LECTURE 10 | CNS Tumors (1)

In this lecture, we will talk about:

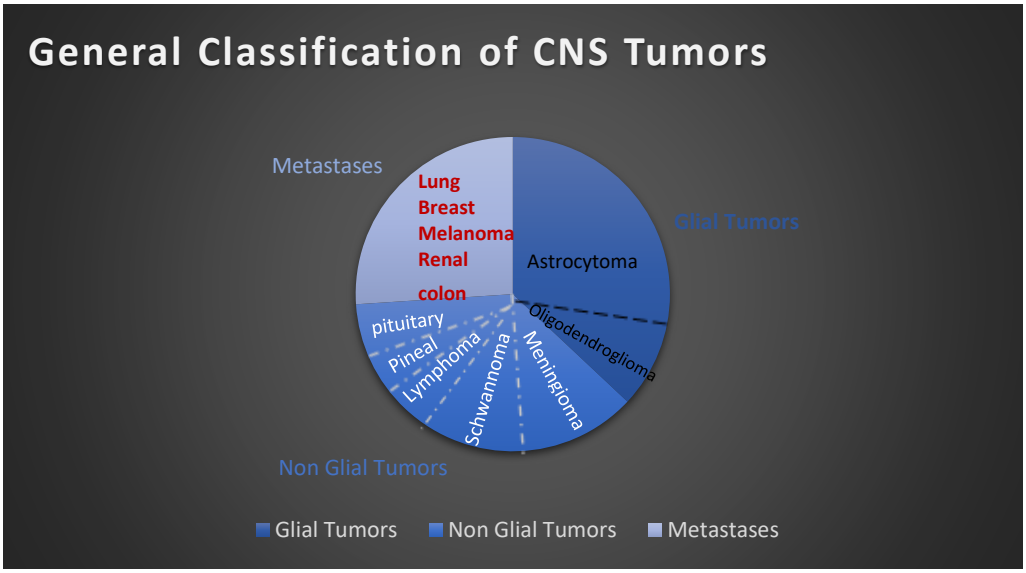
- The General Features related to CNS Tumors
- The Classification of CNS tumors according to the cell of origin
- The General classification of CNS Tumors
- Gliomas classification and different types

General features of CNS Tumors:

- No premalignant or in situ stage
- Low grade lesions can widely infiltrate with serious clinical deficit
- Anatomical site important in outcome regardless of type, grade
- Rarely spread outside CNS

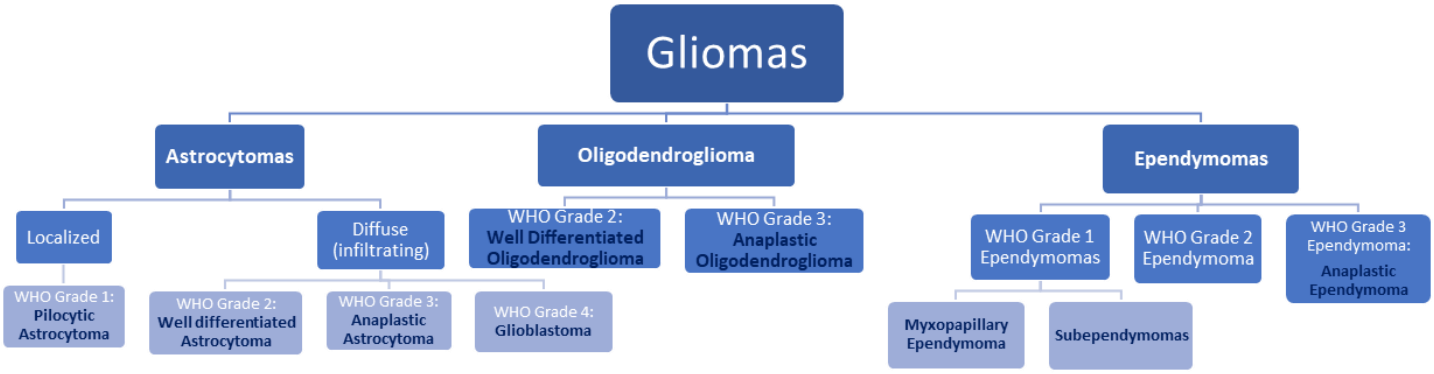
CNS Tumors Classification (According to the cell of origin)

Glioma	Neuronal Tumors	Embryonal (Primitive) Neoplasms
Meningeoma	Metastatic Tumors	Others (Lymphoma and Germ cell tumors)



Note: I tried to make the chart beside similar to the coloured one in the slides, but you can still refer to the other one if you want.

