

MASSES IN THE SPLEEN: WHAT DOES IT MEAN? HOW TO DIAGNOSE AND TREAT HEMANGIOSARCOMA 2024

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WHAT IS IT: Hemangiosarcoma (HSA) is a highly metastatic, aggressive malignant cancer of transformed vascular endothelial cells. It causes local infiltration and rapid systemic metastasis. Dogs with splenomegaly and splenic masses generally follow the “double two-thirds rule”: Two-thirds have splenic neoplasia, and two-thirds of those have hemangiosarcoma. (One-third do not have cancer!) The likelihood of splenic tumor increases with anemia, nucleated RBC, abnormal RBC morphology, or splenic rupture.

WHAT I SAY: Hemangiosarcoma is malignant cancer of blood vessels that can be anywhere from the skin to internal, and the most common internal sites are spleen, heart, and liver. Hemangiosarcoma is the most common primary canine splenic cancer in dogs, and it is locally aggressive and highly metastatic. Dogs with a ruptured hemoabdomen are more likely to have hemangiosarcoma than those without.

CLINICAL APPEARANCE:

Clinical signs are typically vague, non-specific and include enlarged abdomen, anorexia, lethargy, depression, vomiting, and diarrhea. Clinical signs also vary with how advanced disease is, so dogs may have acute and often dramatic acute signs including collapse and hypovolemic shock. In one study 80% of dogs with acute abdomen and no history of trauma had malignant cancer and 88% were hemangiosarcoma. Splenomegaly is readily detectable through abdominal palpation, radiography and ultrasonography. Hemangiosarcoma most commonly arises in the spleen, right auricle or right atrium, and skin and subcutaneous tissues. For the noncutaneous sites, the median age of presentation is 8 years old, and neutered dogs may be at increased risk.

RISK FACTORS:

A genetic predisposition is strongly suspected. Golden Retrievers have a 1 in 5 lifetime risk. Other overrepresented breeds included German shepherds, Labradors, and other large breed dogs. For the cutaneous form, dermal hemangiosarcoma arises on non-haired skin and is associated with UV light exposure. In contrast, the subcutaneous form arises in haired skin and is not associated with UV light exposure.

DIAGNOSTICS: Noninvasive tests do not confirm hemangiosarcoma, and histopathology is required for a definitive diagnosis.

CBC, chemistry panel and urinalysis: The likelihood of splenic tumor increases with anemia, nucleated RBC, abnormal RBC morphology, or splenic rupture. The anemia may be regenerative with splenic rupture depending on the duration or nonregenerative. Neutrophilic leukocytosis may also be present. Other abnormalities include Howell-Jolly bodies, poikilocytosis, acanthocytosis, schistocytosis and/or thrombocytopenia. Thrombocytopenia is common in 75-97% cases and ranges from mild to severe. A coagulation panel should be run if hemangiosarcoma is suspected. Microangiopathic disease (abnormal blood vessels in the tumor) results in platelet aggregation, RBC morphology changes, and DIC. Hypoproteinemia is also common due to blood loss.

Coagulation testing: Disseminated intravascular coagulation (DIC) may arrive because the formation of abnormal tumor-related vascular channels triggers the coagulation cascade. If a coagulation panel cannot be run prior to surgery to look for prolongation of PT and aPTT, consider a toe clip or BMBT.

Imaging: In my opinion, three-view chest radiographs are mandatory prior to surgery to rule out pulmonary metastasis and pleural fluid. Three-views significantly decreases the false-negative rate. Pulmonary metastasis can appear as an interstitial pattern, which consists of hundreds to thousands of 1-2 mm nodules. Abdominal ultrasound confirms the mass, its organ of origin, likelihood of resectability, defines splenic architecture, and provides detailed evaluation of the abdominal organs and is less affected by abdominal effusion than radiographs. Ultrasound can identify the internal structure of the mass, indicating the feasibility of fine needle aspirate.

