Intracranial Neoplasia in the Dog

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Outline

• Clinical background

• Glioma
  • Astrocytoma
  • Oligodendroglioma

• Meningioma
Clinical Information

- Variable incidence (range from 3-5% of all tumors in the dog)
- Generally affect middle aged to older dogs
  - Exceptions:
    - Primitive neuroectodermal tumor
- Breed predispositions
  - Glioma in brachycephalic breeds (Boxer, Bulldog, Boston terrier)
Tumor Grading

• Original veterinary classification scheme:
  • Histologic classification of tumors of the nervous system in domestic animals (1999)

• Human classification scheme:
  • WHO classification of tumors of the central nervous system (2007)

• Pros:
  • Dog has similarities to some human tumors and subtypes
  • More recent and expansive

• Cons:
  • Lack good prospective canine studies to determine if the human WHO classification scheme is appropriate
  • Breadth of tumors seen in the dog does not compare to human
  • Many IHCs don’t work in the dog (or are not validated)
Astrocytoma

• Incidence of 10-20% of primary CNS tumors
• Increased incidence with age
• Most common in the white matter of the cerebral hemispheres
  • Less common sites: Thalamus, midbrain, brainstem, and spinal cord
• Typically an ill-defined mass; can have hemorrhage (especially in high grade)
Low Grade Astrocytoma

• Pilocytic
  • Very rare in the dog
  • Low cellularity with elongate cells, strong GFAP immunoreactivity
  • Mitoses are rare

• Subependymal giant cell
  • Very rare; compress and bulge into ventricle
  • Moderate cellularity with mixed morphologies
  • Mitoses are rare
Low Grade Astrocytoma

- Diffuse astrocytoma
  - Gemistocytic
  - Fibrillary
  - Protoplasmic

- Fibrillary is most common in the dog; followed by gemistocytic
Gemistocytic Astrocytoma

Sox2
Fibrillary Astrocytoma
Higher Grade Astrocytoma

• Anaplastic astrocytoma (grade III)
  • Similar to the diffuse astrocytoma with increased cellularity and cell density
  • Higher proliferative index
• Glioblastoma multiforme (grade IV)
  • Common* in the dog
  • Predilection for frontal and temporal lobes
  • Hypercellularity, microvascular proliferation, pseudopallisading around regions of necrosis
  • Strongly IHC positive for IGFBP2, GFAP, EGFR; variable for PDGFR-α; often abundant Olig2 staining
GBM
Astrocytoma Genetics

- Increased EGFR expression; may be associated with invasion
- Increased VEGF in higher grade tumors
- No current evidence of extensive involvement of mutations in p53
- Variable overexpression of PDGFRα
- Overexpression of IGFBP2
Gliomatosis Cerebri

• Diffuse glioma; most commonly have an astrocytic appearance
• No genetic work done to date
Oligodendroglioma

- Most common glial tumor (20-40%)
- Predilection for frontal, parietal, and temporal lobes, as well as piriform
- Well demarcated, gelatinous; +/- hemorrhage
- Monomorphologic histologic pattern
- Separated into grade II and grade III
  - Grade II: Lack atypia, uniformity to cells, no microvascular proliferation
  - Grade III: Abundant necrosis, microvascular proliferation, widespread involvement
- Typically have strong immunoreactivity to Olig2 and PDGFR-α
Oligodendroglioma

Image courtesy Dr. Marc Kent, UGA
Atypia

Grade II

Grade III
Grade III

Necrosis

Glomeruloid Blood Vessels
Meningeal Spread
Intratumoral Calcifications

HE, 200x
Immune Cell Infiltrates in Oligodendroglioma
Pax-5

- 24/34 cases had no B cells
- 10/34 had low numbers of perivascular infiltrates, but no parenchymal spread
• 32/34 cases had T cell infiltrates

400x; DAB
Iba-1

Normal Brain

Grade II Oligodendroglioma

200x; DAB
Iba-1

Grade III Oligodendroglioma

Grade III Oligodendroglioma

200x

100x; DAB
HLA-DR

Normal brain

Grade III oligodendroglioma

200x; DAB
Comparison

Iba-1

HLA-DR

400x, DAB
Mac387 - Vasculature

Grade III Oligodendroglioma

Grade III Oligodendroglioma

200x; DAB
Mac387-Vasculature

Grade III Oligodendroglioma

Grade III Oligodendroglioma
Oligodendroglioma Genetics

- Little published literature
- Increased VEGF expression
Meningioma

- Most common intracranial neoplasm in the dog (40-50% of primary intracranial tumors)
- Most common spinal tumor in the dog (especially cervical)
- Decreased incidence as move caudally in the CNS (likely associated with decreased density of arachnoid villi)
- Possible increased incidence in dogs >15kg
  - Over-represented in Golden Retrievers and Boxers
Canine Meningioma

• Most common locations:
  • Olfactory bulb
  • Cerebral convexities
  • Falx, tentorium, calvaria
  • Pontomedullary
  • Spinal cord
  • Retrobulbar
Canine Meningioma

• Gross Features
  • Well defined lesions
  • Firm to rubbery, white to tan
  • Often multilobulated
  • Plaque-like lesions most common along ventral brainstem
  • Compression of brain more common than invasion
  • Rarely invade through the dura into the skull
Meningioma
Meningioma
Cerebral convexity- “En plaque”
Vertebral Canal
Histologic Characteristics

• WHO grade is the most predictive indicator of recurrence in man
• Malignant histologic features are associated with shorter survival times in man
  • E.g. Tumoral necrosis (EXCEPT this is really common in canine meningiomas)
• Don’t have a good understanding on what is predictive in veterinary medicine
Histologic Characteristics

