Neuronal and Mixed Neuronal-Glial and Embryonal Tumors

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Considerations

Complex Topic
• Many of these tumors have been re-classified at least once or are “new” entities
• Tumors that are commoner in, but not exclusive to pediatric populations
• Tumors that more often than not demonstrate divergent differentiation (glial and neuronal, +/- other)

Brain Tumor Classifications
• Virchow, 1867
  – Brain tumors arise from brain tissue
• Golgi, 1875
  – Brain tumors contain cells that have the features of cells in the brain
• Cushing & Bailey, 1922-26
  – Studied series of 414 cases
    • Grouped by length of survival
    – Detailed clinical descriptions
  – Identified 13 categories of brain tumors based on demonstration of cell type
Considerations

The First Brain Tumor Classification, circa 1926

A Few Things Have changed …

• Clinically
  – Refined surgical techniques, intra- post-operative care
  – Diagnostic and interventional imaging
  – Non-surgical treatment modalities

• Scientifically
  – More detailed understanding of CNS development
  – IHC, EM, FISH, SNPs, gene arrays
  – Genomics
## Considerations

### Neuronal and mixed neuronal-glial tumours

<table>
<thead>
<tr>
<th>Tumour Type</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysplastic gangliocytoma of cerebellum (Lhermitte-Duclos)</td>
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</tr>
<tr>
<td>Desmoplastic infantile astrocytoma/ganglioglioma</td>
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</tr>
<tr>
<td>Dysembryoplastic neuroepithelial tumour</td>
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<tr>
<td>Gangliocytoma</td>
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<tr>
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<tr>
<td>Anaplastic ganglioglioma</td>
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<tr>
<td>Papillary glioneuronal tumor</td>
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<tr>
<td>Rosette-forming glioneuronal tumour of the fourth ventricle</td>
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<tr>
<td>Central neurocytoma</td>
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<tr>
<td>Extraventricular neurocytoma</td>
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<tr>
<td>Cerebellar liponeurocytoma</td>
<td>9506/1*</td>
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<tr>
<td>Paragangioma of the filum terminale</td>
<td>8680/1</td>
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### Embryonal tumours

<table>
<thead>
<tr>
<th>Tumour Type</th>
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<tr>
<td>Medulloblastoma</td>
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<td>Desmoplastic/nodular medulloblastoma</td>
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<tr>
<td>Medulloblastoma with extensive nodularity</td>
<td>9471/3*</td>
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<tr>
<td>Anaplastic medulloblastoma</td>
<td>9474/3*</td>
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<tr>
<td>Large cell medulloblastoma</td>
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<td>CNS primitive neuroectodermal tumours (PNETs)</td>
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<td>CNS PNET, NOS</td>
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<td>CNS neuroblastoma</td>
<td>9500/3</td>
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<td>CNS ganglioneuroblastoma</td>
<td>9490/3</td>
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<td>Medulloepithelioma</td>
<td>9501/3</td>
</tr>
<tr>
<td>Ependymoblastoma</td>
<td>9392/3</td>
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<tr>
<td>Atypical teratoid / rhabdoid tumour</td>
<td>9508/3</td>
</tr>
</tbody>
</table>
Considerations

Most of These Are Either: Neuronal Histologic Features

- Tumors that have histologic evidence of neuronal differentiation
  - Exclusively neuronal neoplasms are relatively rare (gangliocytoma, central neurocytoma)
- Tumors that show evidence of bi- or polyphenotypic differentiation
  - Histologically these are usually comprised of small undifferentiated cells
  - Evidence for neuronal differentiation based on special techniques
    - Electron microscopy (EM) detection of ultrastructural features
    - Immunohistochemical (IHC) detection of protein expression
    - FISH, gene expression, CNV or sequencing based detection of molecular genetic changes associated with neuronal phenotypes
Considerations

Structural & Functional Elements of Neurons

NeuN

Neurofilament (NFP)

Synaptophysin
Considerations

Glial Differentiation

- Glial derived cell types
  - Astrocytes
  - Oligodendrocytes
  - Ependyma and Choroid Plexus
    - More prominent epithelial features
- Histologically defined
- IHC
  - Astrocytes (GFAP)
  - Oligodendrocytes

Practically Speaking ...

