Canine Hemangiosarcoma: What's New?

Douglas H. Thamm, VMD, DACVIM (Oncology)
Colorado State University
Fort Collins, CO

Canine hemangiosarcoma (HSA), a malignant tumor of blood vessel endothelial cells, is a relatively common malignancy in dogs compared with other species. In fact, owing to its rareness in humans, we do not have abundant human literature from which to extrapolate when making treatment decisions. Certain breeds (e.g. German shepherds, golden retrievers) appear to be at increased risk for the development of HSA, suggesting a possible genetic predisposition. With few exceptions (i.e. purely cutaneous tumors with no evidence of subcutaneous infiltration), canine HSA is an aggressive neoplasm that tends to meastasize widely and early in the course of disease. Although HSA can occur in many locations, this review will focus on HSA of the spleen, probably the most common presentation.

How might a dog with HSA present?

These tumors are extremely well vascularized and very friable, and thus dogs with visceral forms of HSA will often present with a history of acute weakness or collapse as a result of intra-abdominal hemorrhage. Careful history from the owner may reveal similar episodes of weakness having occurred in the past, only to resolve spontaneously within 24 to 48 hours due to "autotransfusion" of red blood cells from the abdominal cavity back into circulation. Occasionally, a more chronic history of weakness, lethargy and inappetance may be reported, or the patient may be asymptomatic and an abdominal mass or effusion detected on routine physical examination.

How should HSA be diagnosed and staged?

Dogs with HSA may have pale mucous membranes, slow capillary refill, and tachycardia or tachypnea. A cranial abdominal mass or abdominal effusion may be palpable in many cases. A complete blood count (CBC) is essential, as many dogs will have evidence of anemia (regenerative or non-regenerative, depending on the duration) and/or thrombocytopenia. The presence of schistocytes, acanthocytes or target cells is highly suggestive of microangiopathic anemia, which can be seen in cases of HSA, DIC and heartworm disease.

Abdominal radiographs will often reveal loss of detail due to the presence of effusion, and/or a mass effect in the cranial abdomen. Abdominal ultrasound is a superior imaging modality, allowing for the assessment of the internal architecture of the organs (even in the presence of effusion) and evaluation for intra-abdominal metastasis. HSA will often appear as a solitary or multifocal, poorly demarcated nodule of mixed echogenicity, often containing large hypoechoic areas. Thoracic radiographs (3 views) should be obtained to evaluate for evidence of pulmonary metastasis or pericardial effusion (as a result of cardiac involvement). Some practitioners will routinely use echocardiography to screen for occult cardiac metastasis, although this is a relatively infrequent finding at the time of presentation in the author's experience.

Abdominocentesis will often yield a hemorrhagic effusion that fails to clot. Although tumor cells are probably present in the effusion, they are difficult to detect given the relatively large quantity of blood cells usually present. Hemoabdomen is often considered an indication for immediate exploratory laparotomy, however euthanasia will be considered by some owners if evidence of gross metastasis is found by the staging methods outlined above. Needle aspiration cytology of suspect lesions is usually unrewarding, and needle-core (Tru-cut) biopsy may precipitate hemorrhage.

Although a definitive diagnosis is rarely reached prior to surgery, the presence of a cavitated splenic mass in an older dog, combined with appropriate historical and hematological findings, is often highly suggestive of HSA. Other important differential diagnoses for splenic masses include benign processes such as hematoma, regenerative hyperplasia and hemangioma, and other malignancies such as leiomyosarcoma and malignant fibrous histiocytoma (a.k.a. fibrohistiocytic nodules). Studies suggest that approximately 45% of canine splenic masses will be HSA, and this number increases to approximately 70% in dogs with a history of nontraumatic hemoabdomen.

Prior to contemplating surgery, a coagulation profile and crossmatch are useful. Platelet count, prothrombin time, partial thromboplastin time, or fibrin degradation products can be abnormal in some patients. In some studies, as many as 90% of dogs with HSA have had one or more hemostatic alterations. If the above tests are not immediately available, evaluation of a peripheral blood smear to estimate platelet number, combined with buccal mucosal bleeding time and/or activated clotting time, can yield important information as to whether whole blood or blood component therapy is necessary prior to surgery.

