“A Triple Threat”
Malignant Mesothelioma in a Dog

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Introduction

Mesothelioma is a rare neoplasia that has been most commonly documented in human medicine. Although considered rare in all species, mesotheliomas have been documented in cattle and dogs, and less frequently in horses and cats. Mesotheliomas arise from the mesothelial cells that line the pleural, peritoneal, and pericardial surfaces within the body. Less commonly, mesothelioma may arise from the tunica vaginalis of the testis in males (1-3). In dogs, mesotheliomas are most commonly diagnosed between ages 4-13 years with a mean age of 7.8 years (4). Most documented cases of mesothelioma in cattle are thought to be congenital in nature and typically occur at young ages (3). Breed predispositions have not been proven, however, studies suggest that German Shepherd Dogs are overrepresented (5).

Over the last fifty years, a sharp rise in the prevalence of mesotheliomas in human medicine has initiated a need for further research into the disease. A strong association has been identified in human medicine between mesothelioma and exposure to asbestos by those individuals with occupations in mines, construction or factories (6). This relationship has not yet been verified in companion animals, but a relationship has been made between dogs who acquire mesothelioma and their owner's occupation (2). Patients with mesothelioma typically present with severe malignant effusions that are highly aggressive. Considering the uncommon nature of this neoplasm in dogs the epidemiology is not fully understood and further research is warranted.

Case Report

An approximately 9-year-old female spayed Jack Russell terrier, presented to MSU-CVM Surgery Department on September 6, 2017, following an extensive 4-month history of idiopathic tricavitary effusion that had been managed by regular thoracocentesies performed by her primary veterinarian. Prior to her surgical consult, an extensive diagnostic workup had been performed

by MSU-CVM's Internal Medicine Department but yielded no definitive diagnosis for the idiopathic effusions.

The patient was adopted at the age of seven by her current family and had an unknown medical history prior to adoption. Aside from seasonal allergies that were well controlled with Apoquel, she was apparently healthy until May 2, 2017. The dog originally presented to Animal Emergency and Referral Center (AERC) of Flowood on May 2, 2017, after her owners noticed an acute change in her behavior, with progressive lethargy and rapid breathing patterns. The veterinarians at AERC diagnosed her with bicavitary effusion (pericardial and peritoneal) by ultrasound and referred her to MSU-CVM for additional diagnostics.

On presentation to MSU-CVM Emergency Services on May 2, 2017, the patient had an extensive problem list previously diagnosed by AERC which included bicavitary effusion that had progressed to tricavitary effusion (pericardial, peritoneal, and pleural), progressive lethargy, hypothermia, and diarrhea. The MSU-CVM Internal Medicine department completed an extensive medical workup for the effusion. A CBC, serum chemistry, coagulation profile, and urinalysis were initially performed. CBC revealed a mildly elevated MCV of 79.7 fL (63.0 - 77.0), and a leukopenia characterized by a moderate lymphopenia of 810/ul (1200-6500). Serum chemistry revealed a mild hypoproteinemia of 4.8 g/dl (5.5-8.0) and moderate hypocholesterolemia of 116 mg/dl (140-360). Urinalysis and coagulation profile were both unremarkable. An ultrasound guided thoracocentesis and pericardiocentesis were then performed, and the effusions were submitted for cytology. Cytology of the pericardial effusion revealed hemorrhagic effusion, but no etiologic agents were found. Cytology of the peritoneal effusion revealed a proteinaceous transudate, but no etiologic agents were found. Advanced imaging was recommended. Thoracic radiographs revealed enlargement of the cardiac silhouette

with rounding of the left and right atrioventricular regions, which were consistent with the previously diagnosed pericardial effusion. Abdominal radiographs supported the previously diagnosed peritoneal effusion as well as spondylosis deformans of the L4-L5 vertebral region. Computed tomography (CT), abdominal ultrasound, and echocardiogram were all performed and revealed no masses or causative agent for the effusion.

Due to the patient's history of diarrhea, an upper gastrointestinal endoscopy was performed with biopsies. Histopathology was supportive of inflammatory bowel disease. She was started on metronidazole (125mg), and the diarrhea resolved. She was discharged on May 6, 2017. The patient would be admitted to MSU-CVM four additional times before her surgical consult on September 6, 2017, for respiratory distress and therapeutic thoracocenteses.

