Hemangiosarcoma and Immunotherapy, an Update

ISU-IVS Partners in Progress; April 3, 2019

Meg Musser, DVM, DACVIM (Oncology)
Assistant Professor, Iowa State University
Outline

• Incidence and Risk Factors
  – Splenic
  – Dermal/SQ

• Biological Behavior
  – Diagnosis, Differentials, and Staging

• Treatment
  • Surgery
  • Chemotherapy
  • Immunotherapy
    – I’m Yunity
    – Yunnan Baiyao
    – Immunocidin
Hemangiosarcoma (HSA)

- Aggressive vascular endothelial cell tumor

- Dogs
  - 5-7% of non-cutaneous primary malignant neoplasms
  - 12-21% of mesenchymal neoplasms
  - 45-51% of splenic malignancies
  - 2/3, 2/3 rule

- 2.3-3.6% of skin tumors
Typical Signalment

• Middle aged to older
  – Dogs: 8-13

• Common Breeds
  – German Shepard Dogs
  – Golden Retrievers
  – Labrador Retrievers
  – Large Breed Dogs
  – Lightly pigmented breeds
Etiology

• Cutaneous
  – UV light
  – Radiation Therapy

Etiology

• Cutaneous
  – UV light
  – Radiation Therapy

• Visceral
  – Ionizing radiation pre or postnatally
  – Genetic Predisposition
Etiology

- Cutaneous
  - UV light
  - Radiation Therapy
- Visceral
  - Ionizing radiation pre or postnatally
  - Genetic Predisposition
- Humans
  - Vinyl chloride, thorium dioxide, arsenicals, and androgens
  - HHV8 infection - Kaposi’s sarcoma
Primary Sites of Disease in the Dog

- Spleen (50-65%)
- Right Atrium (3-25%)
- Skin, Subcutis, Muscle (13-17%)
- Liver (5-6%)
- Kidney (0.01%)
- Rarely, lung, oral cavity, bone, retroperitoneum, urinary bladder, ocular, left ventricle, and uterus
Metastasis of Visceral HSA in Dogs

• Overt metastasis in 80% at presentation
  – 25% to heart
  – 14% to brain
  – Liver, lungs, omentum and mesentery

• Metastasis of cutaneous HSA is rare

Images Courtesy: Withrow and MacEwen, 4th Ed.
Differentials
Differentials

- Hematoma
Differentials

- Hematoma
- Hemangioma

Image Courtesy: Dr. Julius Liptak
Differentials

• Hematoma
• Hemangioma
• Sarcomas
Differentials

- Hematoma
- Hemangioma
- Sarcomas
- Other tumors
Differentials

• Hematoma
• Hemangioma
• Sarcomas
• Other tumors
• Extramedullary hematopoiesis (rarely)
Clinical Signs

- Weakness and collapse
- Signs associated with hypovolemia:
  - Tachycardia
  - Tachypnea
  - Mucous membrane pallor
- Abdominal distention
- Weight loss
- Signs of right heart failure
- Seizures
- Lameness

Diagnostics and Staging

• CBC/Chem/UA
  – Regenerative anemia
  – Neutrophilic leukocytosis
  – Thrombocytopenia (75-97%)
  – Schistocytes
  – Acanthocytes: 50%
  – Hypoglycemia

Image Courtesy: Cornell University ECLINPATH
Diagnostics and Staging

• Coagulation Profile
  – Elevations in PT/PTT
  – Decreases in fibrinogen and antithrombin III, and elevations in fibrin degradation products

• 50% have coagulation abnormalities meeting criteria for DIC
Diagnostics and Staging

- Three-view thoracic radiographs
- Abdominal Ultrasound
- Echocardiogram
- EKG
  - Nonlethal ventricular arrhythmias
    - VPCs
    - Ventricular tachycardia

Image Courtesy: https://www.cliniciansbrief.com/article/top-5-arrhythmias-dogs-cats
Diagnostics and Staging

• Fluid Analysis
  – Hemorrhagic, non-clotting, 25% contain sarcoma cells - rarely diagnostic

• Histopathology is needed for definitive diagnosis

Images Courtesy: Noah's Arkive, University of Georgia
Clinical Staging (where is it?)

• **Primary Tumor (T)**
  – T0: No evidence of tumor
  – T1: <5cm and confined
  – T2: 5cm or greater/ruptured; invading SQ
  – T3: Invading adjacent structures

• **Regional Lymph Nodes (N)**
  – N0: No lymph nodes
  – N1: Regional lymph node involvement
  – N2: Distant lymph node involvement

• **Distant Metastasis (M)**
  – M0: No evidence of distant metastasis
  – M1: Distant metastasis
Clinical Staging (where is it?)