How can HSA be treated?

Surgical excision is the first line of defense in treating HSA. Exploratory laparotomy and splenectomy can be performed in most practices. Cardiac arrhythmias can be encountered during splenectomy, and thus careful electrocardiographic monitoring is recommended. The abdomen should be thoroughly evaluated for evidence of metastasis at the time of laparotomy, with special attention paid to the liver and omentum. Peritoneal and omental metastasis can occur as a result of mass rupture and tumor cell

"seeding". Prior to closure, the abdomen should be copiously lavaged with warm saline solution, and instruments changed. The entire excised specimen should be submitted for histopathology.

With the exception of purely cutaneous HSA, the outcome with surgery alone is very disappointing, with median survival times between 1 and 3 months, and less than 10% of dogs surviving longer than one year. Thus, additional systemic therapy should be offered in all cases of splenic HSA. The most effective treatments are chemotherapy protocols containing doxorubicin (DOX). These treatments are generally well tolerated and relatively inexpensive. Following splenectomy with a DOX-containing chemotherapy protocol extends the median survival times to approximately 5-7 months, however 90% of dogs are still likely to succumb to metastasis within 1 year. The prognosis is somewhat better if surgery is performed prior to rupture of the tumor. Treatment of patients with gross metastasis is usually unrewarding, and survival, even with chemotherapy, is usually measured in weeks. A recent study evaluated the outcome of dogs with gross HSA treated with DOX-based chemotherapy. Approximately 40% responded, with a median response duration of 53 days.

There is some recent evidence that dogs with subcutaneous HSA may have a better short- to intermediate-term prognosis than previously thought, although the current recommendation remains to follow surgery with adjuvant chemotherapy for these tumors. A recent large case series of dogs treated with surgery +/- chemotherapy for cardiac HSA was recently reported. These dogs had acceptable perioperative morbidity and had survival times roughly equivalent to those reported for other visceral sites.

Novel treatments and diagnostics

There is obviously considerable room for improvement in the treatment of dogs with HSA. Investigational therapies that have shown promise include the addition of nonspecific immunotherapy (L-MTP-PE) to standard chemotherapy, and the addition of inhaled DOX to systemic chemotherapy. Unfortunately, these are not generally available at the current time.

A recent small study evaluated the efficacy of postoperative therapy with low-dose, continuous (metronomic) chemotherapy and piroxicam in dogs with splenic HSA undergiong splenectomy. The well-tolerated protocol resulted in an outcome roughly the same as what has been reported with DOX-based chemotherapy, and may be a reasonable consideration in dogs with STS where DOX-based chemotherapy is declined or not feasible.

There is an ongoing study evaluating a combination of splenectomy and doxorubicin, followed by "maintenance" therapy with the receptor tyrosine kinase (RTK) inhibitor toceranib (Palladia®, Pfizer). This is based on the observation that canine HSA cells express a number of RTKs that are inhibited by toceranib (KIT, PDGFR, VEGFR2) and that a toceranib-like drug was shown to inhibit canine HSA growth in a nude mouse model. Many other clinicians are offering "maintenance" therapy with metronomic cyclophosphamide plus a NSAID following doxorubicin. Information regarding efficacy of either of these protocols is not currently available.

There remains a need for presurgical tests capable of distinguishing between HSA and benign/other conditions, that may help owners make more informed decisions regarding whether to move forward with surgical therapy. Furthermore, inexpensive screening tests that may lead to earlier diagnosis would likewise be very useful, especially for at-risk populations such as German shepherds and golden retrievers. One recent study demonstrated that MRI may be useful in distinguishing benign versus malignant splenic lesions. 2 recent studies have suggested that cardiac troponin I (cTnI) may be very useful in distinguishing between hemopericardium from HSA and idiopathic hemopericardium; however, this would not be useful for splenic disease. A recent publication utilized a flow cytometry-based technique for the detection of circulating HSA cells in blood, which may prove useful. Most recently, the enzymatic activity of thymidine kinase 1 (TK1), an enzyme important in DNA replication, was shown to be elevated in the majority of dogs with HSA versus normal dogs, and may prove useful as a screening or diagnostic test for dogs with HSA in the future.

