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STANDARDS of CARE
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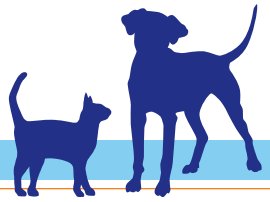

Hemangiosarcoma in Dogs and Cats

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Hemangiosarcoma (HSA) is a malignant tumor of endothelial cells (the basic cells that form blood vessels) and can occur anywhere in the body. It is relatively more common in dogs compared with other species, accounting for 5% to 7% of canine noncutaneous primary malignant neoplasms. In cats, the incidence is only 0.5% to 2%. The most common sites for HSA in dogs are the spleen, right atrium, subcutaneous tissue, and liver; in cats, intraabdominal organs and subcutaneous tissue are common sites.

HSA is highly malignant in most cases, with a metastatic rate of more than 80% at diagnosis. Surgical removal of bleeding masses followed by doxorubicin-based chemotherapy is the current standard of care in dogs, although prognosis is generally poor because of the aggressive nature of this tumor type; most studies report median survival times of around 6 months. In cats, most oncologists recommend surgery followed by chemotherapy; however, published reports to prove efficacy for this approach are lacking. Only superficial cutaneous masses appear to be manageable, with surgery alone providing prolonged survival times. Radiation therapy has been used to manage superficial bleeding masses in a palliative fashion. Immunotherapy has shown promise in some studies, but no commercially available drugs have been tested with controlled clinical trials. Antiangiogenic therapies theoretically have promise, and clinical trials with these drugs should be completed to prove benefit with this modality.

DIAGNOSTIC CRITERIA

Historical Information

Gender Predisposition

- Dogs: Reports vary; there is a possible male predilection for HSA in general and a possible spayed female predilection for atrial HSA.
- Cats: Possible male predilection for cutaneous tumors.

Age Predisposition

- Dogs: Mean age of occurrence, 8 to 13 years.
- Cats: Mean age of occurrence, 8 to 10.5 years.

Breed Predisposition

- Large-breed dogs (German shepherds [Alsatians], golden retrievers, pointers, boxers, Labrador retrievers, English setters, Great Danes, poodles, Siberian huskies): Splenic tumors.
- Lightly pigmented, sparsely haired dogs (beagles, bloodhounds, white bulldogs, English pointers, salukis, Dalmatians, whippets): Cutaneous tumors.
- Domestic shorthaired cats.

Editorial Mission

To provide busy practitioners with concise, peer-reviewed recommendations on current treatment standards drawn from published veterinary medical literature.

Reviewed 2015 for significant advances in medicine since the date of original publication. No revisions have been made to the original text.

KEY TO COSTS

$ *indicates relative costs of any diagnostic and treatment regimens listed.*

Owner Observations

Vary according to tumor site (e.g., space-occupying mass versus a bleeding lesion secondary to rupture or coagulation abnormalities):

- Episodic weakness with recovery.
- Acute collapse or death.
- Distended abdomen.
- General malaise, including depression, anorexia, and weight loss.
- Cutaneous/subcutaneous masses, possibly with active bleeding.
- Active bleeding from sites such as the nose or urinary tract.
- Lameness, paraparesis, or pain.
- Seizures or syncope.

Physical Examination Findings

- Vary according to tumor site and secondary effects, such as hemorrhage secondary to rupture or coagulation abnormalities.
- Palpable abdominal mass and/or abdominal distension; fluid wave may be balloted.
- Hypovolemic shock: Weakness, tachycardia, pale mucous membranes, prolonged capillary refill time, and poor pulse quality.
- Right-sided heart failure: Ascites, muffled heart sounds, and dyspnea.
- Possible auscultable arrhythmia with pulse deficits.
- Petechiation possible with thrombocytopenia and/or disseminated intravascular coagulation.
- Cutaneous/subcutaneous masses, possibly with active bleeding.
- Bony masses or pain.
- Neurologic deficits.

