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# CANINE RHABDOMYOSARCOMA - LITERATURE REVIEW

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***Abstract***

*Rhabdomyosarcoma (RMS) is a rare malignant neoplasm arising from skeletal muscle, occurring predominately in young individuals. In dogs, is most commonly located in the urogenital tract, followed by head, neck, face, limbs and skin, mammary gland included. This article reviews the microscopic patterns, diagnostic and prognostic aspects of RMS in dogs. In veterinary medicine, the classification of RMS into subtypes is based only on histologic characteristics, with no relevance in regard of prognosis. The prognosis depends on the severity and extent of invasiveness, as well as the presence of metastases. Macroscopic aspects are variable, as well as cellular morphology and histological patterns. Immunohistochemistry is used to confirm the diagnosis, RMS being positive for vimentin, desmin, muscle and sarcomeric actin, myoglobin, myogenin and negative for cytokeratin and α-smooth muscle actin. Further investigations are needed to better understand the biological behaviour and outcomes of this tumour.*

***Key words****: rhabdomyosarcoma, canine, immunohistochemistry, prognosis, histopathology.*

## INTRODUCTION

Rhabdomyosarcoma (RMS) is a rare malignant neoplasm arising from skeletal muscle, occurring predominately in young individuals. Due to its rarity and highly variable macroscopic and microscopic patterns, it is considered a diagnostic challenge in both human and veterinary medicine (Caserto, 2013).

Human RMS is diagnosed by various techniques, such as histopathology, immune-histochemistry (IHC), electron microscopy and molecular techniques (Watchtel et al., 2006; Caserto, 2013), the first two being the most commonly used in veterinary medicine. Although in humans the prognosis is established by different histologic patterns of RMS, the prognostic significance of RMS subtypes in dogs still remains undetermined (Tuohy et al., 2021). In veterinary medicine, rhabdomyosarcomas are categorised as embryonal, botryoid, alveolar and pleomorphic. The purpose of this paper it to review the cytological and histological aspects of rhabdomyosarcoma in dogs, with emphasis on current diagnostic and prognostic aspects of this tumour. Being rarely diagnosed in veterinary medicine and having a vast morphology, we present its main characteristics, for a better understanding and approach for both veterinary clinicians and pathologists.

To review the literature describing RMAs in canine patients, we collected the necessary material from the current database, using the following key-words: rhabdomyosarcoma, canine, case report and literature review, immunohistochemistry, prognosis. Selected articles were chosen based on addressing the most important diagnostic and prognostic features of this tumour, referring primarily to dogs and often with comparison to human medicine for a better understanding of the process. The provided information was compared with available data in the reference books of veterinary pathology and oncology. Often, comparison with human rhabdomyo-sarcoma is provided, for a better understanding of the subjects. The common points and important differences which have resulted from this analysis are presented in the following sections.

## BIOLOGY, AND CURRENT DIAGNOSTIC AND PROGNOSTIC ASPECTS OF RMS

### Origins of RMS

Rhabdomyosarcoma is a primitive malignant soft tissue sarcoma of skeletal muscle

phenotype. Its etiology and risk factors remain largely unknown in both human and veterinary medicine; it originates from a primitive mesenchymal cell (Leiner, 2020).

Currently, very few aspects related to the origin of RMS are known in domestic animals. In human medicine literature, there are different hypotheses regarding the histogenesis of rhabdomyomas/rhabdomyosarcomas in all species.

Some authors suggest it may develop from pluripotent stem cells from the primitive urogenital ridge remnants, suggestive of botryoid rhabdomyosarcoma.

Another possibility would be the development from the mesenchymal progenitor cells invading the Müllerian and Wolffian ducts. This process is described as being either local or through the circulation coming from the bone marrow. Mesenchymal stem cells capable of myogenic differentiation identified in the bone marrow and in other locations could explain why rhabdomyosarcomas can be found in tissues which don't have skeletal muscle (Hettmer, 2010).

