TREATING HEMANGIOSARCOMA IN THE DOG AND CAT

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Hemangiosarcoma (HSA) is a malignant mesenchymal tumor arising from vascular endothelium; therefore, it can develop in any site where blood vessels are present. HSA and its risk factors will be reviewed as a diagnostic plan for a patient with suspected or confirmed HSA will be presented. Treatment options and prognoses will follow.

Hemangiosarcoma commonly affects the spleen, right atrium, subcutaneous tissue, and the liver in the dog. In cats, HSA occurs commonly in the liver, spleen, mesentery, omentum, and subcutaneous tissue. In both species, HSA may occur in the skin. Cutaneous HSA typically occurs in areas of poor pigmentation and minimal hair coverage, such as the facial skin in white cats and the glabrous abdominal skin of dogs.

Clinical signs of HSA are variable and may relate to the site of the tumor, presence of metastases, or active tumor hemorrhage. In acute bleeding episodes of intraabdominal or cardiac HSA, affected animals may collapse due to hypovolemia or have circulatory compromise secondary to cardiac tamponade. Dogs and cats that have a bleeding splenic, hepatic, or mesenteric HSA may also have abdominal distention and a palpable fluid wave. Often pet owners report a history of waxing and waning, nondescript, clinical signs that may include lethargy, decreased food intake, exercise intolerance, and episodic weakness. Owners may seek attention for cutaneous HSA because they notice bleeding or self-trauma. Seizures can be the presenting complaint for dogs with HSA if metastatic to the brain.

Physical examination findings are variable for dogs and cats with HSA. The cutaneous lesions are sometimes crusted and may be actively bleeding. Subcutaneous and intramuscular HSA can be soft or firm and may have ill-defined margins. Sometimes they appear bluish or purple depending on the skin pigmentation. Animals affected with visceral HSA may have pallor, prolonged capillary refill time, muffled heart sounds, tachycardia, and tachypnea, a palpable abdominal mass and generalized weakness. It is important to remember that 50% of splenic masses in dogs are benign.

Cutaneous HSA commonly affects dogs with light hair coats and light pigmentation, including Whippets, Dalmatians, English pointers, and similar breeds. Cutaneous HSA has been associated with sunlight exposure and the attendant ultraviolet radiation-mediated damage. Likewise, feline cutaneous HSA occurs predominantly on the facial skin of white cats, or affects the white patches on the faces of multicolored cats. Ultraviolet radiation exposure is also considered a risk factor for cats developing cutaneous HSA.

The presence of other sunlight-induced changes of the skin, including solar elastosis and actinic keratosis, alongside cutaneous HSA lesions supports this notion.

Visceral HSA most commonly affects German shepherd dogs, but other large breeds are also at risk, including the Golden retriever and Labrador retriever. Breed predisposition hints at a genetic cause for HSA in the dog, but specific genes or mutations have been identified. In cats there is no apparent breed predisposition. Although not demonstrated in dogs or cats, exposure to various thorium and arsenic compounds and vinyl chloride is associated with the development of malignant vascular tumors in people, supporting the possibility of environmental causes for canine and feline HSA.

Dogs with suspected or confirmed HSA should undergo a comprehensive diagnostic workup. The vascular nature of HSA makes it a highly metastatic cancer. The initial evaluation for a dog or cat with hemangiosarcoma includes a minimum database (complete blood count, serum biochemistry profile, and urinalysis), three-view thoracic radiographs, abdominal ultrasonography, echocardiography, and potentially computed tomography (CT) or magnetic resonance imaging (MRI) of the brain. Other useful diagnostic tests for animals with HSA include electrocardiogram (ECG), prothrombin time (PT), partial thromboplastin time (PTT), fibrinogen, and fibrinogen degradation products (FDP). Unfortunately, fine needle aspirate of HSA lesions is rarely diagnostic due to the extensive hemorrhage generated by the procedure.

