CNS Tumors

by: Rahaf Naser

CNS TUMORS:

- may arise from the **cells of the coverings** (meningiomas), **the brain cells** (gliomas, neuronal tumors), or **other CNS cell populations** (primary CNS lymphoma, germ cell tumors), or they may originate elsewhere in the body (**metastases**).
- Can involve the **brain or spinal cord**

2

EPIDEMIOLOGY:

- **INCIDENCE**:
  - The annual incidence of CNS tumors in the U.S →
    - 24 /100,000 for intracranial tumors , 1/3 malignant
    - 1-2/100,000 for intraspinal tumors
- **Metastases are more common than primary brain tumors.**

3

Characteristic features of CNS tumors:

- **No Premalignant stage: no** in situ lesions.
- **Metastasis is rare!**
  - Even the most highly malignant gliomas **rarely spread** outside of the CNS.
  - but the brain is **not comparably protected** against the spread of distant tumors.

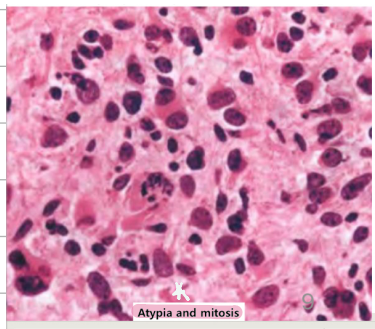
5

Characteristic features of CNS tumors:

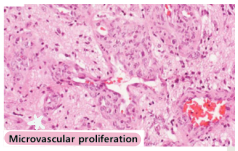
- **Growth pattern (infiltrative or not) and tumor location strongly influence the prognosis:**
  - Even low-grade lesions may infiltrate large regions of the brain, leading to serious clinical deficits, inability to be resected, and poor prognosis.
  - The anatomic site of the neoplasm can influence outcome independent of tumor type or grade due to local effects

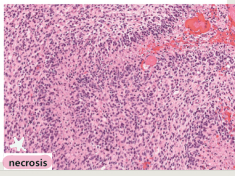
6

* The histologic grading of CNS tumors depends on:



9





Grade 1 lesions

(benign)

- low proliferative activity
- Can be cured after Surgical resection alone
- examples: – pilocytic astrocytoma
  – Subependymal gaint cell astrocytoma
  – Choroid plexus papilloma
  – myxopapillary ependymoma

Grade 2 lesions

- low proliferative activity
- usually infiltrative and often recure
- Some tend to progress to higher grades
- examples: – astrocytoma, IDH-mutant grade 2
  – Oligodendroglioma, IDH-mutand & 1p/19q-codeleted grade 2

Grade 3 lesions

Clear histologic evidence of malignancy (nuclear atypia and higher proliferative activity (mitosis))

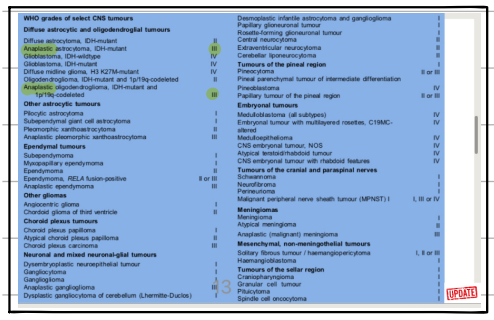
→ In most settings, patients recieve radiation and/or Chemotherapy

- examples:
  – astrocytoma, IDH-mutant grade 3
  – Oligodendroglioma, IDH-mutand & 1p/19q-codeleted grade 3

Grade 4 lesions

(high grade)

- Cytologically malignant, mitotically active, rapid proliferation, necrosis-prone neoplasms & microvascular proliferation
- associated with rapid pre- and postoperative disease evolution & fatal outcome