Laboratory Findings

Complete Blood Count $

- Regenerative anemia: Anisocytosis, polychromasia, increased erythrocyte distribution width, and reticulocytosis. Rarely, a nonregenerative anemia is present if the hemorrhage is peracute (duration <2 to 3 days).
- Schistocytes or acanthocytes in the peripheral blood: Common in dogs; not reported in cats.
- Nucleated erythrocytes: Common in dogs; rare in cats.
- Thrombocytopenia: Disseminated intravascular coagulation, sequestration, and consumption.
- Neutrophilic leukocytosis.

Serum Chemistry Profile $

- Serum alkaline phosphatase or alanine transferase elevations secondary to liver infiltration or hypoxia.
- Paraneoplastic hypoglycemia.

Cytology $

- Serosanguineous or bloody effusion on paracentesis: High packed cell volume, usually similar to or higher than peripheral blood packed cell volume; blood does not clot.
- Cytology of effusion is only occasionally suggestive of malignancy (e.g., 25% of pericardial effusions reveal malignancy).

Coagulation Profile $

- Disseminated intravascular coagulation is present in up to 50% of patients: Thrombocytopenia, increased fibrin degradation products, prolongation of activated partial thromboplastin time and/or one-stage prothrombin time, hypofibrinogenemia, decreased antithrombin III, and increased D-dimers.

Other Diagnostic Findings

Radiography $–$$

- Thoracic films may reveal:
  - — Pulmonary nodules consistent with metastatic disease.
  - — Soft tissue mass at heart base.
  - — Changes consistent with pericardial effusion, with or without right-sided heart failure or tamponade (e.g., globoid heart, pleural effusion).
- Abdominal films may reveal:
  - — Evidence of abdominal effusion secondary to hemoabdomen or ascites secondary to right-sided heart failure or tamponade.
  - — Intraabdominal mass, usually originating from the spleen.
- Bone films: Lesions are generally lytic.

Ultrasonography $–$$

- Thoracic/cardiac ultrasonography may reveal:
  - — Hypoechoic pericardial effusion with compression of the right ventricle and/or cardiac tamponade.
  - — Right atrial mass, usually associated with the auricle.
  - — Hypoechoic pleural effusion.
- Abdominal ultrasonography may reveal:
  - — Hypoechoic peritoneal effusion.
  - — Splenic and/or hepatic mass(es).
  - — Usually hypoechoic to inhomogeneous or mixed echogenic cavitary masses.

Electrocardiography $

- Ventricular arrhythmias, especially ventricular premature complex and ventricular tachycardia, may occur after splenectomy or can be secondary to splenic disease and possibly heart infiltration by tumor.
- Electrical alternans secondary to pericardial effusion.
- Decreased complex amplitude secondary to pericardial or pleural effusion.

Histopathology $

- Spindle-shaped, polygonal, or ovoid neoplastic cells that form vascular channels or clefts.
- Usually a high rate of mitosis.
- May require special staining to differentiate from other mesenchymal tumors:
  - — Usually factor VIII–related antigen positive.
  - — CD31 positive.

Summary of Diagnostic Criteria

- Histopathologic examination of tissue is the only way to definitively diagnose HSA and differentiate it from hematoma, hyperplastic nodules, or other neoplasia (benign or malignant). Submission of the entire mass is recommended because HSA often contains hematomas. The spleen should be sliced like a loaf of bread to facilitate fixation; if submission of the entire spleen cannot be done, multiple characteristic sections of the mass can be submitted. All abnormal tissues found at exploratory surgery should be sampled and submitted to confirm (or discount) the presence of neoplasia.
- Suggestive criteria include:
  - — Signalment: Older, large-breed dog.
  - — History of waxing and waning weakness.
  - — Splenic mass.
  - — Characteristic laboratory findings: Regenerative anemia, thrombocytopenia, nucleated erythrocytes.
  - — Cytology of effusions or masses suggesting malignant mesenchymal neoplasia.
- If metastatic pulmonary nodules are present, a presumptive diagnosis of HSA (or other malignancy) can be made.
- Nodules within the liver in conjunction with a splenic mass should *not* be presumed to be metastatic disease because hepatic nodular hyperplasia is very common in older dogs.

