Cardiac Rhabdomyosarcoma in the Canine

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Introduction

Rhabdomyosarcoma is an uncommon form of neoplasia that may occur in humans and domestic animals. It arises from striated skeletal muscle, progenitor cells of striated muscle, or primitive mesenchymal cells.[1,4] Primary tumors have been reported in various locations, including the bladder, heart, larynx, tongue, and skin of dogs.[2,3,4] Cardiac rhabdomyosarcomas are relatively common in humans but considered very rare in domestic animals, with only a few reports in dogs, pigs, a cat, a calf, a steer and a sheep.[1,7,9] Due to the low number of cases, there are varying opinions on tumor behavior. Some sources report that these tumors are usually aggressive and may have a high rate of metastasis, most commonly to the lungs or abdominal organs.[2,3]

History and Presentation

The case presented is a nine year old neutered male Doberman pinscher named Scout who was referred to the internal medicine service at the Mississippi State University College of Veterinary Medicine on August 15, 2016. His presenting complaint was lethargy and an intermittently productive cough of approximately two weeks. His owner had also noticed tachycardia and a gallop rhythm. Scout had seen his veterinarian previously, and thoracic radiographs demonstrated a diffuse nodular pattern in the lungs and a possible mass in the right caudal lung lobe. Abdominal radiographs showed a previously diagnosed cystolith with no other abnormalities. He was treated with furosemide and nebulized with arformoterol and budesonide. His clinical signs slightly improved, and he was referred to MSU-CVM for further diagnostics.

Upon presentation, Scout was responsive but depressed. He had a normal temperature of 101.3˚ F, an elevated pulse of 120 beats per minute, and an increased respiratory rate of 64

breaths per minute with increased respiratory effort. A grade IV/VI left systolic heart murmur was ausculted along with diffusely increased lung sounds and intermittent crackles. A complete blood count was performed which revealed moderate anemia (PCV 26%) and an inflammatory leukogram with marked neutrophilia, moderate monocytopenia, and mild eosinophilia. A 6-lead echocardiogram showed sinus tachycardia, variable QRS amplitudes, notched QRS complexes, and absent P waves. His SpO_2 was measured at 96%. Thoracic radiographs were repeated and showed a diffuse nodular pattern that appeared more severe than the previous images. Multiple lung nodules were visible on thoracic ultrasound. A nodule in the right caudal lung lobe was aspirated and submitted for cytology.

Pathophysiology

Rhabdomyosarcomas develop from skeletal muscle, myogenic progenitor cells, or myoblast cells. They may also arise from mesenchymal stem cells that are capable of myogenic differentiation, pluripotent stem cells of urogenital ridge remnants, or mesenchymal progenitor cells in Müllerian and Wolffian ducts. This may explain why they are often found in areas with no skeletal muscle, such as the bladder and uterus.[1,5]

Rhabdomyosarcomas can be classified as pleomorphic, embryonal, or alveolar by histopathology. These classifications were created based on tumor features and behavior in humans, but appear to be similar in dogs (See Table 1).[1] Embryonal and alveolar rhabdomyosarcomas are usually diagnosed in juvenile patients and do not involve striated muscle. Pleomorphic tumors likely arise from skeletal or cardiac muscle and are more common in adult patients.[1,5]

Table 1. Classification of Rhabdomyosarcomas, With Variants and Relevant Clinical Aspects.

Subclass	Variant	Distinguishing Histologic Features	Age	Locations
Embryonal		Cells exhibit different stages of development from myoblast to myotubular, in a mucinous stroma	Juvenile/adult	Face, skull, masticatory muscle, oropharynx, trachea, axilla, scapula, perirenal, tongue, flank, leg, mammary gland, hard palate
	Myotubular	Myotube forms predominate		
	Rhabdomyoblastic	Large myoblast cells with abundant cytoplasm		
	Spindle cell	Streams of plump spindle cells		Skull
Botryoid		Characteristic submucosal location and gross appearance; mixed round and myotubular cells in mucinous stroma	Juvenile	Urinary bladder, uterus
Alveolar			Juvenile	Hip, maxilla, greater omentum, uterus
	Classic	Fibrous bands divide small round cells into clusters, loose aggregates		
	Solid	Closely packed cells, ± thin fibrous septa		
Pleomorphic		Haphazardly arranged plump spindle cells with marked anisocytosis and anisokaryosis and bizarre mitotic figures	Adult	Skeletal muscle