Exhaustive imaging is warranted for these cases, because nearly 80% of dogs have demonstrable metastatic disease at the time of diagnosis; up to 25% of dogs have both splenic and atrial lesions; nearly 15% of dogs have metastatic lesions in the brain; and cutaneous HSA lesions may represent metastases from a primary visceral tumor. Furthermore, HSA has been reported to metastasize to most every organ system in the dog. Cats should undergo a similar initial diagnostic workup as dogs; however the frequency of cardiac and CNS metastasis has not been established in cats with HAS, so echocardiography and CT or MRI may be of limited usefulness.

Serum biochemical abnormalities in both dogs and cats with HSA are nonspecific, but may reflect acute hypoxia, manifest by increases in serum ALT activity, or changes consistent with organ infiltration and subsequent dysfunction. Hematology changes often occur in dogs with HSA and can include evidence of a regenerative anemia, characterized by anisocytosis, polychromasia, and reticulocytosis. Changes in red blood cell morphology are a variable finding in dogs with HSA and may include acanthocytes, schistocytes, and nucleated red blood cells (nRBC). Neutrophilic leukocytosis and thrombocytopenia are also variably present in dogs with HSA. Cats with HSA may have similar hematological changes as the dog, but abnormal red blood cell morphology is less common.

The ECG is useful to detect arrhythmias associated with cardiac lesions, such as right bundle branch block, and those ventricular rhythm disturbances that occur secondary to the presence of a splenic mass. The presence of pericardial effusion can result in a decrease in QRS amplitude or electrical alternans. In dogs with splenic HSA, arrhythmias may not become apparent until after splenectomy. Depending on the nature and severity of the arrhythmia, use of antiarrhythmic drugs may be warranted, and general anesthesia protocols may be affected. In both dogs and cats with HSA, the coagulation profile may reveal the presence of disseminated intravascular coagulation (DIC), which is characterized by thrombocytopenia, prolonged PT and PTT, decreased fibrinogen, and increased FDP. The presence of DIC may alter the immediate surgical plans for the patient and requires aggressive treatment with plasma and heparin. In people with malignant vascular tumors, a DIC-like syndrome has been identified, which is responsive to...
glucocorticoid therapy. It is unclear if a similar condition occurs in dogs and cats with HSA. Surgery is the cornerstone of management of the HSA patient. For animals with primary cutaneous HSA, wide surgical excision is the treatment of choice. Because cutaneous HSA have a seemingly less aggressive biological behavior that HSA in other locations, chemotherapy is rarely used after surgery. If the cutaneous HSA occurs in a location where wide surgical excision is difficult, as in the facial skin of cats, photodynamic therapy (PDT) may be useful.

For subcutaneous and visceral HSA, surgery is recommended as the initial treatment. Splenectomy or amputation of the right auricular appendage, in the case of cardiac HSA, can quickly eliminate the risk of tumor rupture and sudden death due to hemorrhage into the abdomen or pericardial space. Likewise, wide surgical excision of subcutaneous HSA is also recommended. Unfortunately, hepatic or mesenteric HSA may not be amenable to surgical intervention. In visceral or subcutaneous HSA, surgery is considered palliative. Chemotherapy is recommended to slow the progression of metastatic lesions, which are eventually fatal for the animal.

A variety of chemotherapy protocols have been described for the treatment of HSA, and all include doxorubicin. Single agent doxorubicin is a widely recommended adjuvant treatment from HSA and is generally well tolerated by dogs and cats. A typical protocol consists of 5 intravenous doses of doxorubicin given 2 to 3 weeks apart. Dogs weighing more than 15 kg are given 30 mg/m² whereas dogs weighing 15 kg or less are given 1 mg/kg. Cats are given 20 mg/m² intravenously. Owners should be counseled about acute hypersensitivity reactions and the cardiac effects of doxorubicin in dogs. Extreme care should be taken when administering doxorubicin as extravasation injuries may require amputation, or in severe cases euthanasia.