- While more complex glial differentiation exists, histology and a single IHC marker (GFAP) that is associated with astrocytic differentiation are used to define ...
Considerations

Neuronal Differentiation

• Histology: what is a “neoplastic neuron?”
  – Neurons present where none would normally be found
  – Neurons that are irregularly arranged
  – Neurons that are cytologically atypical (binucleation)
• “Ganglioid” cells (small, less prominent nucleoli, inconspicuous Nissl substance)
• IHC to identify biphenotypic differentiation in an embryonal tumor

Neuronal “Structures”

• Indirect histologic evidence
  – Homer Wright rosettes (MB, PNET)
  – Neurocytic rosettes (Neurocytoma, Pineocytoma)

Schematics from: [Image]
# Archetypal Tumors

## Neuronal & Mixed Neuronal-Glial (mostly biphenotypic tumors)
- Ganglioglioma
  - Gangliocytoma
- Dysembryoplastic neuroepithelial tumor (DNET)
- Central Neurocytoma

## Embryonal (tumors w/ bi- or polyphenotypic differentiation)
- Medulloblastoma
  - Most common embryonal tumor (90%)
  - 20% of all pediatric brain tumors
- CNS Primitive neuroectodermal tumor (CNS PNET)
  - Relationship to MB
  - Specific histologic patterns or subtypes of PNET
- Atypical Teratoid / Rhabdoid Tumor (AT/RT)
Neuronal & Mixed Neuronal-Glial

Ganglioglioma, Dysembryoplastic Neuroepithelial Tumor (DNET), Central Neurocytoma
Ganglioglioma

Terminology

• Definition
  – Tumor containing well-differentiated neoplastic neurons (ganglion cells) with or without (gangliocytoma) associated neoplastic glial cells

Clinical Issues

• Epidemiology
  – Age (diagnosis)
    • 8.5 – 25 years
  – Gender (M:F)
    • 1.1:1 to 1.9:1
• Presentation
  – Seizures
    • 15-25% of surgery for seizures
    • Most common tumors associated with temporal lobe epilepsy
    • Length of duration of seizures prior to diagnosis correlates with location:
      – Cerebrum (6-25 years)
      – Brainstem / spinal cord (~1.5 years)
  – Mass effect for brainstem and spinal cord
• Prognosis
  – Benign tumors (WHO grade I) with exception of small number that present with or develop anaplastic features in glial component (anaplastic ganglioglioma, WHO grade III)
  – Surgical resection is typically curative
Ganglioglioma

Image Findings

• General Features
  – Location
    • Supratentorial, particularly temporal lobe (>80%)
    • Anywhere along neuraxis
  – Morphology
    • Cortically based
    • Most commonly cystic with mural nodule
    • Can be solid
    • Typically enhancing
Ganglioglioma

Macrosopic Features

• Pale - gray
• Firm - rubbery
• Variably gritty due to focal calcification
• Presence of hemorrhage or necrosis can be seen in anaplastic lesions
Ganglioglioma

Microscopic Pathology

• Predominant Pattern Type
  – Ill-defined lobules, non-infiltrative growth
• Predominant Cell Type
  – Ganglion cells
    • Wrong location
    • Wrong parts
    • Too many nuclei
  – Glial cells
    • Fibrillary or pilocytic astrocytoma, occasionally oligodendroglial
    • Typically low grade
    • Large swollen astrocytes that may mimic neurons
Ganglioglioma
Ganglioglioma

GFAP
Ganglioglioma

Microscopic Pathology, Cont’d.

- Histologic Features
  - Perivascular inflammatory infiltrates (vascular hyalinization is not uncommon)
  - Calcification
  - Eosinophilic granular bodies are common
  - Glial and neuronal elements may be admixed or separate
  - Leptomeningeal infiltration (not a sign of malignancy)
  - Neuronal element may relative inconspicuous in some tumors, highlighted with IHC markers (NFP, synaptophysin, etc.)
Ganglioglioma
Neuronal & Mixed Neuronal-Glial

Ganglioglioma, Dysembryoplastic Neuroepithelial Tumor (DNET), Central Neurocytoma
Dysembryoplastic Neuroepithelial Tumor (DNET)

Terminology

• Definition
  – A multinodular cortical tumor associated with refractory epilepsy

Clinical Issues

• Epidemiology
  – Age (diagnosis)
    • Diagnosis typically in 2nd - 3rd decade
  – Gender
    • Males > Females