References

Bulakowski EJ, Philibert JC, Siegel S, et al. Evaluation of outcome associated with subcutaneous and intramuscular hemangiosarcoma treated with adjuvant doxorubicin in dogs: 21 cases (2001-2006). JAVMA 200;233(1):122-8.

Chun R, Kellihan HB, Henik RA, Stepien RL. Comparison of plasma cardiac troponin I concentrations among dogs with cardiac hemangiosarcoma, noncardiac hemangiosarcoma, other neoplasms, and pericardial effusion of nonhemangiosarcoma origin. JAVMA. 2010;237(7):806-11.

Clifford CA, Pretorius ES, Weisse C, et al. Magnetic resonance imaging of focal splenic and hepatic lesions in the dog. JVIM 2004;18(3):330-8.

Hammer AS, Couto CG, Filppi J, et al.: Efficacy and toxicity of VAC chemotherapy (vincristine, doxorubicin, and cyclophosphamide) in dogs with hemangiosarcoma. JVIM 5: 160-166, 1991.

Lamerato-Kozicki AR, Helm KM, Jubala CM, et al. Canine hemangiosarcoma originates from hematopoietic precursors with potential for endothelial differentiation. Exp Hematol. 2006;34(7):870-8.

Lana S, U'ren L, Plaza S, et al. Continuous low-dose oral chemotherapy for adjuvant therapy of splenic hemangiosarcoma in dogs. JVIM 2007;21(4):764-9.

Ogilvie GK, Powers BE, Mallinckrodt CH, Withrow SJ: Surgery and doxorubicin in dogs with hemangiosarcoma. JVIM 10: 379-384, 1996.

Pintar J, Breitschwerdt EB, Hardie EM, Spaulding KA: Acute nontraumatic hemoabdomen in the dog: a retrospective analysis of 39 cases (1987-2001). JAAHA 39: 518-522, 2003.

Schultheiss PC: A retrospective study of visceral and nonvisceral hemangiosarcoma and hemangiomas in domestic animals. J Vet Diagn Invest 16: 522-526, 2004.

Shaw SP, Rozanski EA, Rush JE. Cardiac troponins I and T in dogs with pericardial effusion. JVIM 2004;18(3):322-4.

Thamm DH, Kamstock DA, Sharp CR, et al. Elevated serum thymidine kinase activity in canine splenic hemangiosarcoma. Vet Comp Oncol, epub ahead of print 2011.
Vail DM, MacEwen EG, Kurzman ID, et al. Liposome-encapsulated muramyl tripeptide phosphatidylethanolamine adjuvant immunotherapy for splenic hemangiosarcoma in the dog: A randomized multi-institutional clinical trial. Clin Cancer Res 1: 1165-1170, 1995.
Ward H, Fox LE, Calderwood-Mays MB, et al.: Cutaneous hemangiosarcoma in 25 dogs: a retrospective study. JVIM 8: 345-348, 1994.
Weisse C, Soares N, Beal MW, et al.: Survival times in dogs with right atrial hemangiosarcoma treated by means of surgical resection with or without adjuvant chemotherapy: 23 cases (1986-2000). JAVMA 226: 575-579, 2005.
Wiley JL, Rook KA, Clifford CA, et al. Efficacy of doxorubicin-based chemotherapy for non-resectable canine subcutaneous haemangiosarcoma. Vet Comp Oncol. 2010 8(3):221-33.
Wood CA, Moore AS, Gliatto JM, et al.: Prognosis for dogs with stage I or II splenic hemangiosarcoma treated by splenectomy alone: 32 cases (1991-1993). JAAHA 34: 417-421, 1998.