FNA and cytology: Fine needle aspirate (FNA) is not recommended for splenic masses of mixed echogenicity and high vascularity suspicious of HSA. These masses are often extremely friable, so there is an increased risk of hemorrhage in addition to the low diagnostic yield due to hemodilution. Hemangiosarcoma effusions are serosanguinous or frank blood and usually do not clot. Unfortunately, fluid analysis and cytology are typically non-diagnostic. But even with ultrasound-guidance, if non-representative tissues are sampled, you may get a false negative of benign or reactive. In one study, only 61% of cases did cytology match histologic diagnoses. FNA is recommended of regional lymph nodes for cases with cutaneous and subcutaneous hemangiosarcoma.

Cardiac evaluation: Since 25 to 45% of dogs with splenic hemangiosarcoma have concurrent right atrial hemangiosarcoma, an echocardiogram is often recommended. In my experience, the incidence is lower at presentation, so I do not routinely recommend an echocardiogram for the workup of a splenic mass. Arrhythmias can occur with benign and malignant lesions. An ECG is recommended at surgery, and post-operatively if arrhythmias are present.

T-STAT: In 2021, an online calculator (T-STAT.net or T-STAT.org) was developed in a study that can be used as an aid to estimate the probability of malignancy in dogs with splenic masses and has potential to facilitate owners' decisions regarding splenectomy. A multivariable model was developed with preoperative clinical data obtained retrospectively from the records of 422 dogs that underwent splenectomy. The final multivariable model contained 8 clinical variables used to estimate splenic malignancy probability: serum total protein concentration, presence (vs absence) of ≥ 2 nRBCs/100 WBCs, ultrasonographically assessed splenic mass diameter, number of liver nodules (0, 1, or ≥ 2), presence (vs absence) of multiple splenic masses or nodules, moderate to marked splenic mass inhomogeneity, moderate to marked abdominal effusion, and mesenteric, omental, or peritoneal nodules. Areas under the receiver operating characteristic curves for the development and validation populations were 0.80 and 0.78, respectively.

The Nu.Q® Vet Cancer Screening Test The Nu.Q® Vet Cancer Screening Test is a simple, low-cost, easy to use ELISA based screening blood test to be used with the **annual wellness check** for older dogs (7 years and older) and can also be a **complementary test** for younger dogs at high risk for developing cancer in their lifetimes such as, Golden Retrievers, Boxers, Flat Coated Retrievers, Beagles, Bernese Mountain dogs, Rottweilers and Shetland Sheepdogs as they age. I hope using the Nu.Q® Vet Cancer Screening Test can help streamline the diagnostic process and shorten the path to diagnosis thereby allowing treatment to be initiated earlier.

In a peer-reviewed and published case series of 662 dogs, the Nu.Q® Vet Cancer Test was shown to detect 76% of systemic cancers; lymphoma (77%), hemangiosarcoma (82%), and histiocytic sarcoma (54%), and was able to identify approximately 50% of all cancers researched at 97% specificity⁴. Lymphoma is the most common form of canine cancer and together with hemangiosarcoma make up approximately one-third of all cancers. Nucleosome levels were consistently low across normal healthy control dogs, and nucleosome levels were elevated in lymphoma and hemangiosarcoma and variable across patients. The Nu.Q® Vet Cancer Screening test also has high specificity and sensitivity in detecting all stages of hemangiosarcoma. Note - elevated levels have been observed in a variety of infectious and inflammatory diseases and are not specific for a particular cancer type. Results should be interpreted in clinical context in combination with history, physical exam and other diagnostic methods.

How can you use Nu.Q® in dog with splenic mass? If there is no hemoabdomen, you can use the test to help distinguish benign vs malignant. If NuQ is elevated, there is an increased likelihood of malignancy. If the NuQ is normal, still a chance that the splenic mass is malignant but less likely.

