doi: http://dx.doi.org/10.22201/fmvz.24486760e.2023.1149
Vol. 10 | 2023

Veterinaria México OA
Publicación Digital de la Facultad de Medicina Veterinaria y Zootecnia https://veterinariamexico.fmvz.unam.mx/

Review of canine hemangiosarcoma: an aggressive and lethal neoplasm

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Abstract

Hemangiosarcoma (HSA) is an aggressive and malignant tumor that occurs in endothelial cells and invades blood vessels. It typically occurs in canines aged 6 to 13 years, with certain breeds, including German Shepherds, Golden Retrievers, Labradors, and Boxers, are predisposed. It can occur in any part of the animal's body and can be found in the heart, liver, skin, and bones, although its most common location is in the spleen. Its importance lies in the fact that few canines can be diagnosed before the tumor ruptures and causes severe abdominal bleeding, leading to anemia, weakness, and collapse. This study provides an updated review of various methods for diagnosis and treatment, placing emphasis on ontogeny, genetics, mutations, signaling pathways, and significant markers like CD133, CD117, CD45, and CD34. The goal is to facilitate a timely diagnosis through molecular biology and effective treatment, thereby enhancing the survival time of the canine with HSA. Likewise, the aim is to broaden the outlook for professionals at the time of early detection of HSA, to reduce the damage caused to the canine, which is extremely traumatic and painful during this pathology.

Keywords: Hemangiosarcoma; Canine; Neoplasm; Diagnosis; Angiogenesis.

Submitted: 2022-11-22
Accepted: 2023-09-04
Published: 2023-12-13

Additional information and declarations can be found on page 10

Cite this as:

Hernández Salas A, Páez Bonelo AM, Moscoso Gama JM, Méndez Hurtado WA. Review of canine hemangiosarcoma: an aggressive and lethal neoplasm. Veterinaria México OA. 2023;10. doi: 10.22201/fmvz.24486760e.2023.1149.

doi: http://dx.doi.org/10.22201/fmvz.24486760e.2023.1149
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Contribution to the study

HSA is one of the most aggressive and deadly diseases in canines. However, diagnosing it is not always straightforward due to the nonspecific clinical manifestations. Typically, it is diagnosed when the tumor ruptures, leading to the collapse of the animal. Therefore, through this compilation and literature review, our aim is to furnish veterinarians with comprehensive information about this neoplasm, encompassing generalities, types, diagnosis, and treatment.

Introduction

Canine hemangiosarcoma, abbreviated as HSA, is a malignant tumor originating from endothelial cells with a high metastatic capacity, affecting almost all breeds of dogs. However, certain breeds, including German Shepherds, Golden Retrievers, and Labradors, show a higher predisposition due to its incidence compared to other breeds such as Boxers, Rottweilers, Dobermans, and Schnauzers. The average age of dogs diagnosed with HSA is 9 to 12 years.[1] While no sex predilection has been demonstrated, a higher prevalence in males has been indicated.[2] HSA can affect any tissue in the body, with the three common primary sites being the spleen, right atrium, and skin or subcutaneous tissue.[3]

Conventional diagnostic methods include physical examination, which involves palpation, auscultation, and temperature measurement, as well as clinical examination and diagnostic tests such as hemogram, biochemical profile, histopathological profile, and ultrasound and computed tomography images. However, the utilization of various molecules proposed as tumor markers has gained attention due to their association with neoplasia.[4]

Treatment options typically involve surgery and chemotherapy. Surgery is considered advantageous, as the removal of the tumor increases canine survival times, reducing the risk of cancer cell dissemination. On the other hand, chemotherapy, utilizing antineoplastic drugs such as doxorubicin and cyclophosphamide, extends survival times between 40 and 202 days, depending on the employed protocol.[5]

The clinical presentation of this disease is not always straightforward; nonspecific signs such as lethargy, loss of appetite, weight loss, and an increase in abdominal diameter are reported. However, these manifestations can vary depending on the origin of the primary tumor.[6]