**Clinical aspects of RMS**

Canine RMS is reported to appear mainly in young dogs, of 2 years or younger. Taking into account the age of all dogs diagnosed with rhabdomyosarcoma from the total cases reported so far, over 80% were under 10 years old of age (Caserto, 2013; Murakami et al., 2010). Most affected breeds reported in the literature are Saint Bernards and Retrievers (Gerber et al., 2009; Bae et al., 2007). Different subtypes of RMS are reported in adult or old dogs (Brockus et al., 2004, McDonald et al., 2017, Avallone et al., 2010; Dagher et al., 2017). This may be an indicator that age predilection in dogs is not as accurate as in people, where RMS occurs in children younger than 15 years (Hettmer, S. and Wagers, A.J., 2010). Caserto mentions in his review from 2013 that in dogs, the most common location for RMS is in the urogenital tract (49%). Following this type of location are the head, neck and face (37%), with limbs (8%) and skin, mammary gland included (3%) being the less common.

Cases of orbital RMS have been described recently (McDonald et al., 2017; Scott et al., 2016), but remain rarely reported in dogs. Da Roza et al. (2010) identified in an 11-month-old male boxer dog an uncommon spindle cell variant of RMS that affected the frontal region of the skull.

A primary meningeal spindle cell variant of rhabdomyosarcoma has been described for the first time within the T9 - T11 spinal cord of a 7-week-old male black Labrador retriever, who also presented many cutaneous neurofibromas (Hoon-Hanks et al., 2018). This case marks a novel differential diagnosis for spinal tumours, especially in young dogs.

Mammary RMA are rare in dogs. Dagher et al. (2017) described for the first time a mammary localisation of this type of tumour with pulmonary metastasis in a 10-year-old female mixed-breed dog. The diagnosis was established by histology, IHC and electron microscopy. Unique for both the type of tumour and localisation, the authors describe areas where large lobules and trabeculae of cartilage and immature bone were present among the neoplastic cells.

Laryngeal RMS has been described only in dogs and in the vast majority of the cases, in those over 2 years of age (Cooper, 2017; Yamate, 2011).

On gross examination, RMS is usually described as solitary mass. Gombert et al. (2020) reported in a five-year-old male Labrador Retriever two concurrent embryonal rhabdomyosarcomas, located in the oesophageal and perilaryngeal regions. The first oesophageal RMS case was reported in a 15-month-old great Dane dog and characterised as embryonal type RMS (Devriendt et al., 2017).

Cutaneous RMS are rarely reported. One of the main causes for the small number of cases could be misdiagnosis as poorly differentiated soft tissue sarcoma or anaplastic neoplasias in absence of immunohistochemical investigations (Caserto, 2013; Avallone et al., 2010).

A first report of a cutaneous multifocal form of alveolar type RMS in veterinary medicine has been described in an 8.5-month-old Labrador Retriever. The animal presented a cutaneous mass in the right maxillofacial region and swelling of the right maxillary gingiva. Based on cell morphology, this case shows that alveolar RMS could be included in the

differential diagnosis of cutaneous round cell tumours in dogs (Otrocka-Domagala et al., 2015).

Cardiac RMS is reported in the literature among malignant cardiac muscle tumors. The few cases reported up to present were in dogs of 7-year-old. Right atrium and right ventricle appear to be the most frequently involved (Treggiari et al., 2017; Perez et al., 1998). Akkoç et al. (2006) reported the first case of cardiac metastasized rhabdomyosarcoma in a 7-year-old great Dane, with multiple metastases in the heart, lungs, diaphragm, liver, kidney and omentum, thus confirming that this type of tumour with this localization has the potential to metastasize.

Taking into account the complexity of the diagnosis and the need to make a differential diagnosis with mesenchymal tumours with round and fusiform cells, in the recent literature a third situation appears, when myoid differentiation may morphologically resemble rhabdomyosarcoma. Recently, a case of unusual myoid differentiation has been reported in a 13-year-old crossbreed female dog diagnosed with benign mixed mammary tumour (Brunetti et al., 2021). In this case, the authors describe the mesenchymal components identified in the tumour (smooth and striated muscle, cartilage and bone) as well-differentiated, with no signs of cellular atypia, therefore of metaplastic origin. On immunohistochemistry, the mesenchymal cells were positive for all the markers of the IHC panel for rhabdomyosarcoma. The cell morphology and the benign biological behaviour ruled out a possible malignant neoplasia of striated or smooth muscle origin. This case is similar to the of Dagher et al. (2017), where the mammary tumour had areas of cartilaginous and osseous metaplasia, but the cell atypias, IHC results and presence of pulmonary metastasis confirmed the presence of a RMS.