WHO grades of select CNS tumours	
Diffuse astrocytic and oligodendroglial tumours	
Diffuse astrocytoma, IDH-mutant	II
Anaplastic astrocytoma, IDH-mutant	III
Glioblastoma, IDH-wildtype	IV
Glioblastoma, IDH-mutant	IV
Diffuse midline glioma, H3 K27M-mutant	IV
Oligodendroglioma, IDH-mutant and 1p/19q-codeleted	II
Anaplastic oligodendroglioma, IDH-mutant and 1p/19q-codeleted	III
Other astrocytic tumours	
Pilocytic astrocytoma	I
Subependymal giant cell astrocytoma	I
Pleomorphic xanthoastrocytoma	II
Anaplastic pleomorphic xanthoastrocytoma	III
Ependymal tumours	
Subependymoma	I
Myxopapillary ependymoma	I
Ependymoma	II
Ependymoma, *RELA* fusion-positive	II or III
Anaplastic ependymoma	III
Other gliomas	
Angiocentric glioma	I
Chordoid glioma of third ventricle	II
Choroid plexus tumours	
Choroid plexus papilloma	I
Atypical choroid plexus papilloma	II
Choroid plexus carcinoma	III
Neuronal and mixed neuronal-glial tumours	
Dysembryoplastic neuroepithelial tumour	I
Gangliocytoma	I
Ganglioglioma	I
Anaplastic ganglioglioma	III
Dysplastic gangliocytoma of cerebellum (Lhermitte-Duclos)	I
Desmoplastic infantile astrocytoma and ganglioglioma	I
Papillary glioneuronal tumour	I
Rosette-forming glioneuronal tumour	I
Central neurocytoma	II
Extraventricular neurocytoma	II
Cerebellar liponeurocytoma	II
Tumours of the pineal region	
Pineocytoma	II or III
Pineal parenchymal tumour of intermediate differentiation	II or III
Pineoblastoma	IV
Papillary tumour of the pineal region	II or III
Embryonal tumours	
Medulloblastoma (all subtypes)	IV
Embryonal tumour with multilayered rosettes, C19MC-altered	IV
Medulloepithelioma	IV
CNS embryonal tumour, NOS	IV
Atypical teratoid/rhabdoid tumour	IV
CNS embryonal tumour with rhabdoid features	IV
Tumours of the cranial and paraspinal nerves	
Schwannoma	I
Neurofibroma	I
Perineurioma	I
Malignant peripheral nerve sheath tumour (MPNST)	I, III or IV
Meningiomas	
Meningioma	I
Atypical meningioma	II
Anaplastic (malignant) meningioma	III
Mesenchymal, non-meningothelial tumours	
Solitary fibrous tumour / haemangiopericytoma	I, II or III
Haemangioblastoma	I
Tumours of the sellar region	
Craniopharyngioma	I
Granular cell tumour	I
Pituicytoma	I
Spindle cell oncocytoma	I

UPDATE

- Widespread infiltration of surrounding tissue and risk of craniospinal dissemination
- examples:
  – Glioblastoma, IDH-wild type
  – Medulloblastoma
  – Pineoblastoma
  – most embryonal neoplasms

Pediatric CNS tumors:

- 20% of all pediatric tumors.
- Childhood CNS tumors differ from those in adults in:
  - **Location:**
    - 2/3 infratentorial in kids (posterior fossa)
    - 2/3 supratentorial in adults (cerebral hemispheres above tentorium)
  - **Mutation profile & histologic subtype:**
    - Kids: medulloblastoma, pilocytic astrocytoma, ependymoma
    - Adults: glioblastoma, metastases, meningiomas, diffuse gliomas constitute most gliomas in adults(including astrocytomas and oligodendrogliomas)

14

CLASSIFICATION OF CENTRAL NERVOUS SYSTEM TUMORS

Courtesy of Dr. Pieter Wesseling

16

- For nearly a century, the classification of brain tumors has been done according to their **microscopic similarities** with what's thought to be their cell of origin (based on the light microscopic appearance, the immunohistochemical expression of proteins, and the electron microscopic assessment of ultrastructural features).
- The 2016 classification breaks with this nearly century-old tradition and **incorporates well-established molecular parameters into the classification.**

17

- the classification includes diagnostic categories that depend on **genotype.**
- The 2016 WHO classification implemented the **combined phenotypic-genotypic diagnostics based on histologic features & tumor genetic profile (integrated diagnoses)**
- The 2016 classification helped **improving treatment protocols and predicting prognosis.**

18

CNS tumors

- Glioma, Neuronal and glioneuronal tumors
  - adult type diffuse glioma
    - Astrocytoma: IDH-mutant, grade 2,3,4
    - Glioblastoma: IDH-wild-type, Grade 4
    - Oligodendroglioma: IDH-mutant & 1P/19q-codeleted, grade 2 or 3
  - Pediatrice type glioma
    - Circumscribed
    - diffuse: high grade / low grade
  - Circumscribed astrocytic gliomas
  - Glioneuronal and neuronal tumors
  - Ependymoma
- Embryonal (Primitive) tumors
  - Medulloblastoma
- Other parenchymal tumors
  - Primary CNS lymphoma
- Meningioma
- Metastatic tumors: Lung, breast, Kidney, Skin (melanoma) and Colon