Cyclophosphamide and vincristine have been combined with doxorubicin for the adjuvant treatment of HSA in dogs. These combination chemotherapy protocols are associated with a slightly higher risk of adverse gastrointestinal and hematological events. Reported survival times of dogs treated with single agent doxorubicin, doxorubicin and cyclophosphamide (AC protocol), and doxorubicin, cyclophosphamide, and vincristine (VAC protocol) are similar. This observation suggests that combination chemotherapy does not confer a survival advantage to dogs with HSA. However, prospective, randomized, phase III clinical trials will be necessary to determine which protocol, if any, is superior. Anecdotally, the VAC protocol may be most effective at decreasing tumor volume of subcutaneous and intramuscular HSA that are not surgical candidates. In many cases, the HSA decreases in size such that surgery becomes possible and in a few cases the tumor may disappear completely. The effect of preoperative chemotherapy on survival of dogs with HSA is unknown.

The role of chemotherapy for the management of HSA is largely unknown. Anecdotal reports and the similar metastatic potential of canine and feline HSA suggest that chemotherapy will play an important role in feline HSA. However, no prospective clinical trials or retrospective studies have been compiled to support the efficacy of chemotherapy for HSA in cats. As with dogs, doxorubicin-based chemotherapy protocols are typically recommended for cats with visceral or subcutaneous HSA.

Other treatments for HSA include immunotherapy, radiation therapy, and angiogenesis inhibitors. The addition of mixed bacterial vaccines or administration of liposomes containing the bacterial cell wall component muramyl tripeptide to doxorubicin-based chemotherapy has been studied. The mixed bacterial vaccine was not very effective, but the liposome encapsulated muramyl tripeptide produced median survival times longer than those reported for surgery alone and surgery plus chemotherapy, suggesting a role for non-specific immunotherapy in dogs with HSA. Unfortunately, the muramyl tripeptide formulation is not commercially available. Radiation therapy may be useful for palliation of superficial tumors and for HSA of bone. However, additional studies are needed to define the role of radiation therapy for the management of HSA. The antiangiogenic effects of the tetracycline antibiotic minocycline have been studied in canine HSA, but unfortunately did not produce useful clinical effects. However, given the vascular nature of this tumor, it is possible that other antiangiogenic agents may be useful for treating HSA in dogs and cats.

The information gained from the diagnostic workup can be compiled and a clinical stage assigned to the HSA patient. However, unlike many cancers, clinical stage for HSA has not been strongly correlated with patient survival. One study suggests that the presence of hemoperitoneum at the time of splenectomy is correlated with shorter survival times. Anatomic location of HSA affects outcome, with cutaneous HSA having the longest reported survival times. There is apparently no difference in survival time between visceral HSA and subcutaneous HSA. Therefore, it is important that veterinarians communicate with their pathologists if there is any suspicion that a dermal HSA extends deep into the hypodermal or subcutaneous tissues.

Reported survival times for dogs with splenic HSA treated with surgery alone range from 19 - 168 days. Death of these patients is rarely from local recurrence, but is most commonly due to the presence of metastatic disease. Doxorubicin-based chemotherapy after surgical intervention for splenic HSA results in reported survival times ranging from 96 - 180 days. The survival time of cutaneous HSA treated with surgery alone is more than 700 days, whereas subcutaneous HSA treated by surgical excision and doxorubicin-based chemotherapy has a reported survival time of approximately 200 days. Incomplete surgical excision of HSA in various non-cutaneous sites followed by single agent doxorubicin chemotherapy, results in survival times of 60 days, which is notably shorter than the 172 day survival time reported when doxorubicin is given after complete surgical excision.

Clearly HSA remains a therapeutic challenge for veterinarians. Prolonged survival for dogs and cats affected by visceral and subcutaneous HSA may come from improved methods for early detection, novel chemotherapy protocols, and effective antiangiogenesis strategies. A thorough evaluation of each patient at the time of diagnosis may identify metastatic disease and help the pet owners with the decision about pursuing aggressive therapy.

**SUGGESTED READING**