- **Stages**
  - I: T0/T1, N0, M0 - Unruptured, confined to the spleen
  - II: T1/T2, N0 or N1, M0 - Tumor rupture, no gross metastatic disease
  - III: T2/T3, N0, N1, or N3, M1 - Gross metastatic disease

- **Surgery Alone**
  - Stage I ST: 5.5 mo
  - Stage II/III ST: 2mo/1mo

- **Surgery and Doxorubicin**
  - Stage I ST: 9 mo
  - Stage II/III ST: 4mo/1mo

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Treatment

• Surgery
  – Chemotherapy
  – Immunotherapy
    • I’m Yunity
    • Yunnan Baiyao
    • Immunocidin

Image Courtesy: http://7-themes.com/6914363-german-shepherd-in-snow.html
Surgery - Gross Pathology

- Solitary
- Multifocal
- Disseminated
- Pale grey to dark red/purple
- Soft, gelatinous, blood filled, necrotic
- Nonencapsulated
- Friable
# Grading

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Criterion</th>
<th>Score</th>
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<tbody>
<tr>
<td>Tumor differentiation</td>
<td>Well differentiated (well formed); numerous irregular vascular channels predominate in all fields</td>
<td>1</td>
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<tr>
<td></td>
<td>Moderately well differentiated; ≥ 50% of the tumor has well-defined vascular channels</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Poorly differentiated; most of the tumor is solid sheets of spindle cells with few vascular channels</td>
<td>3</td>
</tr>
<tr>
<td>Nuclear pleomorphism</td>
<td>No difference in nuclear size and shape</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Minimal variation</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Moderate variation (2X size difference)</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Marked variation (&gt; 2X size difference)</td>
<td>3</td>
</tr>
<tr>
<td>Tumor necrosis*</td>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>&lt; 25%</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>25–50%</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>&gt; 50%</td>
<td>3</td>
</tr>
<tr>
<td>Mitoses (No./10 hpf)†</td>
<td>&lt; 11</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>11–20</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>21–30</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>&gt; 30</td>
<td>3</td>
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</table>

*Areas of hematoma were excluded from these determinations. †Pathologists were instructed to scan for the area of the section with the highest mitotic activity and count 10 adjacent fields in that area, omitting regions of hemorrhage or necrosis. All histologic scores were summed to determine an overall histologic score for the tumor (grade 1 = 1 to 5; grade 2 = 6 to 9; and grade 3 = 9 to 12).
Grading Impact on Patients with Stage II HSA

<table>
<thead>
<tr>
<th>Variable</th>
<th>Category</th>
<th>No. of dogs</th>
<th>MST (d)</th>
<th>P value</th>
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<tbody>
<tr>
<td>Tumor differentiation score</td>
<td>1</td>
<td>7</td>
<td>336</td>
<td>0.014</td>
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<tr>
<td></td>
<td>2</td>
<td>16</td>
<td>158</td>
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<tr>
<td></td>
<td>3</td>
<td>5</td>
<td>116</td>
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<tr>
<td>Nuclear pleomorphism score</td>
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<td>137</td>
<td>0.765</td>
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<tr>
<td></td>
<td>1</td>
<td>3</td>
<td>132</td>
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<td></td>
<td>2</td>
<td>17</td>
<td>217</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>7</td>
<td>116</td>
<td></td>
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<tr>
<td>Tumor necrosis score</td>
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<td>3</td>
<td>—</td>
<td>0.549</td>
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<tr>
<td></td>
<td>1</td>
<td>19</td>
<td>132</td>
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</tr>
<tr>
<td></td>
<td>2</td>
<td>3</td>
<td>145</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>3</td>
<td>228</td>
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<tr>
<td>Mitotic score</td>
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<td>292</td>
<td>0.002</td>
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<td>2</td>
<td>7</td>
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</tr>
<tr>
<td></td>
<td>3</td>
<td>5</td>
<td>116</td>
<td></td>
</tr>
<tr>
<td>Overall histologic grade</td>
<td>1</td>
<td>9</td>
<td>336</td>
<td>0.018</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>16</td>
<td>145</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>3</td>
<td>116</td>
<td></td>
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</tbody>
</table>

MI Impact on Patients with Stage II HSA

- MST for MI < 11/10 HPF: 9.7 mo
- MST for MI 11-20/10 HPF: 7 mo
- MST for MI 21-30/10 HPF: 4 mo
- MST for MI > 30/10 HPF: 4 mo

Why does this information matter?

• Standard of care
  – Splenectomy
    • ST: 1-3 months
  – Chemotherapy
    • Single-agent *doxorubicin*
    • Combination doxorubicin, vincristine, cyclophosphamide
    • ST: 6 months
Stage I/II vs III Patients Treated with Combination Chemotherapy

- 67 dogs
  - Splenectomy and chemotherapy (vincristine, doxorubicin, cyclophosphamide)

- Overall response rate: 86%

- MST stage I/II: 6.3 months
- MST stage III: 6.5 months

- DON’T DENY TREATMENT BASED ON STAGE

How do we improve survival time?