• Presentation
  – Seizure
    • 90% present with first seizure before age 20

• Prognosis
  – Benign tumors (WHO grade I)
  – Cured by gross total resection in most cases
Dysembryoplastic Neuroepithelial Tumor (DNET)

Image Findings

• General Features
  – Location
    • Temporal lobe, particularly mesial structures
    • Any supratentorial cortex
    • Erosion, deformation, thinning of overlying skull
  – Morphology
    • Cortically based
    • Ribbon-like multi-nodular areas of cortical thickening and abnormal signal
Dysembryoplastic Neuroepithelial Tumor (DNET)

Macroscopic Features

- Cortex thickened by one or more mucoid nodules
- Semi-translucent
- Gray color
- Blurred gray-white junction
- May have exophytic or raised component associated with secondary changes in overlying skull
Dysembryoplastic Neuroepithelial Tumor (DNET)
Dysembryoplastic Neuroepithelial Tumor (DNET)

**Microscopic Pathology**

- Predominant Pattern Type
  - Nodular
- Predominant Cell Type
  - Glioneuronal
    - Oligodendrocyte like cells (OLCs)
    - Ganglion cells
- Histologic Features
  - Loosely textured cortical nodules
    - Well-defined
    - OLCs arrayed along bundled axons and blood vessels, perpendicular to cortical surface (“specific glioneuronal element”)
    - Variable amounts of extracellular mucopolysaccharide (MPS)
    - Ganglion cells floating in pools of MPS
Dysembryoplastic Neuroepithelial Tumor (DNET)

Microscopic Pathology Cont’d.

• Histologic Features
  – Internodular areas
    • OLCs infiltrate cortex
    • Mimics oligodendroglioma
    • May extend into and through the subpial surface
  – “Complex DNET”
    • Compact elongated cells (JPA)
    • Nuclear atypia and hyperchromasia (diffuse astrocytoma)
    • Arcades of proliferative glomeruloid vasculature and scattered mitotic activity are NOT indicators of malignant transformation
  – Associated cortical dysplasia
Dysembryoplastic Neuroepithelial Tumor (DNET)
Neuronal & Mixed Neuronal-Glial

Ganglioglioma, Dysembryoplastic Neuroepithelial Tumor (DNET), Central Neurocytoma
Neurocytoma

Terminology
• Definition
  – A neuronal tumor comprised primarily of “neurocytes” (small to medium sized cells lacking overt histologic evidence of neuronal differentiation)
  – WHO 2007 added recognition for extraventricular occurrence of this tumor with slightly broader spectrum of histologic features

Clinical Issues
• Epidemiology
  – Age
    • Young adults, mean age of 29 yrs at presentation
    • 2/3 of tumors between 20 – 30 yrs.
    • Have been reported in patients up to the 7th decade
  – Gender (M:F)
    • Equal
• Presentation
  – Increased intracranial pressure in “central” neurocytomas; less commonly, hormonal disturbances
  – Typically short duration of symptoms (~3 months)
  – Extraventricular neurocytomas associated with mass effect and seizures
• Prognosis
  – Generally benign tumors (WHO grade II)
  – Surgical resection is mainstay of therapy with XRT for subtotal excision
  – Partial resection and increased Ki-67 labeling (> 2%) may be associated with increased risk of recurrence; dissemination is rare
Neurocytoma

Image Findings

• General Features
  – Location
    • Supratentorial, involving lateral and 3rd ventricles
      – 50% in anterior portion of one of the lateral ventricles
      – Attachment to the septum pellucidum is frequent
      – Often adjacent to the foramen of Monro
      – Frequently extend into opposite ventricle, less often the 3rd
    • Extraventricular locations
      – Intraparenchymal w/ or w/o impinging on ventricles
  – Morphology
    • Intraventricular
    • Often partially calcified
    • Enhancing
    • Extraventricular tumors can be solid or cystic with mural nodule
Neurocytoma

Macroscopic Features

- Well circumscribed
- Fleshy
- Soft
- Flecks of calcification

Microscopic Pathology

- Predominant Pattern Type
  - solid, non-infiltrative growth
- Predominant Cell Type
  - Central Neurocytoma
    - “Neurocytes”
      - Small, mature round neurons
      - Artifactual nuclear halo (oligodendroglial mimic)
  - Extraventricular Neurocytoma
    - “Ganglioid” cells
    - Ganglion cells
- Histologic Features
  - Fine fibrillary neuropil matrix
    - Neurocytic rosettes (ependymoma mimic)
  - Occasional necrosis, not prognostic
  - Rarely cytologic atypia, vascular proliferation, not clearly prognostic
  - Mitotic activity is rare
  - Ki-67 labeling > 2% is associated with increased risk of recurrence and designated as “atypical neurocytoma”
Neurocytoma