Gliomas

Genetic alterations in gliomas

Mutations in isocitrate dehydrogenase (IDH) genes

- Observed as EARLY event in gliomagenesis
- Seen in astrocytomas & oligodendrogliomas
- Gain of function mutation
  - IDH1 codon 132: The most frequent is IDH1 R132H mutation (83–91%) of IDH mutant gliomas
  - IDH2 codon 172: R172K is the most frequent IDH2 mutation
- Can be detected by immunohistochemical
  - Stains & molecular studies:
    - IDH1-R132H immune stain
    - IDH sequencing for IDH1 codon 132 & IDH2 codon 172

✳ Gain of function mutation → lead to increased production of 2-hydroxyglutarate (oncometabolite) → interferes with the activity of several enzymes that regulate gene expression → DNA hypermethylation & maintaining the cells in stem cell-like physiological states → self-renewal and tumorigenesis

Whole arm co-deletion of 1p and 19q chromosomal segments

- Diagnostic of oligodendrogliomas in the presence of IDH mutation

& the vast majority of IDH mutant and 1P/19q co-deleted oligodendrogliomas Carry TERT promotor hotspot mutation.

→ telomerase Stabilization

Cellular immortalization & proliferation

ATRX and P53 loss of function mutation

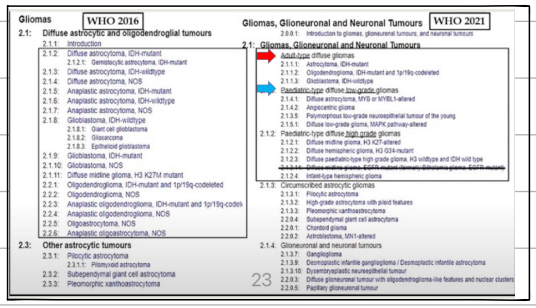
- Both occure in IDH mutant astrocytomas

- **ATRX mutation** induces abnormal telomeres maintenance mechanism known as **"alternative lengthening of telomeres"**

→ ATRX mutation is mutual exclusive with the activating promoter mutation of the TERT gene (1p/19q codeletion)

→ P53 mutation: enable tumor survival

- ATRX → associated with genomic instability → induces P53 dependent cell death → mutation in P53 helps these cells to survive

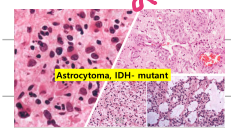


✳ Glioma, Neuronal and glioneuronal tumors

adult type diffuse glioma
Astrocytoma IDH-mutant grade 2,3,4
Glioblastoma IDH-wild-type Grade 4
Oligodendroglioma, IDH-mutant & 1P/19q-codeleted, grade 2 or 3
Pediatrice type glioma
Circumscribed
diffuse
high grade
low grade
Circumscribed astrocytic gliomas
Glioneuronal and neuronal tumors
Ependymoma

Adult type diffuse glioma

Astrocytoma



Phenotype

It's a diffusely infiltrating glioma

Genotype

- IDH1 or less frequently IDH2 mutation
- Inactivating mutation in TP53 and/or ATRX
- absence of 1p/19q codeletion

* Age at diagnosis : 40-60
* cerebral hemispheres ± cerebellum, brainstem, or spinal cord

* Presentation :

- Seizures, headaches, and focal neurologic deficits related to the anatomic site of involvement
- Clinically : Static for years or progressive.

