Canine Hemangiosarcoma: Current Concepts

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HSA Basics:
- Highly malignant
- Originates from vascular endothelial cells
- Dogs vs. other species
  - 2% of all canine tumors
- Older, larger breed (GS, GR)
- High fatality rate

HSA: Etiology
- Unknown
- Genetic predisposition
- Chronic UV (skin, conjunctiva)
- In humans:
  - Various chemicals → visceral form
  - UV or previous RT → cutaneous form

HSA - Oncogenesis
- Multiple steps
- Activating mutations of oncogenes
  - STAT3: 22 HSA overexpressed
  - Cox-2: 19/19 Negative
- Inactivating mutations of TSG
  - p53 and PTEN: recently identified

HSA - Angiogenesis
- Tightly controlled process
- New blood vessel formation
- Pro-angiogenic factors:
  - VEGF inc in plasma/effusions
  - Overexpress angiopoietins
- Antiangiogenic factors:
  - Endostatin ↑ in serum

Angiogenesis
- HSA cells in vitro:
  - Produce numerous pro-angiogenic factors
    - VEGF and bFGF
- Antiangiogenic therapy with IL-12 in vivo.
HSA- Biologic behavior

- Primary sites
  - Most common: spleen, heart, skin/SQ, liver
  - Others: bone, kidney, muscle, oral, lung, etc.
- Disseminates early
  - Hematogenous
  - Seeding on serosa

Prognosis

- Dermal and conjunctival HSA
  - Prolonged UV exposure
  - Lower metastatic rate
  - Better prognosis

- Splenic and cutaneous HSA
  - Higher clinical stage = shorter survival
  - Difficult to determine primary

Splenic HSA

- Spangler & Kass, JVIM, 1997
  - 500 spleens
  - 51% non-neoplastic disease
  - 48% neoplastic disease with 51% being HSA

- Eberle et al. Tierarztl Prax, 2012
  - 249 spleens
  - 47% non-malignant disease
  - 53% malignant disease with 74% being HSA

Diagnosis & Staging

- Complete clinical staging
  - Highly metastatic and stage impacts Prognosis
  - Perform if patient stable
  - Delay in critical patient

Diagnosis & Staging

- Complete blood cell count
  - Anemia (regenerative)
  - Thrombocytopenia
  - Neutrophilic leukocytosis
  - Abnormal red cell morphology

Serum Chemistry & U/A

- Often normal
  - Abnormalities reflect specific organ involvement
Diagnosis & Staging

- Three-view thoracic radiographs

Abdominal ultrasound

- Echocardiography

Coagulation profile
  - PT, PTT, FDP, fibrinogen, d-dimers
  - R/O DIC
  - ECG, telemetry
  - Watch for arrhythmias

Advanced Imaging

Advanced Imaging for Splenic/Hepatic HSA
Diagnosis & Staging

- Cytopathology
  - Poor exfoliation
  - Not recommended (hemorrhage potential)
  - Effusion cytology:
    - 25% diagnosis

Histopathology

- For definitive diagnosis
- Characterized as:
  - Malignant spindle cells forming irregular blood-filled cavities
- For less differentiated samples:
  - Factor VIII related antigen (vWF)
  - CD31
  - Vimentin
  - C-kit

Diagnosis & staging

- Histopathology
  - For definitive diagnosis – not on U/S probes!

Flow cytometry

- Cell surface markers
  - Early detection?
  - Better Prognosis?
  - Thymidine Kinase
    - Increased in neoplastic effusion
  - Cardiac troponins
    - Increased HSA vs. NonHSA pericardial effusion

Hemangiosarcoma vs. Hemangioma

- Clinical signs
  - Hemoabdomen more common in HSA
    - 63%-76% of dogs with HSA
    - 24%-30% of dogs with hemangioma
  - Abdominoacentesis
    - ↓ glucose concentrations (73 mg/dL v. 110 mg/dL)
    - ↑ lactate concentrations (3.7 mmol/L v. 1.7 mmol/L)

Therapeutic Options

- Surgery alone:
  - Removes primary tumor
  - Prevents fatal hemorrhage
  - Considered palliative
    - Does not prolong survival!
  - Survival: 19 - 65 days
  - Better Prognosis for dermal
Treatment – Liver Biopsy

- Clendaniel et al, JAAHA, 2014

  - 50% of dogs with grossly abnormal livers had metastasis
  - 0% of dogs with grossly normal livers had metastasis
  - Hepatic metastases more likely in dogs with
    - Multiple nodules
    - Dark-coloured nodules
    - Actively bleeding nodules

Hemangiosarcoma vs. Hemangioma

- Mallinckrodt & Gottfried, JAVMA, 2011

  - 65 dogs treated with splenectomy
    - 30 dogs with HSA
    - 10 dogs with non-HSA malignancies
    - 25 dogs with benign disease
  - Benign splenic masses had significantly greater
    - Mass-to-splenic volume ratio
    - Splenic weight as a percentage of body weight

Splenectomy – Hemangioma

Splenectomy – HSA

Splenectomy – Metastasis
**Traditional Tx**
- Surgery alone for visceral, cardiac, or SQ/IM
  - Palliative only, MST 1-3 months
  - Pericardectomy can be palliative
  - Better Px with dermal or conjunctival

**Adjuvant Tx**
- Adjuvant chemotherapy
  - Dox-based (A, AC, VAC, Doxil ...)
  - Improves ST to 6-7 months
  - Did not help more than doxorubicin:
    - Intracavitary Doxil, dox + minocycline, doxorubicin + COX-2 inhibitor, dox q2w, dox + ifosfamide,