Diagnostic Differentials

- Splenic masses should be approached with the "two-thirds rule": Two-thirds of splenic masses are malignant, and two-thirds of the malignant tumors are HSA. *Only histopathologic examination should be used for definitive diagnosis.* Differentials for splenic masses include:
- Other neoplasia (benign or malignant):
  - — Leiomyoma/leiomyosarcoma.
  - — Fibroma/fibrosarcoma.
  - — Malignant fibrous histiocytoma/histiocytic sarcoma.
  - — Undifferentiated sarcoma.
  - — Mesenchymoma.
  - — Lipoma/liposarcoma.
  - — Osteosarcoma.
  - — Lymphoma.
  - — Mast cell tumor.
- Hemangioma.
- Hematoma.
- Nodular hyperplasia.
- Extramedullary hematopoiesis.

TREATMENT RECOMMENDATIONS

Initial Treatment

Stabilization $–$$$

Intravenous crystalloids and/or colloids (including whole blood) may be needed before surgery to stabilize central venous and blood pressure in animals that are hypovolemic because of blood loss.

Surgery $$$–$$$$

Because of the highly metastatic nature of this disease in all sites except superficial cutaneous lesions, surgery can only be considered palliative.

- Splenectomy.
- Partial hepatectomy.
- Pericardiectomy (palliative for pericardial effusions secondary to the tumor).
- Right auricle amputation.
- Amputation.
- Removal of tumors from other sites.

Chemotherapy $$$$

Dogs

- Doxorubicin: 30 mg/m^2 IV q3wk; usually diluted to a concentration of 0.5 mg/ml in saline and given slowly over 15 to 30 minutes. $$
  - — Cyclophosphamide (100–200 mg/m^2 IV q3wk [same day as doxorubicin]) can be added to the protocol; alternatively, the oral form can be given at 50 mg/m^2 on days 3 through 6 after doxorubicin administration. $
  - — Vincristine (0.5–0.75 mg/m^2 IV on weeks 2 and 3) can also be added to the protocol; however, the doxorubicin–vincristine combination using the high-end vincristine dosage (0.75 mg/m^2) resulted in hospitalization of approximately 50% of patients. $
- The protocol should be repeated for four to six cycles or until the disease progresses. $$$$
- Some oncologists recommend premedicating with an antiemetic and 0.1 mg/kg dexamethasone and/or 2.2 mg/kg diphenhydramine IM 20 minutes before doxorubicin administration.
- Many oncologists decrease the dose of doxorubicin to 1 mg/kg in dogs weighing less than 10 kg.
- Decreasing the dosage interval to every 2 weeks has not been shown to increase survival times.
- Doxorubicin must be given through a well-placed "first-stick" IV catheter to prevent tissue damage secondary to extravasation.

Cats

- While the following protocol has been recommended for cats with HSA, no controlled studies have been performed. I premedicate with an antiemetic and dexamethasone and use a combination of doxorubicin (20 mg/m^2 IV) and cyclophosphamide (100 mg/m^2 PO or IV) administered on the same day.
- Doxorubicin: 20–30 mg/m^2 or 1 mg/kg IV q3wk; usually diluted to a concentration of 0.5 mg/ml in saline and given slowly over 15 to 30 minutes. $$
  - — Cyclophosphamide (100–200 mg/m^2 IV q3wk [same day as doxorubicin]) can be added to the protocol; alternatively, the oral form can be given at 50 mg/m^2 on days 3 through 5 after doxorubicin administration. $
  - — Vincristine (0.5–0.75 mg/m^2 IV on weeks 2 and 3) can also be added to the protocol; however, the doxorubicin–

vincristine combination using the high-end vincristine dosage (0.75 mg/m^2) resulted in hospitalization of approximately 50% of canine patients. The cat response is unknown.

- The protocol should be repeated for four to six cycles or until the disease progresses. **$$$$**
- Some oncologists recommend premedicating with an antiemetic and 0.1 mg/kg dexamethasone and/or 2.2 mg/kg diphenhydramine 20 minutes before doxorubicin administration.
- Doxorubicin must be given through a well-placed "first-stick" IV catheter to prevent tissue damage secondary to extravasation.
- Cats are more likely to develop anorexia after doxorubicin therapy than are dogs. Most oncologists use the a doxorubicin dosage of 20 to 25 mg/m^2 in an attempt to moderate this effect.