The prognosis gets poorer as the grade increases

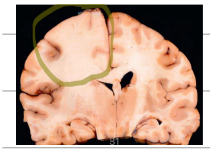
- On the basis of histologic features astrocytomas, IDH- mutant are stratified into three groups:
  - astrocytomas, IDH- mutant, grade 2, median survival is >10 years.
  - astrocytomas, IDH- mutant grade 3, median survival is 5-10 years
  - astrocytomas, IDH- mutant grade 4, median survival is 3 years.
- NO grade 1 astrocytoma, IDH- mutant, because by convention grade 1 implies benign behavior and all diffuse gliomas are considered malignant

Morphology

Macroscopic

Grade 2&3

- Poorly defined infiltrative tumors
- expand and distort the invaded brain
- No discrete mass, infiltration beyond the grossly evident margins



Grade 4

- Poorly defined infiltrative tumors
- lacks large area of central necrosis & hemorrhage seen in IDH-wild type GBM

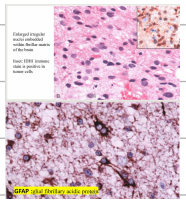
Microscopic

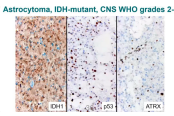
Grade 2

* The transition between neoplastic and normal tissue is indistinct.
* Tumor cells infiltrate normal tissue many centimeters from the main lesion.

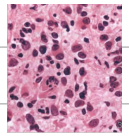
- Hypercellular: (Compared to normal white matter) mild to moderate ↑ in number of glial cell nuclei
- Cytologic atypia: mild enlarged, elongated or irregular hyperchromatic nuclei NO prominant atypia

+ Fibrillary background made of a network of fine astrocytic cell processes
NO or rare mitotic activity
NO necrosis
NO microvascular proliferation





Grade 3



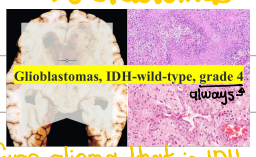
More densely cellular
More nuclear pleomorphism
Mitotic figures are present
NO necrosis
NO microvascular proliferation

Grade 4

Same as 3 With microvascular prolif. and/or necrosis

- The presence of homozygous deletion of CDKN2A and/or CDKN2B in astrocytomas, IDH-mutant, grade 4 (EVEN IF THE HISTOLOGY SUGGESTS A LOWER GRADE).

Glioblastomas



→ Diffuse glioma that is IDH-wildtype and H3 wildtype and has one or more the following features:

- Microvascular proliferation
- Necrosis
- TERT promotor mutation
- EGFR gene amplification
- combined gain of entire chromosome 7 and loss of entire chromosome 10 [+7/-10]

→ The most common malignant glioma (50% of all primary malignant brain tumors in adults)

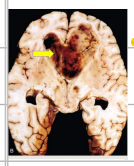
Age : 6th-8th decades of life

cerebral hemispheres → temporal, parietal, frontal, thalamus, basal ganglia

Radiology : Ring enhancing lesion

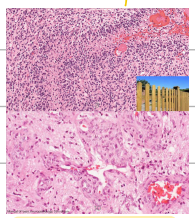
- Clinically:
  - rapid progression
  - Sezures, neurocognitive impairment, neursea, vomitting, and headache
  - Rapid infiltration of the corpus callosum with growth to the contralateral hemosphere leading to bilateral syymmetrical lesion (butterfly glioma)
- Prognosis: Very Poor even with resection, chemotherapy and radiotherapy the median survival is only about 15-18 months.

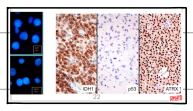
Macroscopic



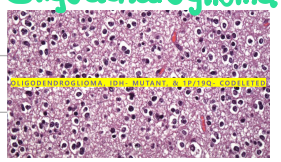
- variation in the gross appearance of the tumor from region to region is characteristics (was called glioblastoma multiforme)
- Some areas are firm and white, others are soft and yellow (due to tissue necrosis), others show regions of cystic degeneration and hemorrhage.

Microscopic





Oligodendroglioma



→ a diffusely infiltrating slow growing glioma with IDH1 or IDH2 mutation and codeletion of chromosomal arms 1p and 19q.
→ 5-15% of gliomas

Age : 40-50 yrs

mostly cerebral hemispheres mainly frontal or temporal lobes, white matter

- The combination of surgery, chemotherapy, and radiotherapy yields an average survival of:
  - 10-20 years for WHO grade 2.
  - 5-10 years for WHO grade 3.
- Grade 3 is more aggressive than grade 2 oligodendroglioma

NO grade 1 or 4

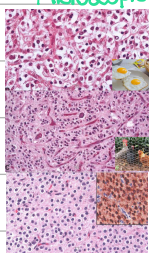
When corrected for tumor grade, Oligodendrogliomas (CNS WHO grade 2/3) Have best prognosis among diffuse glial tumors

