Pathology of tumors of the central nervous system

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Plan of Discussion...

- WHO classification -
- Diagnostic tools -
- Glioma - grading
  - Astrocytoma
  - Oligodendroglioma
  - Ependymoma
- Embryonal-
  - Medulloblastoma
- Meningioma
General Considerations...

- **Primary** - children
  - 50% infiltrative

- **Metastatic** - Adults
  - well-demarcated

- **Prognosis**
  - Tumor factors
    - Histologic type & grade
    - IHC-proliferation markers & molecular parameters
  - Patient factors
    - Age/status
    - Tumor site - Limited space, Vital structures
  - Rare: extra neural metastasis
Types of Brain Tumors

- **Meninges**: meningioma, hemangiopericytoma
- **Glia**: astrocytoma, oligodendroglioma, ependymoma, choroid plexus tumors
- **Primitive cells**: neuroblastoma, germinoma, medulloblastoma, pineoblastoma, retinoblastoma
- **Neuronal**: ganglioglioma, gangliocytoma
- **Pituitary**: adenoma, craniopharyngioma
- **Nerves**: schwannoma, neurofibroma, MPNST
WHO classification [2000]

1. NEUROEPITHELIAL
   - Astrocytic
     - Diffuse - Fibrillary/Protoplasmic/Gemistocytic [II]
     - Anaplastic Astrocytoma [III]
     - GBM [IV]
     - PA [I]/SEGA [I]/PXA [II]
   - Oligodendroglial: Oligodendroglioma [II]/anaplt. [III]
   - Mixed glioma - OA [II]/anaplastic OA [III]
1. NEUROEPITHELIAL contd/-
   - Ependymal
     - Ependymoma & variants [II]/anaplastic [III]
     - Myxopapillary E [II]/Subependymoma [I]
   - Glial tumors of uncertain origin- A’ blastoma, Gl. cerebri, chordoid glioma of III ventricle
   - Neuronal & mixed glial neuronal
     - Ganglioglioma/ G. cytoma/ DIGG/ DIA/DNET/ CN
WHO classification [2000]

I] NEUROEPITHELIAL contd/-

- Neuroblastic- Olf Nb/N.epithelioma
- Pineal parenchymal tumors
  - P.cytoma/P.blastoma/PPTI
- Embryonal tumors
  - Medulloepithelioma/Ependymoblastoma
  - Medulloblastoma/ ST-PNET/ATRT
WHO classification [2000]

II] TUMORS OF MENINGES
- Meningothelial - Meningiomas
- Non - meningothelial - Mesenchymal

III] LYMPHOMA/HEMOPOEITIC TUMORS
- Lymphoma/Plasmacytoma/Granulocytic sarcoma/HD

IV] GERM CELL TUMORS - germinoma/EC/YST
WHO classification [2000]

VI] TUMORS OF SELLAR REGION-
- Craniopharyngioma/Granular cell tumor

VII] TUMORS OF PERIPHERAL NERVES
- Schwannoma/NF/Perineurioma/MPNST

VIII] METASTATIC
# Diagnostic Tools: Histologic Typing

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Microscopic</th>
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<tbody>
<tr>
<td>Astrocytoma</td>
<td>Fibrillary background; different cell types</td>
</tr>
<tr>
<td>Glioblastoma</td>
<td>Pseudopalisaded necrosis; microvascular proliferation (MVP)</td>
</tr>
<tr>
<td>Oligodendroglioma</td>
<td>Mosaic/poached-egg appearance</td>
</tr>
<tr>
<td>Ependymoma</td>
<td>Perivascular pseudorosettes</td>
</tr>
<tr>
<td>Medulloblastoma</td>
<td>undifferentiated round cells; rosettes (Homer-Wright)</td>
</tr>
<tr>
<td>Meningioma</td>
<td>Whorls and psammoma bodies</td>
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</tbody>
</table>
Diagnostic Tools - Immunohistochemistry

- **Glial:** GFAP
  - Astrocytic / oligodendrogial / ependymal
- **Neuronal:** Synaptophysin / chromogranin / NSE
- **Vascular:** CD34, CD 31
- **Epithelial markers:** EMA, CK
- **Proliferation marker:** Mib-1 (Ki-67) labeling index

**Special stains:** Reticulin / PTAH / PAS

**Molecular markers:** 1p 19q del - FISH

**EM:** Ependymoma / meningioma
GLIOMA

BIOLOGICALLY:

- **Diffuse**
  - Young adults, cerebral hemisphere and brainstem
  - Astrocytoma II - IV Oligodendrogloma

- **Circumscribed**
  - Children, characteristic location/morphology
  - PA/PXA/SEGA/Ependymoma
  - No vascular changes
  - BBB intact
  - No edema/enhancement
GRADING

- Nuclear atypia,
- Mitotic activity
- Necrosis (sign of uncontrolled growth)
- Vascular changes (tumor neovascularity; microvascular proliferation - MVP)

- 4-tiered system-
- **GRADE I** - "Low-Grade" - Surgery curative
- **GRADE II** - nuclear pleomorphism
  - Surgery mainstay of treatment
  - RT for incomplete resection
GRADING...