On September 6, 2017, she presented to MSU-CVM Surgery Department for chronic tricavitary effusion and cardiac tamponade that was diagnosed prior to admission by AERC. Pericardoiocentesis and thoracocentesis were performed to stabilize the patient prior to transport. Her owners noted that the pericardial effusion had progressed requiring emergency thoracocentesis every 4 weeks as compared to every 7 weeks as previously required. On examination, she was quiet, but alert and responsive. She was moderately tachycardic and tachypneic (HR: 178 beats per minute, RR: 60 breaths per minute). Mucous membranes were pale pink, with a capillary refill time of less than two seconds. Cardiac auscultation revealed muffled heart sounds bilaterally, but thoracic auscultation was unremarkable. A distended abdomen was noted on physical exam. Abdominal FAST scan revealed moderate to severe peritoneal effusion. Thoracic FAST scan revealed mild to moderate pleural and pericardial effusion.

A subtotal pericardectomy via a right lateral thoracotomy with implantation of a chest tube was performed on September 7, 2017. Upon entry into the thoracic cavity, the pericardium and pleural lining were diffusely covered by thickened and nodular cellular infiltrates. A subtotal pericardectomy was performed followed by the placement of a chest tube. The pericardium was submitted post-operatively for histopathology. Post-operative radiographs revealed appropriate placement of the chest tube, and recovery was uneventful. Over the next four days she was maintained on a Fentanyl CRI at 3 mcg/kg/hr in addition to intravenous fluid therapy of LRS at 30 ml/hr (1.5 x maintenance). A considerable amount of fluid was drained from her chest tube every 6 hours post-operatively and she was housed in the oxygen cage. Fortunately, her vital parameters began to normalize post-operatively as the pleural effusion was routinely managed by aspiration of the chest tube. The patient was transitioned from a fentanyl CRI to Tylenol #4 (15 mg) and Rimadyl (12.5 mg) on September 10, 2017.

On September 11, 2017 histopathology results returned and confirmed a diagnosis of mesothelioma. It was discussed with the owners that although some of the malignant tissue was removed during surgery, mesothelioma is a highly malignant and progressive disease. A consultation with the oncologist confirmed that the malignant tissue left behind in the thoracic cavity would continue to produce effusions causing breathing difficulty. Chemotherapy was the only additional treatment option that could be offered at that time. Weighing the risk of future, necessary thoracocentesis and possible intracavitary chemotherapy, a more permanent chest tube was placed. A PleuralPort[1] was implanted using blunt dissection to the level of the epaxial muscles and fascia on September 12, 2017. The patient recovered from both anesthesia and surgery uneventfully and was maintained on the same oral pain medications. She was

[1] *PleuralPort:* Norfolk Vet Products. 7350 N. Ridgeway Skokie, Illinois 60076.

discharged from MSU-CVM on September 13, 2017 with instructions to return for chemotherapy.

On September 15, 2017, she returned prematurely on emergency for labored breathing and lethargy. T-FAST was performed and revealed moderate pleural effusion. Due to her previous PleuralPort placement, quick access could be obtained into the thoracic cavity where 110ml of fluid was aspirated from the chest cavity. Her respiratory rate normalized, and she was discharged with instructions for her owners to continue to monitor her behavior and breathing patterns.

On September 18, 2017, she presented to MSU-CVM for her first round of chemotherapy. A CBC and serum chemistry were obtained and revealed her cell level was adequate to receive chemotherapy. She received 7mls of carboplatin (10mg/kg) intravenously. The patient was discharged with instructions to have routine bloodwork completed at her primary veterinarian to ensure her cell levels remain adequate as not to render her more susceptible to infection.

Over the next few months, her owners reported that she was doing well at home and only had to undergo emergency thoracocenteses a few times. In January, she began developing more pleural effusion and it was decided to switch chemotherapy agents. She was started on intravenous mitoxantrone on January 29, 2018. Unfortunately, she soon became refractory to mitoxantrone. Intracavitary carboplatin was administered on March 16, 2018 through her PleuralPort. The pleural effusion began to accumulate over the next month. A last effort was made, and she was scheduled to receive intracavitary mitoxantrone. She received 5mg/m2 of mitoxantrone on April 10, 2018. Unfortunately, she began to require thoracocenteses every other day. On May 19, 2018, she began to decompensate. Her quality of life could no longer be

maintained, and her owners elected humane euthanasia, 382 days after clinical signs were first noticed.