• Can be graded from grade I to a grade III
  • Most human tumors fit into grade I and the same is presumed in veterinary medicine; some data to indicate that grade II tumors may be more common in the dog than in human

• Can also define them based on predominant cell pattern
  • Diverse array:
    • Meningothelial
    • Fibrous
    • Transitional
    • Psammomatous
    • Angiomatous
    • Microcystic
    • Secretory
    • Lymphoplasmacyte rich
    • Metaplastic
    • Chordoid
    • Clear cell
    • Atypical
    • Papillary
    • Rhabdoid
    • Anaplastic
# Meningothelial

**Human**

- Tumor cells form lobules separated by fibrous connective tissue
  - Cells may give the appearance of syncytium
- Cells are uniform with fine chromatin patterns
- Nuclear inclusions can be seen
- Whorls and psammoma bodies are NOT common

**Veterinary**

- Same histologic pattern
- Common variant

**GRADE I**
Meningothelial
Meningothelial
Fibroblastic

**GRADE I**

**Human**

- Spindle cells forming parallel, storiform, and interlacing bundles
  - Form large fascicles
- Abundant collagen
- Nuclear features approximate those in the meningothelial variant

**Veterinary**

- Same histologic features
- Common, but not as frequent as transitional and meningothelial

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Fibroblastic
Transitional

**GRADE I**

Human

• Coevolution of fibroblastic and meningothelial patterns
• Typically interlacing regions of fascicles with tight whorls

Veterinary

• Same histologic pattern
• Commonly associated with infiltration by neutrophils
• Very common in dogs
Transitional
Psammomatous

**Human**
- These tumors contain a predominance of psammoma bodies over the tumor cells
- Typically a transitional pattern

**Veterinary**
- Same histologic features
- Uncommon in the dog

**GRADE I**
Psammomatous
## Angiomatous

### Human
- Features a predominance of blood vessels
- Typically small vessels; hyalinization of walls is common
- Nuclear atypia can be high, but typically have a benign behavior

### Veterinary
- Same histologic appearance
- Rare variant

**GRADE I**
Angiomatous
Microcystic

**Grade I**

**Human**
- Cells with elongate processes that surround microcysts
  - Microcysts contain pale mucinous fluid
- Pleomorphic cells can be numerous

**Veterinary**
- Same appearance
- Incidence not known, but a common feature in many subtypes
Metaplastic

Human

- Widespread mesenchymal metaplasia (osseous, cartilaginous, lipomatous, xanthomatous)

Veterinary

- Rare variant
- Metaplasia is more common in extraocular types of meningioma

**GRADE I**
Metaplastic
Other

• Secretory
  • Rarely reported in the dog

• Lymphoplasmacytic
  • Not well described; some variants can have robust mononuclear infiltrates

**GRADE I**
### Atypical

<table>
<thead>
<tr>
<th>Human</th>
<th>Veterinary</th>
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<tbody>
<tr>
<td>- Increased mitotic activity (&gt;4 per 10 40x fields) or &gt;3 of the following:</td>
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<tr>
<td>- Increased cellularity</td>
<td>- Same histologic features</td>
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<td>- Small cells with high N:C ratio</td>
<td>- One of the more common variants</td>
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<td>- Prominent nucleoli</td>
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<td>- Sheet-like growth</td>
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<td>- Foci of necrosis (geographic)</td>
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**GRADE II**
Atypical
Other

• Chordoid
  • Similar features in the dog; very rare

• Clear cell
  • Not reported in the dog

**GRADE II**
Papillary

**GRADE III**

Human

- Perivascular pseudocapillary pattern predominates
- Frequency increases with recurrences
- Commonly invade the brain parenchyma

Veterinary

- Same histologic features
Papillary
Anaplastic

**Human**
- Histologic characteristics of frank malignancy including cytologic atypia, markedly elevated mitotic rate (20 per 10)

**Veterinary**
- Same histologic features

**GRADE III**
Anaplastic
Miscellaneous Histologic Features
Miscellaneous Histologic Features
## Immunohistochemistry

### Human
- **Positive**
  - Epithelial membrane antigen
  - Vimentin (all)
  - S-100 (faint, not consistent)
  - CEA (secretory variant)
  - Claudin-1
  - Ki67
  - Estrogen/Progesterone receptor

### Veterinary
- **Positive**
  - Vimentin
  - Claudin-1
  - Ki67
  - Cytokeratin (spotty)
  - NSE (spotty)
  - S100 (faint, inconsistent)
  - Estrogen/Progestrone Receptor (variable, PR>ER**)
  - Laminin
  - CD34
  - Cox-2
  - MMP
  - VEGF
  - E-cadherin/N-cadherin (N=invasive)

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Negative for: Synaptophysin, GFAP

**PR expression inversely related to Ki67 and positive response to radiation**
Immune Cell Infiltrates in Canine Meningioma

- CD3+ T lymphocytes and CD18+ macrophages are common
- Rare B lymphocytes
- Scattered numbers of FoxP3 and CD45RA positive cells

Boozer LB et al., Vet Pathol 2012 49(5):784-795
Genetic Abnormalities

• One study showed described 4.1B (tumor suppressor protein)
  • 6/30
• Same study showed decreased TSLC1
  • 15/30
• NF2 varies considerably on WB and RT-PCR
• No relationship to grade, subtype, or location
• Role of tumor suppressor gene loss?
• Small study of three animals suggested abnormalities in DNA repair, cell cycle progression, and apoptosis
• Another study indicated upregulation of ribosomal proteins are common; down regulation of CREG also reported
Hierarchical Clustering

11,574 detectable genes

334 genes with differential expression between meningioma subgroups
SOX4, SOX10 increased in subset of samples
Shift in cell adhesion gene expression
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