+ **GRADE III - ANAPLASTIC**, + mitoses
  + Surgery for HPR & debulking + RT +/- CT

+ **GRADE IV - MALIGNANT**, + ‘vasculartiy’/MVP
  +/- necrosis: Glioblastoma multiforme
  + Surgery for debulking + RT + CT (PCV/Temozolamide)
PILOCYTIC ASTROCYTOMA [WHO I]

- **Cell of Origin:** Astrocyte (bi-polar, hairlike)
- **Associations:** in ON (optic nerve) w/ NF-1
- **Location:** Cerebellum (85%), Cerebral hemisphere (10%), Chiasm/Hypothal, Optic Nerve, Cx spinal cord
- Circumscribed – Enhancing;
- Cyst with a mural nodule
- **Treatment:** Surgery, patience (radiation and chemotherapy uncommon)
Pathology

- Biphasic pattern -
  - dense pilocytic glia
    - Rosenthal fibers: Dense, eosinophilic fibers (intermediate filaments) within cytoplasmic processes of astrocytes
  - loose microcystic areas with EGB
- Abnormal capillaries - pericystic MVP
- +/- necrosis, occasional mitosis
- Degenerative nuclear changes
- Low grade
- Mib1 LI > 2% - ↑risk of recurrence
DIFFUSE ASTROCYTOMA WHO II

<table>
<thead>
<tr>
<th>Point</th>
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<tbody>
<tr>
<td>(Fibrillary, Protoplasmic, Gemistocytic)</td>
</tr>
<tr>
<td>&quot;Adult type&quot; or &quot;Hemispheric&quot; Astrocytoma</td>
</tr>
<tr>
<td>Diffusely infiltrate brain irrespective of grade</td>
</tr>
<tr>
<td>continuum from low-grade to high-grade; progress over time</td>
</tr>
<tr>
<td>Grade 2 $\Rightarrow$ 3 $\Rightarrow$ 4 (GBM)</td>
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<tr>
<td>Imaging correlates with histology</td>
</tr>
</tbody>
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Fibrillary Astrocytoma

- WHO grade II; Nuclear atypia +: enlarged, irregular, hyperchromatic
- No mitotic activity / necrosis / MVP
Gemistocytic Astrocytoma [II]
PROGRESSION

Astrocytoma II

Mib1 > 6 %

p53 +

L - 9p, 19q, 11p; CDK4 amplifiien
(4 - 5 years)

Anaplastic Astrocytoma III

PTEN mutn, MDM2 amplifiien,
EGFR amplification*
(< 2 years)

GBM (secondary); young adults, BS in children

* in Primary (de novo) GBM; older adults, rapid progression
Prognostic factors

**Good**
- Young
- Gross total resection
- M/S
- Microcysts
- Perivascular
- Lymphocytes

**Poor**
- TP53 mutation
- Mib-1 > 5%
- M/S
- Gemistocytes ++
GLIOBLASTOMA MULTIFORME

Pseudopalisaded necrosis
Microvascular proliferation
GLIOBLASTOMA MULTIFORME

**Good**
- < 50 years
- \( \uparrow \) preop KPS
- Resection of enhancing tumor
- M/S:
  - Giant cell
  - Capillary MVP
  - Oligodendroglial component
- MGMT

**Poor**
- \( \uparrow \uparrow \) Mib1
- Glomeruloid MVP
- Molecular
  - *VEGF+
  - *EGFR+
  - *her2 amplificn
  - *PTEN/ Rb1 mutn

* Stealth invasion’ - hinders surgical disease control
* CT/ RT resistance
MODES OF SPREAD

- Natural passages
- Along surfaces - leptomeningeal
- Along tracts - corona radiata, peduncles, corpus callosum, anterior commissure, arcuate fibres
- Across the meninges
Pleomorphic Xanthoastrocytoma WHO II

- Meningocerebral
- Pleomorphic & foam cells
- EGB
- Pericellular reticulin

Anaplastic PXA: III

- Mitoses > 5/10 HPF
- +/- palisaded necrosis → D/D- GBM
• *Mib-1* < 1%
ASTROCYTOMA: 5 Year survival