Cardiac hemangiosarcoma

Cardiac HSA is one of the most common heart neoplasms in dogs. Typically, when the tumor is diagnosed, it has already metastasized, leading to often invasive palliative treatments. Pericardiocentesis initially improves fluid removal from the pericardial sac, but over time, it reappears, causing death in most cases. However, if the tumor is identified early without metastatic lesions, surgical removal of the primary tumor is recommended. Chemotherapy with Doxorubicin can also be performed.[7] Diagnosis can be made through echocardiography or a chest radiographic study.[8]

doi: http://dx.doi.org/10.22201/fmvz.24486760e.2023.1149
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Cutaneous hemangiosarcoma

Cutaneous HAS can be classified as capillary, cavernous, or solid.[9] Typically, it presents with subcutaneous and muscular infiltrations, with solar radiation considered a predisposing factor for neoplasm development. The classification is based on histological depth: stage I (dermal), stage II (subcutaneous), and stage III (under the muscles).[10]

It is often detected by the presence of an ulcerated mass during physical examination and through diagnostic tests such as hemogram, biochemical profile, and relevant ultrasound scans. Emphasizing the importance of timely diagnosis, metastatic dissemination can occur through tumor rupture or hematogenous dissemination, limiting the canine's survival.[4]

Differential diagnosis should distinguish between the primary tumor and metastatic tumor, hemangioma, lymphangioma, and lymphangiosarcoma.[2]

Hepatic hemangiosarcoma

The growth pattern of primary hepatic HSA in dogs and cats is highly invasive, spreading to the peritoneum, lung, kidney, and abdominal lymph nodes. It has an incidence of 92.3 % in geriatric patients and 7.7 % in adults. In terms of gender distribution, 69.2 % of cases were males, and 30.8 % were females.[2] Table 1 illustrates the anatomical presentation and various clinical signs associated with the types of hemangiosarcomas mentioned above.

While the spleen is the most common location, authors such as García, Molina, and Yamamoto,[7,11,12] assert based on their experience, that cardiac hemangiosarcoma is one of the most frequent neoplasms affecting the canine heart. Unfortunately, it presents challenges in management and carries an unfavorable prognosis in most cases.[11-12] Contrary to common belief, Nóbrega and Weinborm emphasize the significance of the cutaneous type, often underestimated and lacking the necessary attention. It is the most painful among the three types and has the highest incidence in Brazil.[10, 13]

Table 1. Types of hemangiosarcomas, their anatomical presentation, and clinical signs

Type of hemangiosarcoma	Anatomical presentation	Clinical Signs
Cardiac hemangiosarcoma	Right atrial orifice, atrial wall, atrioventricular groove, or coronary groove.[11]	Prostration, dyspnea, weak pulse, pale mucous membranes, moderate cardiomegaly. Pericardial effusion and cardiac tamponade.[12]
Cutaneous hemangiosarcoma	Hypodermis, dermis, and muscles.[13]	Stage I: Small, raised red or purple nodules. Stage II and III: Larger, soft, and hematoma-like lesions.[10]
Hepatic Hemangiosarcoma	Hepatic lobes with dissemination to the peritoneum, lung, kidney, and abdominal lymph nodes.[2]	Liver failure, weight loss, polyuria, vomiting, diarrhea, weakness, abdominal pain, and jaundice.[2]

doi: http://dx.doi.org/10.22201/fmvz.24486760e.2023.1149
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Epidemiology

HSA accounts for approximately 7 % of canine neoplasms and predominantly affects geriatric males aged 8 to 10 years. The most predisposed breeds include German Shepherds (32.7 %), Golden Retrievers (31.5 %), Labradors (22 %), Boxers (7.5 %), and Rottweilers (6.9 %).[1] In felines, no specific breeds have been identified. However, short-haired cats with non-pigmented skin have been associated with the development of cutaneous HSA.[14] The cutaneous type represents 14 % of HSA, with a higher prevalence in canines of breeds with little pigmented and glabrous skin or sparse fur. Subcutaneous and muscular types do not have a specific anatomical predilection, indicating they can appear in any part of the animal's body, such as extremities, trunk, and cervical regions.[15]