Microtubules, Synapses & secretory vesicles

SYN
Atypical Neurocytoma
Embryonal Tumors

Medulloblastoma (MB), CNS Primitive Neuroectodermal Tumors (CNS PNET), Atypical Teratoid / Rhabdoid Tumors (AT/RT)
Medulloblastoma

Terminology

• Definition
  – Embryonal tumor comprised of primitive neuroectodermal cells involving the cerebellum, with a propensity for CSF dissemination

Clinical Issues

• Epidemiology
  – Age (diagnosis)
    • Median age ~ 8 yrs.
    • Most occur between ages 3 – 10 yrs.
    • In patients age = < 1 yr. Accounts or nearly 25% of all pediatric brain tumors
    • Not exclusively a pediatric tumor, 20-25% of all MB reportedly occur beyond the age of 20 years.
  – Gender (M:F)
    • 1.6 : 1

• Presentation
  – Increased ICP due to obstructive hydrocephalus
    • H/A (morning), vomiting, lethargy
  – Ataxia (with tumor progression)
  – Increased head circumference
  – Backache, voiding difficulties (CSF dissemination)
Clinical Issues, cont’d.

- Prognosis
  - Crude risk based stratification (age, extent of post-operative disease, metastasis)
  - Metastatic staging of MB
    - M0 - No gross subarachnoid or hematogenous metastasis
    - M1 - Microscopic tumor cells found in CSF
    - M2 - Gross nodular seeding in cerebellum, cerebral subarachnoid space, or in the third or fourth ventricles
    - M3 - Gross nodular seeding in spinal subarachnoid space
    - M4 - Extraneuraxial metastasis.

Clinical Issues, cont’d.

- Three basic categories:
  - Average risk (> 3 years, < 1.5 cm², M0)
    - 5-year survival rate > 80%
  - Poor risk (> 3 years, > 1.5 cm², M1-M4)
    - 5-year survival rate 40 – 60%
  - Infants (< 3 years irrespective of other variables)
    - 5-year survival rate ~ 30%
    - Worse with metastatic disease
    - Better survival with desmoplastic tumors
Medulloblastoma

Image Findings

• General Features
  – Location
    • Cerebellum, midline/vermis (children)
    • Cerebellum, hemispheres
      – In children as tumor enlarges
      – In some adults as primary site
      – Maybe associated with nodular/desmoplastic MBs
    • Extension into 4th ventricle where it may form a discrete mass
    • Gelatinous opacification of SA (‘sugar icing’) with CSF dissemination
  – Morphology
    • Well circumscribed
    • Solid, sometimes cystic or nodular
    • Contrast enhancing
Medulloblastoma

Macroscopic Features

• Gray – pink
• Soft and gelatinous – firm (depending on degree of desmoplasia)
• Necrosis typically limited to small foci
Medulloblastoma
Medulloblastoma

Microscopic Pathology

- WHO 2007 recognizes four types of MB
  - Classic/undifferentiated (73%)
  - Desmoplastic/Nodular (7%)
  - Extensive nodularity and advanced neuronal differentiation (3%)
  - Large cell/anaplastic (17%)
Medulloblastoma

Microscopic Pathology cont’d.

• Predominant Pattern Type
  – Classic/undifferentiated
    • Patternless sheets
  – Desmoplastic/nodular
    • Not leptomeningeal reaction
    • Collagen rich, separating tumor cells into thick columns
    • Nodular collagen free zones (pale islands) with neuropil diff.

• Predominant Cell Type
  – Primitive neuroectodermal cells
    • Small, inconspicuous cytoplasm, oval to carrot shaped hyperchromatic nuclei
  – Anaplastic/large cell
    • Anaplasia, elevated mitotic and apoptotic indices, cell “wrapping”
    • Large nuclei with prominent nucleoli (rare)
Medulloblastoma

Classic MB
Medulloblastoma

Nodular Desmoplastic MB
Medulloblastoma

Microscopic Pathology, Cont’d.