**Chemotherapy Protocols**

<table>
<thead>
<tr>
<th>Treatment</th>
<th># dogs</th>
<th>Survival (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sx alone</td>
<td>131</td>
<td>19-86</td>
</tr>
<tr>
<td>Sx + A</td>
<td>46</td>
<td>Between 60 &amp; 172</td>
</tr>
<tr>
<td>Sx + AC</td>
<td>32</td>
<td>141-202</td>
</tr>
<tr>
<td>Sx + AC + minocycline</td>
<td>17</td>
<td>170</td>
</tr>
<tr>
<td>Sx + VAC</td>
<td>15</td>
<td>172</td>
</tr>
<tr>
<td>Sx + A (q 2 wk)</td>
<td>18</td>
<td>I: 257; II: 210; III: 107</td>
</tr>
<tr>
<td>Sx + Ifosfamide</td>
<td>6</td>
<td>147</td>
</tr>
<tr>
<td>Sx + Ifosfamide/A</td>
<td>27</td>
<td>149</td>
</tr>
</tbody>
</table>

A- Adriamycin; C- Cytoxan; V- Vincristine

**Prognosis – Hemangiosarcoma Splenic**
- Surgery alone
  - MST 19-86 days
  - 6%-7% 1-year survival rates
- Surgery and chemotherapy
  - MST 133-182 days
- Surgery and metronomic chemo
  - MST 178 days

**Prognosis – Hemangiosarcoma Splenic**
- Surgery and chemotherapy
  - Stage (Kim et al, JAVMA, 2007)
    - MST 345 days for stage I HAS
  - Residual disease (Ogilvie et al, JVIM, 1996)
    - No – MST 172 days and 80% 1-year survival rate
    - Yes – MST 60 days and 0% 1-year survival rate

**Prognosis – Hemangiosarcoma Splenic**
- Stage I HSA - MST 257-345 days
Prognosis – Hemangiosarcoma

**Splenetic**

- **Stage II HSA** - MST 93-210 days
  
  Alvarex et al, JAAHA 2013
  - No survival difference: Stage II vs III
  - Kahn et al Can Vet J 2013 (Deracoxib+Adria)
    - Overall MST 150 days (range: 21 to 1506 days)
    - Stage II (n=11) MST of 149 days

SQ/IM HSA

- Bulakowski et al. 2008 JAVMA
  - Sx + adriamycin (n=21)
    - SQ: MST 1,189 d
    - IM: MST 272d
  - Kai-Biu Shiu et al. 2011 JAVMA
    - Sx + adriamycin n=71
    - Overall MST 172 d

Alternative Tx

- SQ/IM HSA
  - Radiation therapy
    - MST ~100 days
    - May help to palliate SQ/IM HSA

Cardiac Hemangiosarcoma

- Right atrium most commonly involved
- Breed predisposition
  - German Shepherd Dogs
  - Poodles
  - Golden Retriever

What about Cardiac HSA?

- Aronsohn, JAVMA 1985; CHSA (sx alone)
  - n = 9 dogs with right auricular HSA
  - 6 completely excised; n = 3 incompletely excised
  - Mean survival time = 4 months (2 days – 8 months)

- Ogilve et al, JVIM 1996; HSA (n = 46; sx + doxorubicin)
  - n = 5 right auricular HSA, all completely excised
  - MST 172d (all HSA sites)

- Weisse et al, JAVMA 2005; CHSA (sx+pericardectomy +/- adjuvant chemotherapy)
  - n = 23 dogs; n = 8 received doxorubicin-based chemo
  - MST 42d vs. 175d
  - No large study evaluated chemotherapy alone
Prognosis – Cardiac Hemangiosarcoma

- Pericardectomy
  - MST 16 days
- Right atrial resection
  - MST 42-124 days
- Surgery + chemo
  - MST 175 days
- Chemotherapy alone
  - MST 116 days

Problems

- High metastatic rate
  - 20% of dogs are alive > 1yr

Novel Therapy

- Novel therapies may increase survival time
- Finding molecular targets is crucial

Tumors and Angiogenesis

- Tumors cannot grow > 1-2 mm under existing vasculature
- Angiogenesis delivers oxygen and nutrients to tumor growth and survival
- VEGFR-2 and PDGFR-β both regulate angiogenesis
- VEGFR-2 is important for:
  - Endothelial proliferation/migration and survival signal
- PDGFR-β is important for:
  - Maintenance of blood vessels

Angiogenesis

- Ongoing/unpublished studies
  - IL-12, IFNa2a, TSP-1, protease inhibitors
  - Thalidomide
    - n=14 dogs with HSA
    - MST 60 days
  - Palladia?
    - Targets VEGF, PDGF
    - Clinical Trial n=35 dogs
    - Adriamycin x5 Palladia maintenance

Chemotherapy

- Novel administration of old drugs?
  - Inhalational therapy
  - Metronomic therapy
    - Targets vascular endothelium
    - Use in maintenance Tx?
Metronomic Therapy

S Lana et al. JVIM 2007;21:764-9

Protocols
Feldene+cytoxan+etoposide x 6mths n=9
MST 178 days
Dox q 3 weeks x 5 n=24
MST 138 days

No significant difference in ST

Current combination Adria q 2 weeks x 5 + low dose cytoxan N=60 cases

Alternative Medicine

- Polysaccharopeptide (PSP) is the bioactive agent from the mushroom Coriolus versicolor
  - Cloud mushroom, turkey tail, or Yunzhi mushroom
- U Penn Study:
  - N=15
  - High dose (TTP)
  - 112d vs. 30d

Conclusion

- HSA remains a highly metastatic cancer
- More research is needed
  - Earlier diagnosis may improve prognosis
  - Identify new targets
- Novel targeted therapies offer hope

Questions???