As for the prognosis of the disease, it is generally negative when the pathology is not diagnosed early. The prognosis can also vary depending on the type of HSA the canine is experiencing, with splenic and cardiac types usually having the most unfavorable outcomes. In the case of cutaneous HSA, prognosis is contingent upon the tumor classification; a low-grade tumor typically has a more favorable prognosis compared to an intermediate- or high-grade tumor.[15]

Etiology

Concerning ontogeny, various research hypotheses propose that canine hemangiosarcomas are linked to an endothelial origin and can also arise from abnormal changes in hematopoietic progenitor cells. The first hypothesis suggests an origin from hematopoietic precursors with endothelial differentiation potential, meaning from differentiated vascular endothelial cells that undergo mutations.[16] The second hypothesis proposes an origin from incompletely differentiated bone marrow-derived multipotent stem cells that are near or at the stage of endothelial involvement, such as hemangioblasts. Expression patterns can aid in confirming an HSA diagnosis, monitoring the disease, and detecting it at early stages.[17]

Predisposing factors

The disease can arise from predisposing factors and hereditary features that promote the survival of malignant cells. Age, breed, and neutering are often indicators of an increased predisposition to HSA, with neutered male dogs showing heightened susceptibility.[18] Although the exact reason for this is not clear, some studies have suggested the possibility that the loss of androgen receptors after castration may favor tumor progression, irrespective of the breed.[19] Additionally, it has been analyzed how the presence of luteinizing hormone (LH) receptors in vascular endothelial cells is associated with HSA. In canines with gonadectomy, elevated levels of circulating concentrations of this hormone have been observed.[20] DNA and mRNA sequencing have identified characteristic molecular features for distinguishing HSA. Additionally, mutations in the VHL and Ras family genes have been linked to HSA.[21] The fusions of different genes appear to be associated with the various molecular subtypes of HSA.[22] Currently, sequencing technologies have allowed the identification of three molecular subtypes concerning the tumor: angiogenic, inflammatory, and adipogenic.[23]

doi: http://dx.doi.org/10.22201/fmvz.24486760e.2023.1149
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HSA cells have been found to harbor somatic coding mutations in TP53, PIK-3CA, and PIK3R1.[24] The PIK3CA mutation is considered a driver of HSA due to its increased enzymatic activity and active oncogenic signaling, making it a cancer driver. The TP53 gene is the second most mutated gene in the disease, leading to functional consequences and truncations.[25] The p53 gene and retinoblastoma are tumor suppressors; p53 induces apoptosis or halts growth in damaged cells, while retinoblastoma encodes a protein regulating the transition from G1 to S phase via CDK4. In HSA, these two genes are inactivated, contributing to resistance to apoptosis and tumor progression.[26]

The KIT protein, encoded by the c-kit gene, serves as a tyrosine kinase growth receptor for stem cell factor, and it is expressed in canine HSA. Activating mutations in the c-kit gene play a contributory role in the initiation and progression of neoplasms.[27]

Signaling pathways

One approach considered to gain a deeper understanding of HSA involves drawing parallels with other diseases. In this instance, similarities were identified with Kaposi's sarcoma, owing to the constitutive activation of the viral G-protein receptor driven by MEK activity. Consequently, it is hypothesized that the growth and survival of HSA may be dependent, among other factors, on MEK signaling.[28]

Dysregulation of the Janus kinase (JAK)-signal transducer and activator of transcription (STAT) cell signaling pathway, a highly conserved signaling pathway, is associated with the development and progression of human cancers. STAT3 has been identifiedin veterinary cancers along with mutations in the JAK1 and JAK2 pathways. Increased expression or activation of JAK1 has been observed to decrease the survival of canines with HSA.[29]

There is another pathway, PI3K/mTOR, associated with cell survival, proliferation, and apoptosis. Activation of this pathway typically occurs through initial tyrosine kinase activity. Notably, this pathway is activated in several canine cell lines, including HSA. Consequently, the proteins within the pathway are activated, inhibiting canine hemangiosarcoma cells and thereby reducing cell proliferation, as well the capacity to migrate and invade cells.[30]

Different signaling pathways, such as Janus kinase (JAK), PI3K/mTOR, and MEK, are involved in tumor cell growth, survival, and proliferation. For this reason, emphasis is placed on making the different signaling pathways known, given that at the time of developing future treatments specifically with drugs, these could be directed to inhibit the signaling pathway involved in the growth and proliferation processes of tumor cells.