- Maintenance chemotherapy?
- Immunotherapy?
Maintenance Chemotherapy - Low-dose Chemotherapy

- Low-dose/metronomic chemotherapy
  - Alter tumor microenvironment
  - Inhibit tumor angiogenesis
  - Module immune cells
  - Reduce efficacy of T-regulatory cells

- No improvement in OST
  - IV chemotherapy alone: 6 mo
  - IV chemotherapy and metronomic: 7 mo

Maintenance Chemotherapy - Palladia

- Small molecule inhibitor
  - KIT
  - PDGFR
  - VEGFR

- Canine HSA cell lines express
  - KIT
  - PDGFR
  - VEGFR

Maintenance Chemotherapy - Palladia

- 43 dogs (stage I or II)
  - Splenectomy, doxorubicin
  - Palladia (if free of gross disease)

- MST: 5.7 months

- No impact on ST
Immunotherapy?

• L-MTP-PE\(^1\)
  – Survival advantage (MST 9 months)

• Novel tumor DNA vaccine\(^2\)
  – Survival advantage (MST 6 months compared to historical controls of 4 months)

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Immunotherapy - I’m Yunity

- Product containing *Coriolus versicolor*

- Polysaccharides
  - Immunomodulatory
  - Inhibit tumor cell growth
  - Free radical scavenger

- ST: 6 months

Immunotherapy - Yunnan Baiyao

- Anti-inflammatory
- Hemostatic
- Wound healing
- *In vitro*
  - Dose and time dependent HSA cell death via apoptosis

Immunotherapy - Yunnan Baiyao

- Anti-inflammatory
- Hemostatic
- Wound healing

*In vivo*
- Administration prolongs DFI

Immunotherapy - Immunocidin

• Mycobacterial cell wall fraction (MCWF) from *Mycobacterium phlei*

  – Non-pathogenic, gram-positive, ubiquitous bacteria

  – *M. phlei* cell wall with bacterial DNA and RNA

  – MCWF contains *mycolic acid* and *muramyl dipeptide* which activate the immune system
Immunotherapy - Immunocidin

- Biological Modulator
- Induces cytokine production
- Induces apoptosis

Slide courtesy of Dr. Jeannette Kelly, DVM, DACVIM (Oncology)
Immunotherapy - Immunocidin

- Humans with bladder cancer
- USDA-approved for intratumoral treatment of canine mammary tumors
Immunotherapy - Immunocidin

- Recent study looking at IV administration
- Variety of tumor types
  - 4 dogs with HSA
  - Average ST: 7 mo
  - Few AEs
Immunotherapy - Immunocidin

- ISU clinical trial evaluating the impact of Immunocidin + doxorubicin for HSA launched in March, 2019

Immunotherapy - Immunocidin

Inclusion Criteria
i. Dogs with histopathologically confirmed stage I or stage II splenic hemangiosarcoma (HSA) that have undergone splenectomy;
ii. Surgical biopsy of the liver, lymph nodes, and mesentery not required unless there is a clinical suspicion of metastatic disease at surgery.
iii. Dogs must have an ECOG performance score of 0-1

Exclusion Criteria
i. Dogs with any serious systemic disorder (e.g., clinically significant cardiac disease or renal disease that would preclude the use of doxorubicin)
ii. Dogs with concurrent malignancies other than HSA
iii. Dogs with evidence of metastatic disease on diagnostic imaging or intraoperatively
iv. Dogs that have received chemotherapy prior to enrollment
v. Dogs that have received steroids or immunotherapy (including Cytopoint and Apoquel) for any reason within 4 weeks prior to enrollment.
Immunotherapy - Immunocidin

• Currently enrolling!
• Contact the oncology department with any questions
  – Meg Musser, DVM, DACVIM (oncology)
  – Chad Johannes, DVM, DACVIM (oncology)
  – Giovanna Coto, DVM

Phone: 515-294-4900; https://vetmed.iastate.edu/vmc/clinical
# Prognosis

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Treatment</td>
<td>Less than 1 month</td>
</tr>
<tr>
<td>Splenectomy</td>
<td>1 - 3 months</td>
</tr>
<tr>
<td>Splenectomy + Doxorubicin</td>
<td>4.7 - 6 months</td>
</tr>
<tr>
<td>Splenectomy + I’m Yunity</td>
<td>4 - 6.6 months</td>
</tr>
<tr>
<td>Splenectomy, Doxorubicin + Immunocidin</td>
<td>?</td>
</tr>
</tbody>
</table>
Questions?

The Hixson-Lied Small Animal Hospital

Email: mmusser@iastate.edu