Prognostic factors: Prognosis for splenic masses cannot be determined without histology which usually requires surgery. A common clinical error is to assume hemangiosarcoma based on the presence of a splenic mass. Large masses are not necessarily malignant. Several splenic lesions have similar ultrasound and gross appearances. Dogs with hemangiosarcoma treated with local therapy and chemotherapy live longer than dogs without treatment and with local therapy only, but 1-year survival rates are still low (10%). Chemotherapy is generally well-tolerated in most dogs, and only a minority develops significant toxicity. Adjunctive chemotherapy improves the median survival time (MST). Stage I, non-ruptured tumors may have an improved prognosis when chemotherapy is administered after surgery. Low grade tumors may also have a better prognosis.

TREATMENT: Treatment for hemangiosarcoma is ideally both local and systemic. Chemotherapy improves the median survival time, but hemangiosarcoma is still a frustrating cancer for owners and veterinarians with shorter survival times than many malignant cancers in dogs. Most dogs tolerate chemotherapy quite well and will maintain a good to excellent quality of life even during chemotherapy.

Surgery: Splenectomy is the treatment of choice for splenic HSA when there is no evidence of metastasis based on staging tests. Even at surgery, it is often impossible to distinguish various diseases based on gross appearance of the spleen or liver – including hematoma, nodular hyperplasia, hemangioma and

hemangiosarcoma. Nodules of ectopic splenic tissue on omentum and regenerative hepatic nodules can be misdiagnosed as metastasis if not biopsied. Splenectomy reduces the tumor burden and prevents future hemorrhagic episodes. Without adjunctive chemotherapy, surgery alone is palliative. Ideally the entire spleen should be submitted fresh on cold packs or in formalin. Biopsy of normal liver is controversial and may not be useful. The abdomen should be thoroughly explored and lavaged and change instruments and gloves. Remove or biopsy any suspicious lesions removed or biopsied. About 25% of dogs develop arrhythmias post-operatively. An ECG should be monitored during and after surgery, and arrhythmias usually resolve within 24-48 hours.

Chemotherapy: The goal of chemotherapy is to delay the metastatic disease that develops quickly after splenectomy. Since chemotherapy improves the median survival time (MST), it is considered part of the standard of care post-operatively. Single agent doxorubicin is the most common, given every 3 weeks for 5 to 6 doses. Chemotherapy is typically started 10-14 days after surgery. For metastatic disease, multi-drug protocols are likely better. New therapies are needed, and the best chemotherapy protocol is not known. A recent 2021 study showed efficacy for carboplatin for dogs with hemangiosarcoma. The median survival time (MST) of dogs receiving carboplatin was 160 days (48 to >559 d) vs 139 days (54 to >975 d) for the dogs that received doxorubicin. The MST was 265 days for dogs whose monocyte counts decreased between surgery and start of chemotherapy, vs. 66 days for dogs with increasing monocyte counts.

Recently low dose oral chemotherapy (metronomic) was comparable to conventional doxorubicin. This protocol included low dose cyclophosphamide, piroxicam and etoposide. Current studies are evaluating whether conventional chemotherapy followed by maintenance metronomic chemotherapy for VEGF-receptor kinase inhibitors such as toceranib will improve outcome. Unfortunately, recent studies show conflicting results about the benefit of a metronomic approach and often use thalidomide, which is a teratogen.

A new drug is currently being evaluated called eBAT, but it is not commercially available. It is an engineered toxin that targets EGFR/uPAR-positive tumor cells. It is currently being investigated at the University of Minnesota and is given after splenectomy. The patients also receive doxorubicin. It appears to be most effective for dogs with minimal residual disease. eBAT is also being studied as a chemopreventative in the Shine ON study for high-risk dogs. Losartan is a common blood pressure medication and is being investigated with a randomized placebo-controlled study at the AMC in NYC. Propranolol is also being investigated but neither are currently standard of care as we are waiting for study results.