Diagnosis

For diagnosis, it is crucial to consider the predisposing factors, along with hematological changes. In this neoplasm, regenerative or non-regenerative anemia, erythroid forms like schistocytes and acanthocytes,[31] thrombocytopenia, and disseminated intravascular coagulation are significant indicators.[32]

Cancer can lead to the release of nucleosomes (encapsulated DNA), which can be obtained through fasting blood samples taken from the jugular or peripheral

doi: http://dx.doi.org/10.22201/fmvz.24486760e.2023.1149
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vein of dogs, including buccal swabs. These nucleosomes have been utilized as biomarkers for cancer detection. In dogs with HSA, the highest concentration was observed in the splenic type, followed by the cardiac type, and, finally, the cutaneous type. Additionally, the concentration of nucleosomes increases with the disease stage and is not influenced by factors such as age or sex.[33]

In the case of canine HSA, few cellular and molecular investigations have been conducted, thereby limiting the availability of markers that could aid in the early diagnosis of the disease.[34] However, there are important markers for this neoplasm: hematopoietic stem cell markers CD133, CD117, CD45, and CD34, endothelial cell markers (VEGF-R2, CD31, and FVIII-RA), and a myeloid marker CD14,[35] these markers facilitate an immunohistochemical diagnosis.[36]

Vascular endothelial growth factor (VEGF) is a glycosylated polypeptide growth factor with potent angiogenic and mitogenic properties. It is commonly overexpressed by many malignant tumors, leading to increased concentrations in serum and plasma. These levated levels are correlated with poor prognosis, aiding in the determination of tumor burden, response to treatment, and disease progression.[37]

Thymidine kinase 1 (TK1) is a soluble biomarker associated with DNA synthesis during the cell cycle and is expressed in malignant cells undergoing abnormal proliferation. When TK expression was assessed in canines with HSA using a blood sample, serum TK1 activity was found to be elevated, suggesting, its potential as a tumor biomarker in dogs.[38]

Delving further into the existing diagnostic methods, we encounter a patent developed by Modiano. This method involves obtaining a cell population from an individual through a blood sample and determining whether the cells express various cell markers. Among these markers, there should be at least one marker of primitive hematopoietic cells and one marker of endothelial cells. An increased expression level, combined with the absence of specific markers such as CD18, CD3, CD5, and CD21, serves as an indication of HSA.[39]

IL-8 (CXCL8) is a proinflammatory and proangiogenic chemokine that promotes chemotaxis and neutrophil degranulation. Given its involvement in the angiogenic process and its promotion of the tumor microenvironment, the expression of IL-8 may be of great importance for HSA. Overexpression in tissues could indicate the production of new cancer cells, including fibroblasts and inflammatory cells.[40]

To achieve the early diagnosis sought, it is crucial to determine the optimal timing for sample collection. The proposal involves obtaining blood samples or oral swabs from canines to conduct a screening process aimed at detecting genetic anomalies or mutations, along with an increase in concentrations or expressions of biomarkers that may indicate the potential development of the disease. Additionally, for canines displaying clinical manifestations or the presence of masses or abnormal tissues, blood sampling and histopathological examinations are recommended, if possible, to confirm the diagnosis and initiate early treatment. This approach aims to prevent the spread of cancerous cells and enhance the survival time of the canine.