The 3 major subclasses of rhabdomyosarcoma (RMS) are embryonal, alveolar, and pleomorphic. Botryoid RMS is often considered a separate subclass but is technically a subset of embryonal RMS. In addition, embryonal RMS has 3 variants that are differentiated by the predominant cell morphology. Myotubular embryonal RMS is dominated by multinucleated and elongated tubular cells. Rhabdomyoblastic embryonal RMS is dominated by large round cells with abundant cytoplasm. Spindle cell embryonal RMS is dominated by fusiform, elongated cells arranged in streams. Alveolar RMS is divided into the classic alveolar pattern with distinct fibrous septa lined by neoplastic round cells with a central open space. The solid variant of alveolar RMS lacks the clear space and often lacks obvious fibrous septa. The pleomorphic RMS most often occurs in adult animals and is composed of haphazard spindle cells with large myoblast cells often containing large pleomorphic nuclei and bizarre mitotic figures. Adapted from Parham.[109]

From Caserto, B G. A Comparative Review of Canine and Human Rhabdomyosarcoma With Emphasis on Classification and Pathogenesis

In humans, a series of genetic mutations is thought to be involved in tumor formation. A large number of genes have been implicated as possible contributors via uncontrolled cell growth, failure of tumor suppressor genes, and interruption in development of undifferentiated myoblast cells. Many other genetic mutations have been associated with tumor migration and metastasis. Because very few cases of canine rhabdomyosarcoma have been studied, there is not enough information to determine which mutations may be involved in dogs.[1]

Diagnostic Approach

Diagnostic imaging is an important tool to detect primary and metastatic tumors. Soft tissue masses in the heart, lungs, bladder, or other abdominal organs may be visible on echocardiography, radiographs, ultrasound, CT, or MRI. Imaging can also be used to monitor tumor progression or guide other diagnostic techniques, such as aspirates and biopsies.[2]

Immunohistochemistry is the most common method for obtaining a diagnosis of rhabdomyosarcoma. The neoplastic cells are stained for muscle-specific markers, including vimentin, desmin, actin, myosin, and myoglobin. These proteins are found in normal cells as well as tumor cells, so it is important to distinguish neoplastic populations before staining. Skeletal myocytes express certain proteins at different points in development, and their presence can be used to identify muscle cells and determine their relative degree of differentiation. Although some of these markers are not specific to skeletal muscle, they are used in conjunction with each other to aid in diagnosis (See Table 2).[1]

Vimentin and desmin are present in myoblast cells of all types. Muscle actin is found in skeletal, cardiac, and smooth muscle as well as myofibroblasts, myointimal cells, and reactive mesothelial cells. Many isoforms of actin exist which can be differentiated by immunohistochemical staining. Smooth muscle actin is only found in smooth muscle cells, while sarcomeric actin and myosin are components of the sarcomeres that are responsible for skeletal muscle contraction. Myoglobin is an oxygen-carrying protein present in striated muscle but absent in smooth muscle. Neoplastic cells that are positive for at least one muscle-specific marker and negative for smooth muscle markers are indicative of rhabdomyosarcoma.[1,3,4,7,9] Myogenin and MyoD1 are nuclear transcription factors that have been used in human medicine to identify undifferentiated rhabdomyosarcomas and distinguish between alveolar and embryonic subtypes. More studies are needed to determine if there is a correlation in dogs.[1,3,7]

Table 2. Common Immunohistochemistry Antibodies in Veterinary Medicine.

Canine, All Ages	Vimentin	Desmin	Ms Actin	Src Actin	Myoglobin	Myogenin	MyoD1	Smooth Muscle Actin
Alveolar	5/5	6/6	1/1	2/2	1/2	1/1	1/1	0/3
Embryonal	10/10	15/15	5/5	7/7	9/10	1/1	2/2	1/5
Botryoid	9/9	13/13	3/3	5/5	5/8	2/2	2/2	0/4
Pleomorphic	2/2	2/2	1/1	1/1	1/1	NA	NA	0/2
RMS NOS	5/5	4/5	2/2	NA	2/2	NA	1/1	0/2

Numbers indicate the number of cases with positive staining (numerator) over the number of cases stained (denominator). Vimentin, desmin, muscle actin (ms actin), and sarcomeric actin (src actin) are consistently positive in canine rhabdomyosarcoma (RMS). Myoglobin staining is inconsistent but positive in many cases of embryonal and botryoid RMS and is rarely used in alveolar RMS. Positive staining with desmin, ms actin, src actin, or myoglobin plus negative smooth muscle actin staining is diagnostic for rhabdomyosarcoma. Rarely is canine RMS positive for smooth muscle actin, making myogenin and MyoD1 necessary for diagnosis. NA, not applicable; NOS, not otherwise specified.[31,109]