0  10  20  30  40  50  60  70  80
OLIGODENDROGLIOMA
## OLIGODENDROGLIOMA

### Good
- Age: < 40 years
- Low grade
- Gross total resection
- 1p 19q del (a/w better chemoresponse)

### Poor
- Mib-1 > 5%
- Anaplasia
- Necrosis & mitosis > 6/10 hpf
- P53 immunohistoexp
MIXED GLIOMA

**OLIGOASTROCYTOMA (II)**
- Conspicuous mixture of 2 distinct cell types
- At least one 100x field of oligo component
- Origin from bipotential glial precursor cells

CKDN 2A, occ EGFR amplifiens

**ANAPLASTIC OA (III)**
EPENDYMOMA

- Children - Infra/ supratentorial
- Adults - spinal cord*/ supratentorial
- Perivascular pseudorosettes/ True ependymal rosettes
- Poor prognosis -
  - Child < 3 years; Post fossa
  - Incomplete resection
  - Anaplasia
  - Mib-1 > 4%
  - CSF seeding

* Most common glioma at this site, a/w NF2
EPENDYMOMA
ANAPLASTIC EPENDYOMOMA

- De novo or rarely progress from preexisting grade II

MYXOPAPILLARY EPENDYOMOMA [I]
- Almost exclusive in cauda equina/ filum terminale; good prognosis

SUBEPENDYOMOMA [I]
- Slow growing, intraventricular grade I, favorable prognosis
NEURONAL/ MIXED GLIONEURONAL TUMORS

- Rare

- Favorable prognosis; usually low grade I/II

- Variable neuronal & glial differentiation

- Precise classification to avoid unnecessary RT/CT
MEDULLOBLASTOMA - [IV]

- Most common pediatric brain tumor (infratentorial)
- Std risk factors - > 3 years; cerebellar tumor; no mets at presentation; little/ no residual (<1.5 cm³)

All others are HIGH risk - + intense CT

- M/<S:
  - Cellular/ Round cell tumor
  - Homer-Wright rosettes
  - Desmoplastic & MBEN- good prognosis
  - Large cell variant- poor
  - IHC- Synaptophysin, chromogranin ++
  - Mib-1 : ↑↑
Homer Wright rosette
MENINGEAL TUMORS

- MENINGIOMA:
  - Meningioma (typical) [I]
  - Atypical Meningioma [II]
  - Anaplastic (Malignant) Meningioma [III]

- MESENCHYMAL (non-meningothelial)

- Primary MELANOCYTIC Lesions

- UNCERTAIN Origin
  - Hemangiopericytoma
  - Hemangioblastoma
MENINGIOMA

- Arise from meningothelial cells of arachnoid granulations
- Adjacent to venous sinuses
- Nodular, capsules, slow growing
- Benign
- Form whorls of cells, Psammoma bodies in the center
- Pressure effect
- No brain infiltration or metastasis (Benign)
<table>
<thead>
<tr>
<th>TYPE</th>
<th>GRADE</th>
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<tbody>
<tr>
<td>MENINGIOMA</td>
<td>I</td>
</tr>
<tr>
<td>ATYPICAL MENINGIOMA</td>
<td>II</td>
</tr>
<tr>
<td>+ Clear cell; chordoid</td>
<td></td>
</tr>
<tr>
<td>(↑mitosis 4 - 19/10HPF; OR 3 of foll- ↑cellularity, ↑N:C, prominent nucleoli, patternless growth, spontaneous/geographic necrosis)</td>
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<tr>
<td>ANAPLASTIC MENINGIOMA</td>
<td>III</td>
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<tr>
<td>+ Papillary; rhabdoid</td>
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<tr>
<td>(↑mitosis &gt; 20/10HPF; appearance like carcinoma/sarcoma/melanoma)</td>
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Meningioma

- **IHC**: EMA +; Mib-1 < 4/8/15%
- **EM**: Interdigitating cell processes
- Surgery if feasible
- **RT**
  - Incomplete resection
  - Recurrent disease
  - Atypical/invasive features
Hemangiopericytoma
Hemangiopericytoma

Reticulin

CD34 +
Metastasis

- Most common brain tumor in adults
- Common primary sites: breast, lung, GI tract, kidney & melanoma
- Most are in cerebrum (MCA territory); at the grey-white junctions due to vascularity
- Discrete, globoid, sharply demarcated tumors
- Tumor heterogeneity
- Limited biopsy material
- Team effort-
  - Surgeon
  - Radiologist
  - Pathologist
  - Radiation oncologist
Thank you!!