The review underscores that tools for early and accurate diagnosis necessitate molecular biology. However, it is crucial not to overlook conventional tests like blood counts and biochemical profiles, which serve as diagnostic guides. Despite the evident advantages of molecular biology, it comes with a significant drawback—

doi: http://dx.doi.org/10.22201/fmvz.24486760e.2023.1149
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its high cost. To address this, authors such as Modiano and Verge suggest the utilization of a diverse array of markers, thereby enabling an immunohistochemical diagnosis.[36, 39]

Nevertheless, the research advances made over the years have enabled the identification of molecular features that define this neoplasm, along with its genetic mutations. This is a crucial aspect for a deeper understanding of its ontogeny and, consequently, for targeting potential early diagnoses and timely treatments to enhance the survival of canines.

Treatment

Over the years, various protocols have been developed to treat dogs with HSA with the aim of improving survival time regardless, of the clinical stage. One widely used protocol is the combination of three drugs, vincristine, doxorubicin, and cyclophosphamide, known as VAC.[41] Vincristine and cyclophosphamide belonging to the alkaloid or alkylating agents class, inhibit the growth of cancer cells, while doxorubicin with antitumor activity, is classified as an anthracyclines. The protocol entails a 21-day cycle including doxorubicin (30 mg/m^2) on day 1, vincristine (0.5-0.75 mg/m^2) on days 8 and 15, cyclophosphamide (200-300 mg/m^2) on day 10, and trimethoprim/sulfamethoxazole (15 mg/kg every 12 h for the complete cycle). However, careful monitoring of administration is necessary due to potential adverse effects, including gastrointestinal issues such as nausea, vomiting, and diarrhea; cardiac toxicity and arrhythmias; vacuolar and metabolic changes; as well as alopecia and medullary suppression.[42]

Surgery has been a treatment of choice for HSA; however, due to the rapid growth and metastasis of the tumor, the use of chemotherapy with drugs is necessary to prolong the lifespan of the canine.[43] Alternative treatments to conventional therapies include immunomodulators, antimetastatic agents, and matrix metalloproteinase inhibitors. Immunomodulators are synthetic molecules that mimic the peptidoglycan of bacterial cell walls. They selectively activate cells of the macrophage lineage in a tumorigenic state while simultaneously acting as encapsulated liposomes to improve drug absorption. On the other hand, antimetastatic agents primarily aim to inhibit angiogenesis, while matrix metalloproteinase inhibitors play a role in preventing the tumor invasion of blood vessels.[3]

The same applies to alpha- and beta-type interferons, angiogenic inhibitors responsible for suppressing angiogenesis by reducing vascular endothelial growth factor levels, which are elevated in vascular neoplasms. Another treatment proposal involves the use of the peptidoglycan recognition protein agonist and the liposome muramyl tripeptide phosphatidylethanolamine (L-MTP-PE) in combination with chemotherapy. This approach leads to delayed metastasis and increased survival, improving the activation state and antitumor toxicity by activating blood cells and aiding the immune system in eliminating cancer cells.[44]

Thalidomide is an immunomodulator that can suppress vascular endothelial growth factor (VEGF). Treatment with this drug has been shown to increase the survival time of canines by reducing VEGF production in neoplastic HSA cells.[45]

Endothelin-1 (ET-1) is a common vasoconstrictor peptide in human tumors, playing a role in cell proliferation, apoptotic inhibition, and metastasis. In HSA tissues, there is an overexpression of preproendothelin-1 (PPET-1), followed by an

doi: http://dx.doi.org/10.22201/fmvz.24486760e.2023.1149
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elevation of ET-1, both of which decrease with tumor removal. This is of great importance because the use of these peptides can be considered as a treatment option for HSA.[46]

The development of an allogeneic tumor vaccine was one of the most significant treatment alternatives proposed until 2007. Administered to dogs at different stages of HSA, it was demonstrated to induce strong humoral immune responses and the development of anti-AHS antibodies after vaccination.[47] Vaccines stimulate effector and memory T cells, theoretically capable of controlling tumor metastases for extended periods. However, the current lack of well-characterized tumor-specific antigens remains a major impediment to the widespread application of tumor vaccines in veterinary medicine. Moreover, checkpoint molecule blockade and modified T cells may ultimately replace the need for cancer-specific vaccines.[48]