**Cytology of RMS**

Cytological examination proved not reliable in diagnosing RMS in dogs, because of the vast appearance of neoplastic cells, from mature myoblasts and rhabdomyoblasts to undifferentiated round cells (Tuohy et al., 2021). Cytologically, smears from both rhabdomyomas and rhabdomyosarcomas consist of individualized, round to polygonal cells with low nuclear-to-cytoplasmic (N:C) ratio. Neoplastic cells have large amount of eosinophilic to sometimes basophilic granular cytoplasm. Cells with a high N:C ratio and indistinct cytoplasm can also typically be encountered.

In order to distinguish between a rhabdomyoma and a rhabdomyosarcoma on cytology, sufficient criterias of malignancy should be present, most of the time a correct diagnosis being difficult. RMS in most cases display increased pleomorphism, bizarre mitotic figures and marked anisocytosis and anisokaryosis (Valenciano, 2020).

Embryonal form of RMS consists of three variants, distinguished also in cytology based on a predominant cell morphology: the myotubular variant (characterised by the presence of multinucleated elongated tubular cells), the rhabdomyoblastic variant (characterised by presence of large round cells containing abundant cytoplasm) and the spindle cell variant (characterised by fusiform, elongated cells placed in streams). It is typical for embryonal RMS to see all three variants together, making the cytological diagnosis of thsese tumours very difficult. Very typical but uncommon, the multinucleated cells have nuclei arranged in a row (*straplike cells*). Rarely, striations could be observed within the cytoplasm. These multinucleated cells result from the fusion of rhabdomyoblasts. The rhabdomyoblasts typically appear as round cells and display high to moderate N:C ratios (Raskin et al., 2023).

The alveolar RMS is cytologically characterized by highly cellular smears. Numerous atypical round cells are identified. These cells are similar to lymphoid cells. Mitotc figures are also frequent (Raskin et al., 2023).

In a case report of an alveolar RMS in a 7-month-old Labrador Retriever, Snyder et al. (2011) describe the cytological appearance of this tumour. The smears contained numerous round/oval cells, had variably distinct cell margins and basophilic cytoplasm. The anisocytosis and anisokaryosis were reported as moderate. Interestingly, on the backround there were many tiny basophilic cytoplasmic fragments.

Pleomorphic RMS exhibits plump splindle cells haphazardly arranged. The tumoral cells display marked anisocytosis and anisokaryosis. The mitotic figures are described as bizarre (Raskin et al., 2023).

**Histology and patterns of RMS**

In veterinary medicine, four variants of rhabdomyosarcoma are described - embryonal, botryoid, alveolar and pleomorphic.

According to data collected from case reports in veterinary medicine, botryoid RMS is the most diagnosed subtype, followed by embryonal, alveolar and least frequently, the pleomorphic subtype (Gombert et al., 2020).

**Embryonal RMS** includes three variants, described previously on cytological patterns: myotubular, rhabdomyoblastic and spindyloid. Histology of myotubular variant consists of presence of characteristic multinucleated "strap cells", which form myutubes (Caserto, 2013). The myotubes frequently contain cross-striations which can only be identified using special staining (phosphotungstic acid hematoxylin). On this staining, the striations appear dark blue or purple, while the myofibers appear as paler blue or purple.

The rhabdomyoblastic variant consist on histology of frequent round to polygonal cells with abundant eosinophilic cytoplasm. Striations are rarely positive for phosphotungstic acid hematoxylin staining, being a main feature in differentiating the two variants of embryonal RMS (Parham, 2001). In human medicine, this variant is difficult to diagnose and commonly needs molecular biology which is unavailable for canine rhabdomyosarcoma. No prognostic significance of these two variants has been demonstrated in either human or canine RMS (Tobar et al., 2000).