- Cytologic Features
  - Desmoplastic/nodular
    - Ganglioid – ganglion cell
    - Atypia in internodular region
  - Anaplastic MB
    - Modestly larger nuclei
    - Irregular nuclear morphology
    - Cell wrapping
  - Large cell MB
    - Large nuclei (2x > classical MB)
    - More vesicular chromatin staining pattern
    - Nucleoli
Medulloblastoma

**Microscopic Pathology, Cont’d.**

- **Immunohistochemistry**
  - Polyphenotypic tumors
  - Markers of
    - Divergent neuroepithelial differentiation (GFAP, NFP, Synaptophysin)
    - Proliferative activity (Ki-67)
  - Patterns of expression of these markers are variable within and between tumors
    - Desmoplastic/nodular
      - Nodules (neuronal)
      - Internodular region (proliferative activity)
  - Entrapped/reactive astrocytes
Medulloblastoma

Syn

Ki-67

GFAP

GFAP
Medulloblastoma

• Histopathology based MB stratification
  – Infants with desmoplastic tumors are classified as low-risk
  – Children with large cell or anaplastic tumors are classified as high-risk
Medulloblastoma

• Genetics informed – hereditary tumor syndromes
  – Gorlin syndrome (*PTCH1*)
    • SHH pathway: *PTCH1/SUFU/SMOH* mutations in ~25% sporadic tumors
  – Turcot type 2 / mismatch repair (*APC*)
    • WNT pathway: *CTNNB1/APC/AXIN1/2* mutations in ~15% sporadic tumors
Medulloblastoma

http://www.rockefeller.edu/labheads/hatten/projects.html

Eberhardt  Cancer Cell 2008; 10(26):2821
The Grand Challenge: Medulloblastoma Classification

Medulloblastoma, histologically defined
- Medulloblastoma, classic
- Desmoplastic/nodular medulloblastoma
- Medulloblastoma with extensive nodularity
- Large cell/anaplastic medulloblastoma

Medulloblastoma, genetically defined
- Medulloblastoma, WNT-activated
- Medulloblastoma, SHH-activated
- Medulloblastoma, non-WNT/non-SHH
CNS Embryonal Tumors

Medulloblastoma (MB), CNS Primitive Neuroectodermal Tumors (CNS PNET), Atypical Teratoid / Rhabdoid Tumors (AT/RT)
CNS PNET

Terminology

• Definition
  – Embryonal tumor comprised of primitive neuroectodermal cells outside of the cerebellum

• Evolving terminology
  – CNS embryonal tumors

Clinical Issues

• Epidemiology
  – Age (diagnosis)
    • Median age ~ 5.5 yrs.
    • Age range 4 weeks – 20 years
  – Gender (M:F)
    • 1.2 : 1

• Presentation
  – Increased ICP
  – Epilepsy
  – Focal neurological signs

• Prognosis
  – Malignant (WHO IV)
  – Worse overall 5 yr survival than MB
  – < 2 yrs worse prognosis than older children
  – Prone to dissemination outside CNS
CNS PNET (embryonal tumors)

Image Findings

• General Features
  – Location
    • Most often supratentorial
    • May involve the spinal cord or other locations
  – Morphology
    • Well circumscribed
    • Solid, sometimes cystic
    • May have necrotic areas
    • Majority show calcification

[Image of brain MRI scan]
CNS PNET (embryonal tumors)

Macroscopic Pathology
- Not substantially different from that encountered in MB
  - No desmoplastic form
- Gray – pink
- Soft and gelatinous
- Necrosis typically limited to small foci

Microscopic Pathology
- Histologic Features
  - Densely packed cells with little cytoplasm
  - Infiltrative growth pattern
  - Neuroblastic (Homer Wright) rosettes
  - Proliferative activity and apoptosis are common
  - Necrosis may produce cystic change
CNS PNET (embryonal tumors)

Microscopic Pathology, Cont’d.

• Specific histologic patterns are recognized in WHO 2007 as subtypes of CNS PNET
  – Cerebral neuroblastoma or ganglioneuroblastoma (neuronal differentiation)
  – Ependymoblastoma (“ependymal” differentiation)
    • Embryonal tumors with multilayered rosettes (ETMR)
    • First decade
    • Aggressive, poor prognosis
CNS PNET (embryonal tumors w/ multilayered rosettes)
CNS PNET (embryonal tumors)

Microscopic Pathology, Cont’d.