Macroscopic

Infiltrative tumors with blurring of grey matter-white matter boundary

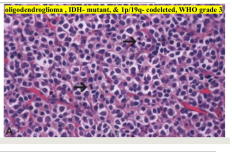
± gelatinous gray mass, cysts, focal hemorrhage and Calcification

Microscopic



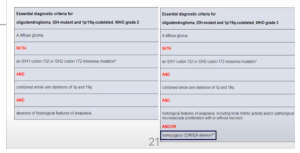
- Sheets of regular uniform cells resembling oligodendrocytes
- Spherical nuclei containing finely granular chromatin (Salt and pepper)
- The nuclei are surrounded by a clear halo of cytoplasm (fried-egg appearance)
- delicate network of "chicken-wire" - like anastomosing capillaries
- Calcification up to 90% of cases
- Mitotic activity usually is absent or low (Ki 67<5%)
- NO Spontaneous necrosis
- NO microvascular proliferation

Grade 3



oligodendroglioma , IDH- mutant, & 1p/19q- codeleted WHO grade 3:

- Defined as: An IDH-mutant and 1p/19q-codeleted oligodendroglioma with focal or diffuse histological features of anaplasia (in particular, pathological microvascular proliferation and/or brisk mitotic activity with or without necrosis)



Glioma, Neuronal and glioneuronal tumors

- adult type diffuse glioma
  - Astrocytoma — IDH-mutant — grade 2,3,4
  - Glioblastoma — IDH-wild-type — Grade 4
  - Oligodendroglioma — IDH-mutant & 1p/19q-codeleted — grade 2 or 3
- Pediatrice type glioma
  - Circumscribed
  - diffuse
    - high grade
    - low grade
- Circumscribed astrocytic gliomas
- Glioneuronal and neuronal tumors
- Ependymoma

Neuronal tumors

Less frequent than gliomas

→composed of cells with neuronal characteristics and express neuronal markers, such as synaptophysin, neurofilaments, and NeuN

Typically, lower grade lesions & often present with seizures

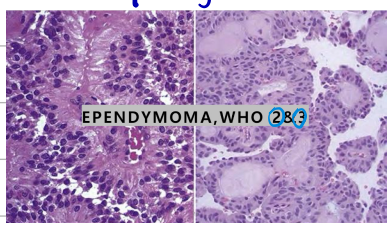
Gangliogliomas
WHO grade 1

* Children & young adults
* Slow growing tumor
* Composed of a mixture of neoplastic ganglion and glial cells
* Most commonly in the temporal lobe
* 20-50% have mutations in BRAF gene

Dysembryoplastic neuroepithelial tumor (DNT)
WHO grade 1

- Rare
- children and young adults
- Slow growing tumor
- Present with seizure
- Most commonly in the Superficial temporal lobe.

Ependymoma



→glioma, Mostly arise next to the ependyma-lined ventricular system, including the central canal of spinal cord

- Posterior fossa: near the 4th ventricle, accounting for 5-10% of tumors in the first two decades of life
- Supratentorial
- Spinal: the most common location in adults & in patients with NF2

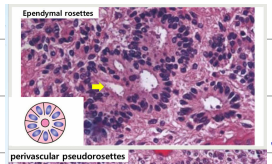
Age:

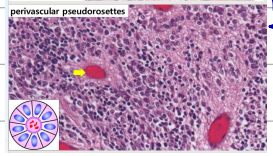
In first 2 decades of life, near the 4th ventricle (Post-Fossa) accounting for 5-10% of primary brain tumors in this age group.

In adults, the spinal Cord & Supratentorial ependymomas occur with almost equal frequency.

* The clinical outcome for completely resected supratentorial and spinal ependymomas is better than for those in posterior fossa.

Grade 2





Ependymoma, WHO grade 2, microscopic:

- uniform small cells with round to oval nuclei and granular chromatin in a fibrillary background
- low cellularity
- low mitotic count
- No necrosis or MVP
- Cilia and microvilli are seen on ultrastructural examination

Ependymoma WHO grade 2, Morphology:

- Tumor cells may form glandlike structures (rosettes) → **Rosette formation**
  - **Ependymal rosettes:** diagnostic hallmark of ependymoma (25%)
  - **perivascular pseudorosettes:** not specific for ependymoma (seen in glioblastoma and medulloblastoma)

Ependymal rosettes:

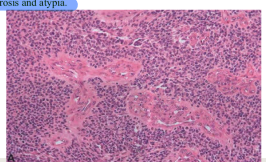
- tumor cells arranged around central canal or lumen that resemble the embryologic ependymal canal, with long, delicate processes extending into a lumen

Perivascular pseudorosettes:

- tumor cells radially arranged around vessels.
- Called "pseudo" because the central structure is not formed by the tumor itself, but instead represents a native, non-neoplastic element.