Alternative/Optional Treatments/Therapy

Palliative Radiation Therapy $$$–$$$$

Radiation therapy can be used to treat actively bleeding superficial masses and to decrease pain associated with bony lesions. It is usually given once weekly for three to five treatments.

Immunotherapy $–$$

When added to doxorubicin–cyclophosphamide combinations after splenectomy, liposome-encapsulated muramyl tripeptide phosphatidylethanolamine (L-MTP-PE) has been shown to increase survival times to a median of 273 days. However, this drug is not commercially available at this time.

Antiangiogenic Therapy $–$$$

Tumors require the development of a vascular supply to grow larger than 1 mm^3, and thus antiangiogenic protocols would appear to be a viable target for antitumor therapy. Most researchers believe that these drugs will be used in conjunction with standard therapy and will work best in the microscopic setting. They will likely be needed for the patient's lifetime. Minocycline (a purported antiangiogenic antibiotic) used in addition to doxorubicin-based chemotherapy was not shown to statistically increase survival times for dogs with surgically excised splenic HSA. The ideal antiangiogenic dose has not been defined. Some practitioners have proposed the use of metronomic (low, continuous dose) chemotherapy for potential antiangiogenic effects. Controlled clinical trials have not been performed, and there is some suggestion that drug resistance mechanisms may be upregulated by some drugs (e.g., doxycycline) in these protocols.

Nutritional Therapy $–$$

Some practitioners have proposed the use of a high-fat, moderate-protein, low-carbohydrate diet with high n-3 fatty-acid supplementation as a method to combat cancer cachexia (metabolic changes found with the presence of cancer) and possibly improve responses to treatment and survival times.

CLINICAL STAGING SYSTEM FOR CANINE HEMANGIOSARCOMA

Primary Tumor (T)
T0: No tumor evident
T1: Tumor diameter <5 cm, confined to single organ, and/or no invasion beyond dermis (cutaneous HSA)
T2: Tumor diameter ≥5 cm, ruptured, or invades into subcutaneous tissues (cutaneous HSA)
T3: Tumor invades adjacent structures

Local Lymph Nodes (N)
N0: No nodal involvement
N1: Regional node involvement
N2: Distant node involvement

Metastasis (M)
M0: No distant metastasis found
M1: Distant metastasis found

Staging
Stage I: T0 or T1, N0, M0
Stage II: T1 or T2, N0 or N1, M0
Stage III: T2 or T3, N0, N1, or N2, M1

Supportive Treatment

- Fluid support may be necessary to maintain blood volume in patients with actively bleeding lesions.
- Pain control may be indicated, depending on tumor site and clinical signs:
  - — NSAIDs (e.g., deracoxib, carprofen) are usually used for mild to moderate pain; however, NSAIDs can decrease platelet function, which may be a concern in patients with coagulopathies, and can cause gastric ulceration, which is a consideration in patients with regenerative anemia.
  - — Opiates (e.g., codeine, hydrocodone, butorphanol, tramadol, fentanyl patch, buprenorphine) are usually used for moderate to severe pain.
  - — Combinations of NSAIDs and opiates may be more effective than either class of drug alone.

Patient Monitoring

Initial and Perioperative

- Central venous and blood pressures should be monitored to determine the need for fluid support before and during surgery.
- Electrocardiography should be performed to monitor for the need to treat ventricular arrhythmias before, during, and after splenic surgery.

Long Term

- For patients undergoing chemotherapy, complete blood counts should be performed before and 7 days after each treatment to monitor for neutropenia.
  - — Patients with an incidental neutrophil count of less than 1,000 cells/µl (no clinical signs of illness) should be given oral broad-spectrum antibiotics for 5 to 7 days.

