. Reschke, and B. C. Mckiernan, 1989: Classification of primary lung tumors in dogs; 210 cases (1975–1985). J. Am. Vet. Med. Assoc. 195, 106–108.
8. Sato, T., Ito, J., Shibuya, H., Asano, K. and Watari, T. 2005. Pulmonary adenosquamous carcinoma in a dog. J. Vet. Med. A. 52: 510–513.
9. Hahn, F. F., B. A. Muggenburg, and W. C. Gri ffith, 1996: Primary Beagle colony. Vet. Pathol. 33, 633–638.
10. Takamori, S., M. Noguchi, S. Morinaga, T. Goya, S. Tsugane, T. Kakegawa, and Y. Shimosato, 1991: Clinicopathologic characteristics of adenosquamous carcinoma of the lung. Cancer 67, 649–654.

11. Bettini, G., M. Morini, L. Marconato, P.S. Marcato, and E. Zini, 2010: Association between environmental dust exposure and lung cancer in dogs. Volume 186, Issue 3, December 2010, Pages 364–369
12. S. S. Withers1, E. G. Johnson 2, W. T. N. Culp 2, C. O. Rodriguez Jr 2, K. A. Skorupski2 and R. B. Rebhun2: Paraneoplastic hypertrophic osteopathy in 30 dogs
13. McGavin MD, Zachary JF. Mosby-Elsevier, St. Louis, Missouri, 2007; Pathologic Basis of Veterinary Disease, 4th Edition; Chapter 9-Respiratory System pg. 158
14. Barrett LE[1], Pollard RE, Zwingenberger A, Zierenberg-Ripoll A, Skorupski KA; Radiographic characterization of primary lung tumors in 74 dogs. Vet Radiol Ultrasound. 2014 Sep-Oct;55(5):480-7. doi: 10.1111/vru.12154. Epub 2014 Mar 27
15. Newton C., Nunamaker D. , Textbook of Small Animal Orthopaedics; Chapter 51 Hypertrophic Osteopathy Lenehan T. and Fetter A., Available at: http://cal.vet.upenn.edu/projects/saortho/chapter_51/51mast.htm Accessed: July 15th, 2016
16. Grillo TP, Brandao CVS, Mamprim MJ, de Jesus CMN, Santos TC and Minto BW. Hypertrophic osteopathy associated with renal pelvis transitional cell carcinoma in a dog. Canadian Veterinary Journal 2007; 48: 745–747
17. Brodey R: Hypertrophic osteoarthropathy in the dog: A clinicopathologic study of 60 cases. J Am Vet Med Assoc 159:1242, 1971
18. Stephens LC, Gleiser CA and Jardine JH. Primary pulmonary fibrosarcoma associated with Spirocerca lupi infection in a dog with hypertrophic pulmonary osteoarthropathy. Journal of the American Veterinary Medical Association 1983; 182: 496–498.
19. Rebhun RB, Culp WTN. Pulmonary Neoplasia. In: Withrow SJ, Vail DM, Page RL. Small Animal Clinical Oncology. Fifth Edition. St. Louis: Saunders Elsevier, 2013; 453-459.
20. Bleakley S., Duncan C., Monnet E. Thoracoscopic Lung Lobectomy for Primary Lung Tumors in 13 Dogs; Veterinary Surgery Volume 44, Issue 8, pages 1029–1035, November 2015
21. Wouda RM, Miller ME, Chon E, Stein TJ. Clinical effect of vinorelbine administration in the management of various malignant tumor types in dogs: 58 cases (1997-2012). JAVMA 2015; 246(11):1230-1237
22. Poirier VJ, Burgess KE, Adams WM, Vail DM. Toxicity, Dosage, and Efficacy of Vinorelbine (Vavelbine) in Dogs with Spontaneous Neoplasia. J Vet Intern Med 2004; 18:536-539.