Grade 3

- **Anaplastic ependymomas, WHO grade 3:**
- Show less evident ependymal differentiation
- brisk mitotic rates, and microvascular proliferation carry more prognostic impact than necrosis and atypia.



CNS tumors

- Glioma, Neuronal and glioneuronal tumors
- Embryonal (Primitive) tumors → Medulloblastoma grade 4
- Other parenchymal tumors → Primary CNS lymphoma
- Meningioma grades 1-3
- Metastatic tumors (Lung, breast, Kidney, Skin (melanoma) and Colon)

Embryonal neoplasms

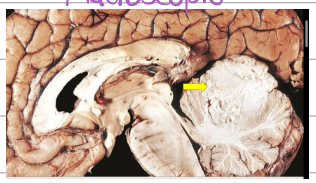
*Primitive or undifferentiated

Small round cell tumor of neuroectodermal origin resembling normal progenitor cells in the developing CNS.

→ The most common CNS embryonal tumor is Medulloblastoma accounting for 20% of pediatric brain tumors.

→ predominantly in children
→ Mainly in cerebellum
→ All are highly malignant, WHO grade 4
→ Radiosensitive
→ The prognosis for untreated patients is dismal
→ 5 year survival rate may be as high as 75% with total excision, chemotherapy, and irradiation

Macroscopic



In children (midline) ↙ ↘ in adults (lateral)
well circumscribed (often)

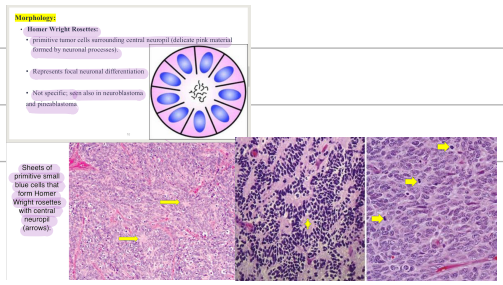
*May extend to the cerebellar surface & involve the leptomeninges

COMPLICATIONS:

↳ Medulloblastoma have tendency to spread to the subarachnoid space → dissemination through the CSF

Morphology

- Sheets of Small primitive Cells ("Small blue"), Each cell with little Cytoplasm & hyperchromatic elongated or crescent-Shaped nuclei
- very cellular
- Mitosis are abundant
- often express neuronal markers such as Synaptophysin, expression of glial markers (GFAP) is less common



Primary CNS lymphoma

- The most common CNS neoplasm in immunosuppressed individuals

→ In non-immunosuppressed populations, the frequency increases after 60 yrs of age.

→ Aggressive disease ←

Poor response to chemo (especially if compared with Comparable histology that occure at non-CNS site)

The most common type:

diffuse large B-cell lymphomas

- Primary brain lymphoma -

- → Multifocal
- → involvement outside of the CNS (in lymph nodes or BM) is rare and late complication
- → Relatively well defined as compared with glial neoplasms but not as discrete as metastases

Meningiomas

tumors that arise from meningothelial cells of the arachnoid matter and usually attached to the dura

Age: adults (F > M)

any of the external surfaces of the brain, spinal cord, within the ventricular system, from the stromal arachnoid cells in the choroid plexus

Presentation: most common
headache, Seizures, weakness (depends on 📍)

Prognosis determind by
lesion size and location; Surgical accessibility; histologic grade

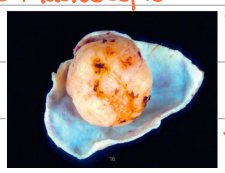
→ Most meningiomas are easily separable from the underlaying brain but some tumors are infiltrative (associated with increased risk of recurrence)

→ Meningiomas express progesterone receptors and may grow more rapidly during pregnancy, only to regress after delivery

Pathogenesis

- The most common cytogenetic abnormality is loss of chromosome 22, especially the long arm (22q). The deletions include the region that harbors the NF2 gene.
- Of sporadic meningiomas, 50% to 60% harbor mutations in the NF2 gene
- In meningiomas without NF2 mutations, mutations occur in other genes.
- Multiple meningiomas + 8th nerve schwannoma or glial tumor → common in the setting of NF2.