– Medulloepithelioma ("neural tube" features), rare but ...
  • Early childhood
  • Aggressive, poor prognosis
  • Often intraventricular, anywhere along neuraxis
CNS PNET (embryonal tumors) - Medulloepithelioma
CNS PNET (embryonal tumors)

Microscopic Pathology, Cont’d.

- Immunohistochemistry
  - Polyphenotypic tumors
  - Markers of
    - Divergent neuroepithelial differentiation (GFAP, NFP, Synaptophysin)
    - Proliferative activity (Ki-67)
  - Patterns of expression of these markers are variable within and between tumors
  - Additional markers (EMA on luminal surface of ependymoblastoma/ETANER; nestin on basal surface of medulloepitheliomas)
Molecular Genetics of CNS PNET (embronal tumors)

Fig. 1 Histologic spectra of CNS-PNETs with C19MC amplification and LIN28 immunopositivity. Representative H and E stains, C19MC FISH, and LIN28 IHC analyses of CNS-PNETs with histologic features of ETANTR (PNET67), MEP (PNET255), CNS-PNET with divergent differentiation (PNET3) and undifferentiated PNET-NOS (PNET161).

CNS PNET – History Repeats Itself

2007 “Year of the Lumpers”

2015 “Sharpening of the Axes”
Embryonal Tumors

Medulloblastoma (MB), CNS Primitive Neuroectodermal Tumors (CNS PNET), Atypical Teratoid / Rhabdoid Tumors (AT/RT)
Atypical Teratoid / Rhabdoid Tumor

Terminology

- **Definition**
  - Embryonal tumor containing cells with rhabdoid or epithelioid features and/or evidence of loss of \textit{INI1}/\textit{SMARCB1} expression
  - Evolving consensus that diagnosis requires demonstration of inactivation of \textit{INI1}/\textit{SMARCB1} by IHC or other means; and absent this confirmation these should be classified as CNS embryonal tumors with rhabdoid features.

Clinical Issues

- **Epidemiology**
  - Age (diagnosis)
    - Median age = 5 mos. (CHOP)
    - Typically < 3 yrs., with greatest frequency < 1 yr.
      - 40% of all embryonal tumors in infants (CHOP)
    - Rarely encountered in older children and adults
  - Gender (M:F)
    - 1.6-2 : 1

- **Presentation**
  - Increased ICP or seizures, depending on location

- **Prognosis**
  - Malignant (WHO grade IV) with mean post-surgery survival of 11 - 24 months
Atypical Teratoid / Rhabdoid Tumor

General Features

• Location

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<th>(13) months–18 years in age ((n = 25))</th>
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<tr>
<td></td>
<td>( n )</td>
<td>( % )</td>
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<td>Cerebrum</td>
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<td>6.6</td>
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<tr>
<td>Extramedullary cervical</td>
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• Macroscopic
  – Cystic
  – Heterogeneous
  – Hemorrhage or necrosis

Data courtesy of Dr. Rorke-Adams; images Drs. Rorke-Adams & Parham
Atypical Teratoid / Rhabdoid Tumor

Microscopic Pathology

• Predominant Pattern Type
  – Sheets of tumor with infiltrative growth through adjacent parenchymal and leptomeninges

• Predominant Cell Type
  – Primitive neuroectodermal cells
  – Rhabdoid cells
  – Mesenchymal/epithelial cells

• Cytology of Rhabdoid cells
  – Vesicular chromatin staining
  – Prominent eosinophilic nucleoli
Atypical Teratoid / Rhabdoid Tumor

Microscopic Pathology, Cont’d.

• Histologic Features
  – Prominent cell borders
  – Abundant eosinophilic cytoplasm
  – Vacuolar cytoplasmic degeneration
  – Variable mitotic activity
  – Karyorrhectic debris
  – Necrosis
Atypical Teratoid / Rhabdoid Tumor

Microscopic Pathology, Cont’d.