— Patients that are ill should be hospitalized and given supportive care, including IV fluids, IV broad-spectrum antibiotics, antiemetics, and the like. Most recover within 2 to 5 days.
- Renal function assessment, including serum blood urea nitrogen and creatinine and urine specific gravity, should be performed before each doxorubicin treatment in cats.
- Some clinicians advocate electrocardiography in dogs before each doxorubicin treatment to monitor for the development of doxorubicin-induced arrhythmias.
- Periodic (every 2 to 3 months) thoracic radiography with or without abdominal and/or thoracic or cardiac ultrasonography may be used to monitor:
  — Treatment response if gross disease is present.
  — Tumor recurrence or metastasis.
  — Decreased cardiac contractility, which might indicate doxorubicin cardiac toxicity; however, endomyocardial biopsy is the only definitive way to diagnose toxicity.
- For cutaneous masses, monthly monitoring by the owner for any new masses coupled with quarterly veterinary professional examinations can be used to detect recurrence, metastasis, or the development of new lesions in predisposed areas.

Home Management

- Dogs should be restricted from strenuous activity for 7 to 14 days after surgery to allow time for the wound to heal.
- Owners of patients undergoing chemotherapy should observe proper safety precautions when handling drugs or body fluids:
  — Wear latex gloves when handling drugs.
  — Children and pregnant women should not handle chemotherapeutics at all.
  — Return used pill vials to the clinic for proper disposal.
  — Use diluted bleach and wear gloves to clean up all urine or feces within 48 hours after drug administration, including waste in litterboxes. If dogs are allowed to eliminate outside, they should be taken to a low-traffic area that is exposed to sunlight.
- Owners of patients undergoing chemotherapy should contact their veterinarian if any indication of neutropenia or sepsis (e.g., weakness, anorexia, vomiting, diarrhea, collapse) develops or if the animal is not acting normally; a complete blood count should be performed.
- Owners of patients receiving doxorubicin should report signs that indicate the development of cardiac toxicity (arrhythmias or failure), including syncope, exercise intolerance or weakness, coughing, or ascites.
- Owners of patients receiving cyclophosphamide as a component of the chemotherapy protocol should report signs of hemorrhagic cystitis, such as hematuria (discolored urine), pollakiuria (increased frequency of urination), or dysuria (difficulty urinating/straining to urinate).
- Owners of patients receiving vincristine as a component of the chemotherapy protocol should report signs of peripheral neuropathy, such as generalized weakness or constipation.
- Owners should contact their veterinarian if their pet develops such clinical signs as weakness, collapse, difficulty breathing, or any other abnormality that may indicate tumor progression.

Milestones/Recovery Time Frames

- With splenectomy alone, median survival time after surgery is 19 to 86 days.
- With splenectomy and chemotherapy, median survival time is 141 to 179 days.
- With right auricle amputation, median survival time is 42 to 120 days. The addition of chemotherapy may increase survival times (median, 175 days).
- With surgical excision of cutaneous/dermal tumors, median survival time is 780 days.
- With surgical removal of primary tumor from other sites, survival is rarely longer than 6 months. Although chemotherapy is usually recommended, its role in the treatment of tumors located at such sites is undefined.

Treatment Contraindications

- No chemotherapeutic agent should be administered if the patient's neutrophil count is below 2,500 cells/ml.
- In general, dogs with cardiac disease and decreased cardiac function as measured by fractional shortening should not receive doxorubicin. The addition of dexrazoxane (300 mg/m^2 IV given 20 minutes before doxorubicin) may prevent cardiac toxicity. Mitoxantrone (5–6 mg/m^2 IV q3wk) could potentially be substituted, but many clinicians believe that this drug is not as effective as doxorubicin. In patients with a highly malignant neoplasm such as HSA, the use of doxorubicin in the face of cardiac disease may still be justified in some clinical cases.
- Doxorubicin should be used with caution or not at all in cats with confirmed renal insufficiency or failure (azotemia with a paired urine specific gravity <1.035). In patients with a highly malignant neoplasm such as HSA, the use of doxorubicin in the face of renal disease may still be justified in some clinical cases.

PROGNOSIS

Favorable Criteria

- Tumors confined to the dermis/epidermis.
- Stage I disease.

Unfavorable Criteria

- Stage II or III disease.
- Presence of gross metastasis at diagnosis.

RECOMMENDED READING

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