The spindle-cell variant of RMS is rare and a relatively new category. Histological aspect consists of thin spindyloid myoblast cells, usually with formation of bundles and myxoid stroma (Cooper, 2017). It was reported only three times in veterinary medicine: mass arising from the skull of an 11-month-old Boxer dog (da Roza et al., 2010), meningeal mass in a 7-week-old Labrador Retriever (Hoon-Hanks et al., 2018) and left hindlimb mass in a 3.5-year-old Bulldog (Shi et al., 2023). In human medicine it is considered the variant with less aggressiveness (Caroll, 2013).

**Botryoid RMS** is considered a variant of embryonal RMS in both human and veterinary medicine. Macroscopically, it appears as a polypoid, grape-like mass and is encountered most commonly in the urinary bladder, where it can be seen protruding from the mucosa. Histological examination reveals many undifferentiated rhabdomyoblasts and/or strap cells suspended in a myxoid matrix, these being characteristic (Kobayashi et al., 2004). The densely cellular *cambrium layer* located beneath the mucosa is considered a strong diagnostic feature (Caserto, 2013).

**Alveolar RMS** is histologically subdivided in classic and solid variants.

The classic variant is characterized by aggregates of small, poorly differentiated, round cells. The cells have scant cytoplasm and are supported by a fibrovascular stroma. The tendency of centrally located cells to become degenerated and get separated one from each other due to a poor cohesivity gives shape to the so called "alveolar pattern". Differentiated rhabdomyoblasts are uncommon, with cross-striations rarely present (Cooper, 2017). The solid variant in dogs consists of sheets of small round neoplastic cells divided by thin fibrous septa. This pattern is not always present, making the histologic architecture similar to rhabdomyoblastic embryonal RMS, thus the diagnosis is very difficult. Molecular genetic analysis has been proven efficient in this matter (Caserto, 2013).

Kimura et al. (2013) report a gingival alveolar RMS in a 3-year-old Shih Tzu, composed of anaplastic cells arranged in typical alveolar pattern, numerous mitotic figures and multinucleated cells. The cross-striations and glycogen accumulation were absent.

**Pleomorphic RMS** marks the least common variant in human medicine (Parham, 2001). In dogs, like in humans, is diagnosed typically in adults and is extremely rare in young patients. The tumour rises almost exclusively within skeletal muscle of the limbs. Histologically, the architecture consists of exclusively spindle cells with abundant eosinophilic cytoplasm, arranged in a haphazard manner. Rare multinucleated cells may be present. The bizarre or multipolar mitotic figures, lack of

any embryonal or alveolar pattern, general lack of cross-striations and the high degree of pleomorphism are the most characteristic features of this tumour. Glycogen content of the neoplastic cells is commonly seen. The accurate diagnosis always needs immunohistochemistry for confirmation (Cooper, 2017; Caserto, 2013). Yamate et al. (2011) describe a low-grade pleomorphic RMS located in the larynx of a 6-year-old dog.

**Unclassified RMS (RMS NOS)** has been noted in various articles, as its complex morphological patterns could not fall into a specific histologic subtype/variant (Caserto, 2013).

**Immunohistochemistry of RMS**

IHC is the preferred diagnostic technique for confirmation canine rhabdomyosarcoma.

Commonly used immunohistochemical indicators are characterised by positive labeling with vimentin, desmin and myoglobin, and negative labeling for α-smooth muscle actin (α-SMA).

A panel of antibodies is strongly recommended for IHC characterization of these tumors, as various antigens are expressed at different times during cell development. Vimentin, desmin and sarcomeric actin are expressed early, but later vimentin is lost during the muscle fibers development. Myoglobin is expressed later than desmin (Cooper, 2017).

Vimentin is a type III intermediate filament protein. Its expression in IHC demonstrates the mesenchymal origin of the neoplastic cells, making it indispensable in the IHC panel of RMS.

Desmin has also been proven useful in human and veterinary medicine, especially when it comes to prove the myogenic differentiation in alveolar or embryonal RMS. It is not a marker exclusively only to skeletal muscle, being common also in cardiac and smooth muscle, as well as in myofibroblasts. It may raise difficulties in the diagnostic procedure due to its high degree of variability in regard to the staining process and low specificity. Because of these matters, newer methods use myoblast determination protein 1 (MyoD1) and myogenin to identify undifferentiated myoblasts. Myogenin and MyoD1 are early embryological transcription factors. These proteins are involved in the differentiation of mesodermal cells into myoblast cells and also proliferation and differentiation of myoblast cells into multinucleated myotubes (Caserto, 2013).