- Macroscopic

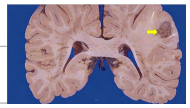


- rubbery, rounded, or bosselated dural masses that compress underlying brain.
- Mostly separable from underlying brain, but some tumors are infiltrative

>50% of intracranial tumors

Mostly carcinomas

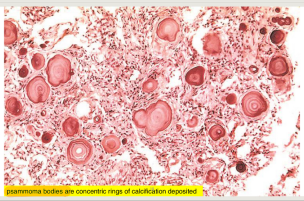
- The most common Primary sites are lung, breast, Skin (melanoma) Kidney and colon (80% of cases)
- Sharply demarcated masses, often at the gray-white matter Junction & elicit local edema & reactive gliosis
- The boundary between tumor & brain parenchyma is sharp at the microscopic level with Surrounding reactive gliosis.



Meningiomas

Meningiomas (WHO grade 1):

- well-defined dura-based masses that may compress the brain but do not typically invade it +/- overlying bone extension.
- Epithelioid cells arranged in whorly (syncytial)pattern +/- psammoma bodies
- Many histologic subtype, with no prognostic difference, including:
  - meningothelial (most common)→clusters of epithelioid cells with fuzzy or indiscernible cell membranes
  - Other patterns include fibrous, transitional, angiomatous, microcystic, lymphoplasmacyte rich, metaplastic, secretory and psammomatous



MENINGIOMAS, WHO grade 2

- recurrence and aggressive local growth (may require radiation & surgery)

1- **4 to 19 mitoses/10 HPF; or**

2- **(3 out of 5):** increased cellularity, small cells with a high N/C ratio, prominent nucleoli, patternless growth, or necrosis; **or**

3- **clear cell** or **chordoid subtypes of meningioma; or**

4- **unequivocal brain invasion**

MENINGIOMAS, WHO grade 3:

- Rare, highly aggressive, resemble a high-grade sarcoma or carcinoma or melanoma morphologically.

1. **≥20 mitoses/ 10HPF;** or
2. Frank anaplasia (sarcoma, carcinoma or melanoma like); or
3. TERT promotor mutation; or
4. Homozygous deletion of CDKN2A/B
5. **Papillary;** or **rhabdoid meningioma.**

Familial tumor Syndromes

Inherited Syndromes caused by mutations in tumor Suppressor genes and associated with increased risk of neoplasms

Tumors of the nervous system make a prominent aspect of some of these Syndromes, including:

Tuberous Sclerosis

→ (Autosomal dominant syndrome)

→ 1 in 6000 births

Characterized by

- Cutaneous lesions
  - → Angiofibromas
  - → localized leathery thickenings (Shagreen patches)
  - → hypopigmented areas (ash-leaf Patches)
  - → Subungual fibromas
- development of hamartomas & benign neoplasms involving the brain & other tissues
- Extracerebral lesions:
  - → Renal angiomyolipomas
  - → Retinal glial hamartomas
  - → Pulmonary lymphangioleiomyomatosis
  - → & Cardiac rhabdomyomas develop during childhood and adolescence
- Cysts at various sites, including liver, Kidneys & Pancreas

Von Hippel-Lindau disease

→ (Autosomal dominant disease)

→ 1 in 30,000 to 40,000

Associated with

- hemangioblastoma of the CNS - in the cerebellum and retina, brainstem, Spinal cord and nerve roots.
- Cysts in Pancreas, liver and Kidney
- Increased risk of renal cell Carcinomas
- Pheochromocytomas

CNS hamartomas

- Hamartomas within the CNS take the form of **cortical tubers** and **subependymal nodules**
- **Cortical tubers** are epileptogenic, and surgical resection can be beneficial.
- **Hamartomas** consist of glioneuronal hamartomas and subependymal hamartomas including **subependymal giant cell astrocytomas (SEGA)**

Hemangioblastomas

- highly vascular neoplasms consists of numerous capillary-size or larger thin-walled vessels with intervening neoplastic cells that have vacuolated, lipid-rich cytoplasm.
- The neoplastic stromal cells express inhibin (useful diagnostic marker).