Diagnosis and Treatment of Canine Hemangiosarcoma

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Hemangiosarcoma (HSA)

Introduction:
- Highly malignant
- Originates from vascular endothelial cells
- More frequent in dogs than other species
  - Approx. 2% of all canine tumors
- High fatality rate
- Older, larger breed (GSD and GR ++)

[Images of dogs]
Hemangiosarcoma (HSA)

Etiology:

Unknown for the most part

- Genetic predisposition
- Chronic UV (skin, conjunctiva)
- In humans:
  - Various chemicals – visceral form
  - UV or previous RT – cutaneous form
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Oncogenesis:

Multiple steps:

Activating mutations of oncogenes:

- STAT3: 22 HSA samples tested overexpressed
- Cox-2: 19 samples tested were negative
  - Inactivating mutations of TSG
- $p53$ and PTEN: recently identified
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Angiogenesis:
- Tightly controlled process
- New blood vessel formation
- Pro-angiogenic factors:
  - VEGF found in plasma/effusions of dogs with HSA
  - Splenic HSA overexpress angiopoietins

Antiangiogenic factors:
- Endostatin ↑ in serum of dogs with HSA…
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Angiogenesis
HSA cells *in vitro*:
- Produce numerous pro-angiogenic factors
- Including potent VEGF and bFGF

Antiangiogenic therapy with IL-12 *in vivo*:


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Biologic behavior:

Primary sites
- Most common: spleen, heart, skin/SQ, liver
- Others: bone, kidney, muscle, oral, urinary bladder, lung.

Disseminates early
- Hematogenous
- Seeding on serosa

Common sites of metastasis
- Liver, lungs, omentum
  - Brain in up to 15%
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Biologic behavior:
Insidious growth and rapid early spread

Metastasis:

1. Hematogenous route:
   - Lungs, liver, brain, skin, bone, adrenals, etc
2. Tumor rupture
   - Serosal surfaces

Mets often multi-organ
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Diagnosis and staging

– Should be done if patient stable
– Highly metastatic so stage impacts prognosis
– In critical patient: may have to be delayed
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Three-view thoracic radiographs
Hemangiosarcoma (HSA)

Abdominal ultrasound
Hemangiosarcoma (HSA)

Echocardiography

[Image of an echocardiogram showing a mass, labeled PE and RA]
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Complete blood cell count

- Anemia (microangiopathic, regenerative), thrombocytopenia (chronic, low-grade DIC), neutrophilic leukocytosis, abnormal red cell morphology (schistocytes)
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Often normal

Abnormalities a result of specific organ involvement
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Coagulation profile
- PT, PTT, FDP, fibrinogen, d-dimers
- Rule out DIC

ECG, telemetry
- Watch for arrhythmias
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Skeletal lesions: x-rays and scintigraphy
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Advanced imaging for SQ or IM

NC STATE UNIVERSITY Comparative Medicine Institute
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Cytopathology

– May help, not always exfoliating well
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Histopathology

– For definitive diagnosis
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Histopathology for definitive diagnosis

Characterized as:

– Malignant spindle cells forming irregular blood-filled cavities

For less differentiated samples:

– factor VIII related antigen (VWF)
– CD31 or CD34
– Vimentin
– C-kit
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Early detection?

– At earlier stage, better Px?
– Flow cytometry
  • Cell surface markers
  • Specific lineage

– DNA-based genetic tests
  • Under development, many studies
  • Identify new targets

Exp Hematol 2006;34:870-878.
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Traditional therapy:
Involves Sx, chemo, RT

Surgery

– Remove tumor burden when feasible
– HSA-ectomies
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Surgery alone for visceral, cardiac, or SQ/IM

– Palliative only, MST 1-3 months

Pericardectomy can be palliative

Better Px with dermal or conjunctival

## 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
Traditional Tx

Adjuvant chemotherapy
  – Doxorubicin-based (A, AC, VAC, …)
  – Improves ST to 6-7 months
  – Did not help more than doxorubicin:
    • Intracavitary Doxil, doxorubicin +
      minoycline, doxorubicin + COX-2 inhibitor,
      doxorubicin q2w, doxorubicin + ifosfamide,
      …
Traditional Tx (cont’d)

Radiation therapy

– No published information
– May help to palliate SQ/IM HSA
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Prognosis:

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

Splenic and cutaneous HSA
- Higher clinical stage = shorter survival
- Often hard to determine primary
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Cutaneous HSA:

- Stage I: confined to dermis
  - Complete excision: MS >2 yrs
- Stage II: hypodermis +/- dermal musculature
- Stage III: invading underlying musculature
  - Stage II & III tumors: 10-60% metastatic rate
  - Complete excision in only 25% of cases (II & III)
  - MS 172-307 days

Bukalowski et al., JAVMA, 2008, Shiu KB et al., JAVMA 2001, Ward et al., JVIM, 1994
HSA Novel Therapy

Traditional tx: reached a wall

Novel therapies may lead to better ST

Finding molecular targets is crucial
Immunotherapy

Initial studies with mixed bacterial vaccines

- Did not provide survival advantage

Study with L-MTP-PE

- Combined with AC protocol
- Only one showing improvement in MST: 273 days
- Established a role for immunoTx in HSA Tx

- Availability?
Immunotherapy (cont’d)

L-MTP-PE

![Survival curve graph showing comparison between L-MTP-PE and Placebo](image)
HSA Immunotherapy

JVIM 2007

– Allogeneic vaccine with 2 K9 HSA cell lines
  • + doxorubicin
  • Vaccine given intraperitoneally (8 doses)
  • 28 dogs treated
– MST of 218d in 7 dogs with stage III disease
– Stage II = 182d MST
HSA Angiogenesis

Central role in many human and veterinary cancers

- Huge area of research

Ongoing/unpublished studies

- IL-12, IFNα2a, TSP-1, protease inhibitors, thalidomide
Avastin (bevacizumab)?

- Humanized monoclonal Ab
- Targets VEGF
- Approved for CRC in people
- Unlikely to work in pets

Small molecule inhibitors?

- Hold promise
- Target VEGF, bFGF, integrins, …
HDAC inhibitors

Recent case report in 1 dog with HSA

– Lived 30 months, no chemo

Valproate

– Anticonvulsant with HDAC inhibiting properties
– Enhance doxorubicin toxicity?
Targeted Therapy: Cox-2 Inhibition

Cox-2 is utilized by cancer for:
- Growth
- Metastasis
- Angiogenesis

Cox-2 expressed by:
- Cancer cells
- New blood vessels

Vioxx® (rofecoxib) is a popular COX-2 inhibitor. Tablets are available in 12.5mg, 25 mg (pictured), and 50 mg strengths.
Chemotherapy

Novel administration of old drugs?

- Inhalational therapy
- Metronomic therapy
  - Targets vascular endothelium
  - Use in maintenance Tx?
HSA Conclusion

HSA remains a highly metastatic cancer

More research is needed

– Earlier Dx – may improve prognosis
– Identify new targets

Novel targeted therapies offer hope
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Questions?