Discussion

Mesothelioma is a rare neoplasia of dogs that targets the mesothelial cells of the body. Mesothelial cells arise from the mesoderm and line serosal cavities of the body. Normally, mesothelial cells exist as a monolayer of squamous epithelial cells. The cells are identified based on their presence of microvilli and phagocytic potential on histopathology (2). Mesothelial cells exist normally within the body; therefore, it is clinically important to identify the contributing factors that can influence malignancy. It is speculated that any disease process that causes inflammation of the mesothelium has the potential to initiate pathology. Irritation and inflammation of the mesothelium results in excessive fluid production by the mesothelial cells. The excessive fluid production can promote tumor development, exfoliation and spread of disease (2).

It is speculated that as in human medicine, asbestos exposure by owners enhances the risk that companion animals may acquire malignant mesotheliomas (2). The asbestos fibers are inhaled and then migrate to the serosal surfaces where they cause tissue irritation and pathology. Asbestos fibers can specifically target the mesothelial cells where they interfere with cell function and mitosis. Mesothelial cells that have been exposed to asbestos are thought to then release inflammatory cytokines and protein kinases that result in disease (7). In veterinary medicine, the relationship between asbestos exposure and mesothelioma has not been confirmed. A study performed on dogs that were previously diagnosed with mesothelioma evaluated necropsy findings and determined that dogs had a significantly lower amount of asbestos fibers

present in their lungs as compared to human medicine (6,8). At this time, further research is warranted to delve into the pathophysiology of mesothelioma in companion animals.

Unfortunately, diagnosis of malignant mesotheliomas is notoriously difficult and typically occurs late in the disease process in canine species. A presumptive diagnosis may be made based on clinical signs, history of asbestos exposure by owners, or progressive effusions. Advanced imaging is recommended as an initial first step as it can offer current staging of disease. Thoracic radiographs, ultrasound, and computed tomography may be suggestive of disease and are indicated in presumptive cases of mesothelioma or idiopathic tricavitary effusion. Thoracic radiographs are indicated as they can highlight pleural effusion, pleural thickening, and even masses within the thoracic cavity. Thoracic ultrasound can offer visualization of effusions or thickening of the pleura (7). Additionally, any gross tumor or nodules can typically be visualized on ultrasound. Although CT is more expensive and cannot be performed in all patients, it may offer a more detailed visualization into the invasiveness of the tumor (7).

After initial staging is complete, it is recommended to proceed with diagnostics until a definitive diagnosis is made. To diagnose mesothelioma, histopathology with immunohistochemistry is recommended. Cytologic evaluation of effusions have historically been used to presumptively diagnose mesothelioma when the patient was not a surgical candidate and a biopsy could be obtained. Cytologic examination of effusions and malignant tissues may support neoplasia, particularly a sarcoma or carcinoma, but a definitive diagnosis cannot typically be made on gross examination alone (9,4).

There are numerous histologic categories of mesothelioma. They are typically broken into three broad categories including epithelial, sarcomatoid, and biphasic (4). Considering the broad nature of mesotheliomas histologically, it can be difficult to differentiate mesothelioma

from other neoplasms grossly. Immunohistochemical evidence with strong expression of cytokeratin and vimentin is often used as a cellular marker to diagnose mesothelioma by clinical pathologists (1,3,9). Ultimately, obtaining a definitive diagnosis of malignant mesothelioma requires histopathology. However, mesotheliomas should always be considered in animals presenting for chronic disease, or with a history of fluid accumulation into body cavities (4).

Unfortunately, there is no known cure for mesothelioma nor has a successful treatment option been identified. Treatment ultimately results in palliative care and efforts to control the effusions (7). If the patient is stable, multimodal therapies are recommended but do not significantly increase survival times (7). Mesothelioma in companion animals is typically associated with a poor prognosis with reported median survival times of 4-12 months in both treated and untreated animals (4). With the diffuse nature of the disease and diagnosis typically made late in the disease, surgical resection acts as a treatment method to debulk malignant tissue, slow down effusions, and reduce patient pain (2,7).