From Caserto, B G. A Comparative Review of Canine and Human Rhabdomyosarcoma With Emphasis on Classification and Pathogenesis

Ultrastructural examination can also be useful for diagnosis. Sarcomeres of skeletal and cardiac muscle are arranged as cross striations within the myocytes. Although these are often difficult to observe with light microscopy, they are visible under a transmission electron microscope.[1,6] Cross striations are frequently present in rhabdomyosarcomas, but poorly differentiated tumors may have few or none at all.[3,4] Attempts have been made in human medicine to use ultrastructural features to classify rhabdomyosarcoma types, but it is unclear if this is possible in dogs.[1]

Treatment

Treatment of a rhabdomyosarcoma requires elimination of the primary tumor by aggressive surgical resection. Chemotherapy and radiation may also be beneficial in most cases, as complete surgical resection is often not possible and metastasis is very common. However, there have not been extensive studies on the effects of chemotherapy and radiation on rhabdomyosarcomas.[2] In one study, a dog diagnosed with a perianal rhabdomyosarcoma and no detectable metastasis received complete surgical resection and post-operative radiation therapy. Chemotherapy with doxorubicin, cyclophosphamide, and vincristine was initiated, but it was discontinued after one cycle due to toxic adverse effects. The dog showed no local tumor

recurrence and no evidence of metastasis until 252 days after initial presentation. The iliac lymph nodes were enlarged, indicating possible metastasis, but no other abnormalities were found on bloodwork or imaging. The dog died suddenly and necropsy was declined.[8]

Prognosis

Prognosis is usually guarded to grave as many rhabdomyosarcomas are in locations such as the heart and bladder where removal is not possible. It may be more favorable if the tumor can be completely resected, but metastasis is common even after successful surgical intervention. Radiation and chemotherapy may prolong survival and improve prognosis.[2,8]

Case Outcome

Approximately one hour after aspiration of his lung nodule, Scout became tachycardic and tachypneic. His mucous membranes were very pale. A FAST scan of the thorax showed free fluid in the area of the right caudal lung lobe. His packed cell volume decreased from 26% to 24%. He received 2 liters of Normasol intravenously, and his PCV decreased to 14%. Severe hypoxemia (P_aO_2 60 mmHg) was detected on an arterial blood gas analysis. Scout's owners elected to humanely euthanize and have a necropsy performed.

Cytology of the fine needle lung aspirate revealed modest suppurative inflammation with mildly increased degenerate neutrophils and fewer macrophages, small lymphocytes, and eosinophils. A few atypical cells and two mitotic figures were also noted. A diagnosis could not be obtained from the aspirate and histopathology would be required for a definitive diagnosis.

On necropsy, a mass measuring 0.5 cm in diameter and 6 cm in length was discovered attached to the right atrial wall. The mass protruded through the tricuspid valve and right

ventricle into the pulmonary artery. The heart and liver were enlarged due to right heart failure and passive congestion. The lungs contained widely disseminated, firm 1 to 3 mm nodules. The cardiac and lung masses were composed of round to elongate cells with up to 4 or more mitotic figures per high power field. Marked anisocytosis and anisokaryosis were present. The tumors were initially presumed to be hemangiosarcoma until rare cross striations were noted. The cells tested positive for actin and myosin and negative for factor VIII on immunohistochemistry. Factor VIII-related antigen is an endothelial cell marker that is found in normal cells as well as endothelial cell neoplasia, including hemangiosarcomas.[10] This indicated that the tumor originated from striated muscle, and it was diagnosed as a cardiac rhabdomyosarcoma with lung metastasis.

Conclusion

Rhabdomyosarcoma is a rare neoplastic disease in humans and domestic animals. It develops from striated muscle and its progenitor cells. Primary tumors are most commonly found in the bladder, heart, tongue and larynx, and metastases are common in the lungs and abdominal organs. Histopathology is required for a definitive diagnosis. Cells must be positive for at least one muscle-specific marker and negative for smooth-muscle markers by immunohistochemical staining to be diagnosed as a rhabdomyosarcoma. Treatment is by surgical resection of the tumor with radiation or chemotherapy to eliminate residual or metastatic cells. Prognosis is usually guarded to grave.

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