Experimental vaccination of dendritic cells, the primary regulatory cells of the adaptive immune response, has been considered as a therapeutic option alongside chemotherapy.[49] Another prominent example of immunotherapy is the autologous tissue vaccine, involving cells extracted from the patient's own tumor. This vaccine presents the patient's complete repertoire of tumor-associated antigens (TAA) unique to the immune system. Studies have demonstrated its ability to upregulate MHC-II and CD80 in cultured canine monocyte-derived cells, essential stimulatory molecules for generating an immune response. This approach has shown promise in improving survival time in dogs with HSA.[48]

Cyclooxygenase-2 (Cox-2), an enzyme that accelerates the formation of substances that cause inflammation and pain, is involved in the formation, growth, and metastasis of tumors such as canine hemangiosarcoma. When adding a Cox-2 inhibitor, it is observed that chemotherapy helps to increase the survival of canines, approximately 150 days after finishing the treatment cycles, although it is important to consider the stage of the disease since this influences the treatment of the canine.[50]

Resveratrol is a non-flavonoid polyphenolic phytochemical with many biological effects. It has been observed through different studies that it also has anticancer and chemo preventive properties, thus highlighting its antiproliferative and apoptotic properties through protein kinase activation, allowing a growth inhibitory effect in multiple canine HSA cell lines.[51] Likewise, tocerabic phosphate is a multi-targeted small molecule inhibitor that blocks KIT, PDGFR, and VEGFR family member signaling, demonstrating activity against multiple tumor types, including mastocytomas, nasal carcinoma, apocrine gland anal sac adenocarcinoma, and osteosarcoma.[52]

One of the latest therapeutic advances for HSA, reported in 2020, is eBAT, which consists of a targeted toxin of Pseudomonas exotoxin deimmunized, which allows inhibition of protein synthesis and fuzes with the urokinase plasminogen activator receptor, UPAR, an anchored cell surface protein that is associated with tumor invasion, migration, and metastasis. The use of this toxin has brought positive results, as it has almost doubled the survival time of the canine after administration.[53]

Conventional treatments, such as surgery and chemotherapy, are the basic procedures for this neoplasm. However, the use of drugs that delay metastasis, such as L-MTP-PE, or that decrease toxicity, such as resveratrol, are alternative therapeutic options that in conjunction with chemotherapy favor an increase in canine survival time. Although vaccines are one of the best alternatives that have been pro-

doi: http://dx.doi.org/10.22201/fmvz.24486760e.2023.1149
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posed, it is necessary to investigate in greater depth the scope of the unfavorable effects that their use and implementation may bring about.

DEN-HSA cell line

One of the cell lines studied, derived from a canine hemangiosarcoma of the kidney, is the DEN-HSA line of endothelial origin. HSA cells have the characteristic of a non-delimited and non-encapsulated proliferation of ovoid shape.(54) When cultured, the morphological identification of elongated and spindle-shaped cells was achieved. They are also cells that proliferate in response to angiogenic growth factors such as recombinant human basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF) through the expression of mRNA, which is of great importance because they are important factors in angiogenesis and promote cell proliferation and survival. Thus, DEN-HSA cells can be used to study therapies that modulate endothelial proliferation.(55)

Conclusions

Despite the studies and research that have been conducted on HSA, this remains a neoplasm with a high mortality rate because of the lack of early diagnosis and treatment that increases the survival time of the canine; therefore, the importance of the use of molecular biology to attack the disease in a timely manner is emphasized.

doi: http://dx.doi.org/10.22201/fmvz.24486760e.2023.1149
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Acknowledgments
We thank the Universidad Colegio Mayor de Cundinamarca for the possibility of carrying out this review article, and also our families for their support and trust.

Funding statement
This narrative review article did not require funding.

Conflicts of interest
The authors declare that there is no conflict of interest related to this publication.

Author contributions
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