- Histologic Features
  - Rhabdoid cells may be focal or rare
  - Epithelioid cells may be more common than rhabdoid cells
  - PNET/MB component often predominates and occasionally is all there is
  - Poorly differentiated epithelial structures are occasionally identified
  - Spindle cell mesenchymal differentiation
  - Chordoid pattern with abundant extracellular myxohyaline material
Atypical Teratoid / Rhabdoid Tumor & Non-CNS MRT: Common Features

• Histology
  – Rhabdoid cells*
  – Polymorphic features
    • Primitive, epithelial and mesenchymal elements are most frequently identified
    • Spectrum of histologic patterns can be observed in all rhabdoid tumors
  – Biologically aggressive
    • Infiltrative margins
    • Frequent lymphatic invasion
    • Necrosis
    • High proliferative rate/mitotic rate (typically)
Atypical Teratoid / Rhabdoid Tumor & Non-CNS MRT: Common Features

- Immunohistochemistry
  - Polyphenotypic tumors
  - Markers of divergent differentiation:
    - Neuroepithelial
    - Epithelial
    - Mesenchymal
  - Intermediate filaments
  - Markers of myogenic differentiation are not typically expressed

<table>
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<td>Actin*</td>
<td>Most - All</td>
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<td>GFAP</td>
<td>Most</td>
</tr>
<tr>
<td>Neural (NSE, synapto, NFP)</td>
<td>Most</td>
</tr>
<tr>
<td>Cytokeratin</td>
<td>Many</td>
</tr>
<tr>
<td>CD99</td>
<td>Many</td>
</tr>
<tr>
<td>Desmin</td>
<td>Some</td>
</tr>
<tr>
<td>Myogenin/Myoglobin</td>
<td>Negative (?)</td>
</tr>
</tbody>
</table>
Atypical Teratoid / Rhabdoid Tumor

• Molecular Genetics
  – Nearly all cases of AT/RT have deletion or mutation in *SMARCB1/INI1* (22q11.2)
    • Component of the SWI/SNF chromatin remodeling complex
  – Typically results in stop or premature truncation
  – ~25% have homozygous deletion of entire coding region
  – Tumors are both sporadic and due to constitutional loss or inactivation of SMARCB1/IN1 (RTPS)
    • Germline mutations in ~35% of cases of AT/RT ...
Atypical Teratoid / Rhabdoid Tumor

Molecular genetics

- SMARCB1/INI1 is ubiquitously expressed in nuclei of normal cells
- IHC staining for SMARCB1/INI1 is a sensitive and specific method for detecting loss of expression and correlates with mutation and deletion of the gene
  - Staining should be performed on ALL embryonal CNS tumors
  - Genetic screening for all newly diagnosed atypical teratoid / rhabdoid tumors
Atypical Teratoid / Rhabdoid Tumor

Rhabdoid Tumors May (Very Rarely!!!) Have Retained SMARCB1 Expression

Nonsense Mutation and Inactivation of SMARCA4 (BRG1) in an Atypical Teratoid/Rhabdoid Tumor Showing Retained SMARCB1 (INI1) Expression

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A remarkably simple genome underlies highly malignant pediatric rhabdoid cancers

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Cancer is principally considered a genetic disease, and numerous mutations are thought essential to drive its growth. However, the existence of genomically stable cancers and the emergence of mutations in genes that encode chromatin remodelers raise the possibility that perturbation of chromatin structure and epigenetic regulation are capable of driving cancer formation. Here we sequenced the exomes of 35 rhabdoid tumors, highly aggressive cancers of early childhood characterized by biallelic loss of SMARCB1, a subunit of the SWI/SNF chromatin remodeling complex. We identified an extremely low rate of mutation, with loss of SMARCB1 being essentially the sole recurrent event. Indeed, in 2 of the cancers there were no other identified mutations. Our results demonstrate that high mutation rates are dispensable for the genesis of cancers driven by mutation of a chromatin remodeling complex. Consequently, cancer can be a remarkably genetically simple disease.
Atypical Teratoid / Rhabdoid Tumor

Epigenetically
Driven Changes in
Gene Expression

Inactivation of SMARCB1

Tumor Suppression

Epigenetic Regulation

SWI/SNF

Epigenetically
Driven Changes in
Gene Expression

Transcriptional activation
of oncogenes
Growth & Develop Pathways
Stem Cell Factors
Cell cycle control

c-MYC
CCND1
GLI1
AURKA
PI3K-AKT
Hippo
ID proteins, EZH2
Cyclin D1
Acknowledgements

Children’s Hospital of Philadelphia
• Dr. Lucy Rorke-Adams
• Dr. Mariarita Santi

AFIP
• Dr. Elisabeth Rushing