Supplements:

Polysaccharopeptide (PSP) mushrooms are Asian mushrooms that are mushroom mixtures of mushroom-derived polysaccharides. The bioactive agent is from mushroom *Coriolus versicolor*, but the brands are proprietary blends. The mechanisms of action (MOA) include increase NK cell activity and cytokines, improved immune function, cause cell cycle arrest, reduction of cell proliferation, and increase apoptosis. Anti-tumor activities have been reported in induced tumors in rodent models and in human colorectal cancers (increased 5-year disease free survival and decreased risk of regional metastasis). In dogs, there was a small double-blind randomized multi-dose pilot study at UPenn of, with no placebo group (Brown, 2012.) Fifteen dogs with splenic hemangiosarcoma underwent splenectomy and did not receive any chemotherapy, only Zun-Zhu PSP (I'm Yunity brand aka cloud mushroom, turkey tail or Yunzhi mushroom). The two highest dose groups had the following median survival times: 50 mg/kg/d; 117 days (4 months), 100 mg/kg/d; 199 days (6.6 months). The MST for splenectomy is 1 to 3 months. Therefore, high-dose PSP delayed progression of metastasis, and these were the longest survival times for HSA without chemotherapy. Additional and larger studies are needed.

Yunnan Baiyao (or Paiyao) is a Chinese herbal mixture of notoginseng from pseudoginseng root. Other ingredients include myrrh, ox bile, Chinese yam, sweet geranium, lesser galangal root, and other antiseptics or astringents. Yunnan Baiyao claims to regulate bleeding and the mechanism of action (MOA) includes hemostatic properties, activates platelets, and decreases bleeding and clotting times. It also comes with a red "hit pill" but the contents are not known. Interestingly, North Vietnamese soldiers would take when seriously wounded, and the Chinese Herbal Patent Formula recommend take for serious wounds or bleeding, "with wine". Yunnan Baiyao is the most popular Chinese herbal formula in veterinary medicine for hemorrhage with a reputation to stop bleeding anywhere in body. It has been shown to decrease clotting times and prothrombin times and initiate platelet release. One recommended dose for hemangiosarcoma: 60-75 mg/kg daily divided or 1/4 tsp. per 10 -15 lbs., divided. (Manual of Natural Veterinary Medicine)

PROGNOSIS: Overall, the prognosis with surgery alone is poor for hemangiosarcoma. Reported MST in dogs treated with surgery alone ranges from 1 to 3 months, and less than 10% of dogs survives 1 year. Adjunctive chemotherapy improves the MST to 6 to 9 months, and doxorubicin-based protocols are the mainstay. Stage I, non-ruptured tumors may have an improved prognosis when chemotherapy is administered after surgery. Low grade tumors may also have a better prognosis.

REFERENCES:

1. Mullin C, Clifford CA. Hemangiosarcoma. In: Small Animal Clinical Oncology. 6th ed. St. Louis Missouri: Elsevier Saunders; 2020: 773-778.
2. Chun R. Hemangiosarcoma. In Clinical Veterinary Advisor Dogs and Cats. 4th edition. St. Louis Missouri: Elsevier Mosby; 2020: 424-427.
3. Schoeman JP. Splenomegaly. In Clinical Veterinary Advisor Dogs and Cats. 2nd edition. St. Louis Missouri: Elsevier Mosby; 2011: web
4. Johnson KD. Splenic Tumors. In Cancer Management in Small Animal Practice. Saunders 2010. 264-268
5. Faulhaber EA, et al. Adjuvant carboplatin for treatment of splenic hemangiosarcoma in dogs: Retrospective evaluation of 18 cases (2011-2016) and comparison with doxorubicin-based chemotherapy. J Vet Intern Med. 2021 Jul;35(4):1929-1934.
6. Burgess KE, et al. Development and validation of a multivariable model and online decision-support calculator to aid in preoperative discrimination of benign from malignant splenic masses in dogs. J Am Vet Med Assoc. 2021 Jun 15;258(12):1362-1371.