Though it is an option, radiation therapy is typically unsuccessful. The high radiation doses that would be effective at controlling disease would indefinitely cause adverse effects including pneumonitis, and myocarditis (10). A recent study completed in human medicine noted that radiation therapy either pre or post-surgical resection can be useful in controlling pain and limit tumor spreading (7,11). Unfortunately, mesotheliomas are typically associated with vital organs including the lungs and heart making a safe radiation dose difficult to determine (7,10). The usefulness of radiation therapy in the canine species warrants further research.

Chemotherapy tends to be the treatment of choice for mesothelioma (11). Almost every chemotherapeutic agent has been utilized in treating mesothelioma, all with limited success. There is not a chemotherapy drug of choice when treating this disease (11). The goal of

chemotherapy is to slow down the effusions and offer the animal a better quality of life. The most common chemical drugs used in dogs are platinum products, doxorubicin hydrochloride, and mitoxantrone (7,9). These chemotherapy agents have been used both intravenously and intracavitary with no significant differences in prolonging survival times. New research has indicated that piroxicam, an NSAID and COX-inhibitor commonly used in treatment for other carcinomas could be a therapeutic option to potentiate other chemotherapeutic agents when treating mesotheliomas (12). It's efficacy in canine mesothelioma is currently unknown.

Conclusion

This case report describes the diagnostic approaches and treatment options of a canine patient diagnosed with mesothelioma. There is a limited amount of literature regarding successful treatment modalities for canine mesothelioma. All treatment regimens have been utilized with limited success in these patients. Although additional research is warranted at this time, a multimodal therapeutic approach is indicated. Treatment should be focused on minimizing effusions and maximizing quality of life. If the patient is considered stable, surgical resection with chemotherapy may maximize quality of life as noted in this case.

References:

1. Churg, Andrew. The separation of benign and malignant mesothelial proliferations. Archives of Pathology laboratory medicine. 2012;136:1217-1226.
2. Dubielzig, R., MacEwen, E. "Miscellaneous Tumors." Clinical Veterinary Oncology. 1989;425-427
3. Regetti, F. Brisson, B., et al. Invasive epithelial mesothelioma in a dog. *Veterinary pathology*. 2005;42:77-81.
4. Head KW, Else RW, Dubielzig RR: 2002, Tumors of serosal surfaces. *In:* Tumors in domestic animals, ed. Meuten DJ, 4th ed., pp. 477-478. Iowa State Press, Ames, IA.
5. Schoning P, Layton CE, Fortney WD, et al.: 1992, Sclerosing peritoneal mesothelioma in a dog evaluated by electron microscopy and immunoperoxidase techniques. J Vet Diagn Invest 4: 217-220.
6. Harbison ML, Godleski JJ. Malignant mesothelioma in urban dogs. *Veterinary Pathology* 1983;20:531-540.
7. Bibby AC, Tsim S, Kanellakis N, Ball H, Talbot DC, Blyth KG, et al. Malignant pleural mesothelioma: an update on investigation, diagnosis and treatment. Eur Respir Rev (2016) 25(142):472-486. Doi:10.1183/16000617.0063-2016
8. Glickman LT, Domanski LM, Maquire TG, et al. Mesothelioma in pet dogs associated with exposure of their owners to asbestos. *Environ Res* 1983;32:305-313.
9. Gumber S, Fowlkes N, Cho DY. Disseminated sclerosing peritoneal mesothelioma in a dog. *Journal of Veterinary Diagnostic Investigation.* 2011;23:1046-1050.

10. Bononi, A., Napolitano, A., Pass, H., et al. Latest developments in our understanding of the pathogenesis of mesothelioma and the design of targeted therapies. *Expert Rev Respir Med. 2015 Oct; 9(5): 633–654.*
11. Rossini, M., Rizzo, P., Bononi, I., et al. New perspectives on diagnosis and therapy of malignant pleural mesothelioma. *Frontiers in Oncology*. 2018;8:91. Doi:10.3389/fonc.2018.00091.
12. Spugnini E., Crispi, S., et al. Piroxicam and intracavitary platinum-based chemotherapy for the treatment of advanced mesothelioma in pets: preliminary observations. *J Exp Clin Cancer Res.* 2008; 27(1):6.