Immature rhabdomyoblasts with high proliferative capacity will express MyoD1. In human medicine, undifferentiated RMS have been shown to express more MyoD1 and myogenin and less actin, myoglobin, myosin and desmin (Sebire, 2003).

Studies show that diffuse expression of myogenin in the nuclei of tumour cells could indicate an alveolar or embryonal RMS (uniform expression for alveolar, heterogenous for embryonal), while for myogenin there is insufficient data to conclude this characteristic. Also, human embryonal RMS exhibits few cells with expression of either myogenin or MyoD1 (Caserto, 2013). However, absence of immunostaining with MyoD and myogenin doesn't exclude a myogenic origin. The expression depends on the degree of differentiation (Kobayashi et al., 2004).

There is no exact correlation between human and canine RMS using myogenin or MyoD1 immunohistochemical staining, as the use of these antibodies is new and rare in veterinary medicine (Tuohy, 2021).

Kobayashi et al. (2004) described the immunohistochemical pattern of a canine botryoid RMS as myogenin staining strap cells preferentially and MyoD1 being limited to the nuclei of numerous small and round myoblast cells, while other studies didn't find such connection between cellular component and staining. Similar to humans, muscle actin antibody can identify α-actin isoforms in all three types of muscles. More specific to skeletal muscle is the expression of α-actin isoform, which can be identified by the sarcomeric actin antibody.

Cases of RMS reported in dogs are consistently immunohistochemically positive using for vimentin, muscle actin, sarcomeric actin and desmin. The lack of cellular differentiation of RMS makes myoglobin expression variable. In dogs, both embryonal and botryoid rhabdomyosarcomas are commonly positive for myoglobin, as the large rhabdomyoblasts or strap cells show immunopositivity (Kobayashi et al., 2004).

**Prognosis of RMS**

A prognosis and accurate diagnosis of canine RMS are difficult to reach in veterinary medicine due to the rarity and often misdiagnosis of this type of tumour. Frequently, they fall under the high-grade soft tissue sarcoma category (Avallone et al., 2010). Absence of follow-up / survival data, election of euthanasia, lack of post-mortem examination and unknown presence of possible metastasis make prognostic value of canine RMS still a challenge for veterinary specialists.

Data gathered up to present in veterinary medicine show that the most aggressive rhabdomyosarcomas are the alveolar and embryonal variants. Very young dogs, under 2 years of age, develop the most aggressive behaviour. Subclassification into the rhabdomyoblastic or myotubular variant in case of embryonal RMS has no prognostic significance (Caserto, 2013; Wachtel et al., 2006).

In humans, clear differentiation between alveolar and embryonal RMS is very important, as the alveolar variant is more locally aggressive, with a higher metastatic rate, thus bearing a poorer prognosis. In veterinary medicine, this prognostic significance is still unavailable, due to lack of sufficient data. Based on the small number of cases reported in dogs, metastatic rate seemed to be the highest in unclassified RMS, followed closely by embryonal and alveolar types, bothryoid RMS reportedly having the lowest rate and better prognosis (Caserto, 2013; Shi et al., 2023).

At present, in canine rhabdomyosarcoma, the extent and severity of invasiveness and the presence of metastasis are used to establish the prognosis (Caserto, 2013).

## CONCLUSIONS

In veterinary medicine, histopathological and immunohistochemical examinations are crucial in diagnosing rhabdomyosarcomas and excluding other types of neoplasia.

In dogs, the prognosis depends on the severity and extent of invasiveness, as well as the presence of metastases, morphological subtypes having no prognostic value.

The vast variability of this tumour, the lack of prognostic significance of its histologic subtypes and the small number of cases reported in animals makes RMS a challenge for both pathologists and clinicians.

Further investigations are needed to better understand the biological behaviour and outcomes of this tumour and to reach an effective way to classify and characterise them.

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