Gliomas Classification



- Gliomas are the most **common** primary brain tumors.
- It is now thought that the different types of gliomas originate from a progenitor cell that can differentiate to these three morphologic types.

General info about "Diffuse astrocytoma"

- Account for **80**% of **adult** gliomas.
- Present at **40- 60** years of age
- Location: **cerebral hemispheres**
- Present with *seizures*, *headache*, *focal neurologic deficit*
- Has a **spectrum** of histological differentiation (unlike the localized pilocytic astrocytoma)
- **Prognosis** is affected by **grade** (Grade 4 has the worst prognosis)
- There is no **grade 1** diffuse astrocytoma.
- Now, we will talk about the different types of gliomas.

Well Differentiated Astrocytoma

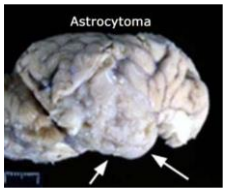
WHO Grade II Astrocytoma

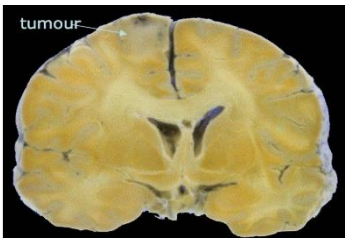
General Info

- Can be static for several years.
- If this tumour progresses, rapid deterioration + anaplastic histological features develop.
- Mean survival is more than **five** years.

Gross Features

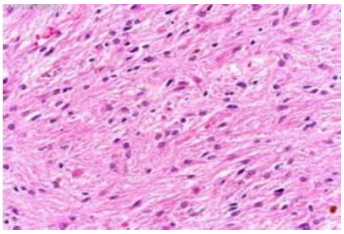
- Poorly defined grey, infiltrative tumours that invade the brain without forming a discrete mass:



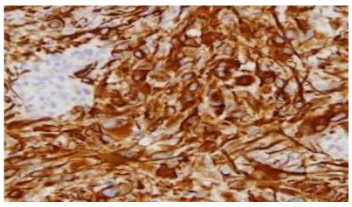


Microscopic Features

- Mild to Moderate increase in glial cells.
- Some nuclear pleomorphism exist.
- Background: fibrillary due to fine astrocytic processes. These are positive with glial fibrillary acidic protein (GFAP)



GFAP staining in astro

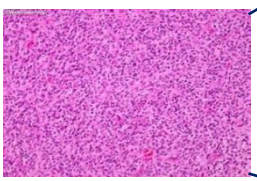


Anaplastic Astrocytoma

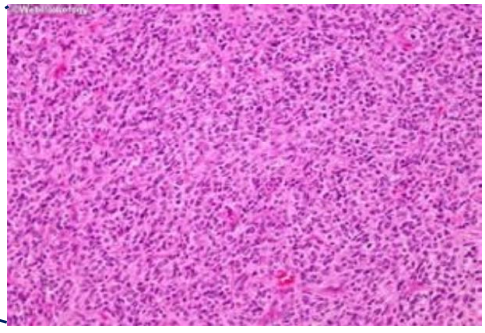
WHO Grade III Astrocytoma

Microscopic Features

- More cellular than well differentiated astrocytoma
- More pleomorphism
- Mitotic figures



Notice the HIGH cellularity



Glioblastoma

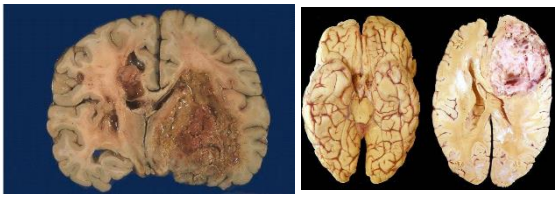
WHO Grade IV Astrocytoma

General Info

- Has poor prognosis.
- 15 months survival.
- Survival rate improved; 25% live up 2 years or more with resection followed by chemo and radiotherapy.
- The tumour can result due to progression from a previous astrocytoma (secondary glioblastoma) or can start as glioblastoma from the beginning (Primary astrocytoma)

Gross Features

- Presence of soft, necrotic, and haemorrhagic areas.



Microscopic Features

- Histologically characterized by **variation** of the tumour appearance (that is why it was called glioblastoma **multiforme**)
- Looks like anaplastic Astrocytoma **plus** Necrosis (usually pesudopalisading) **or** Vascular proliferation
- Notice in figure 1 the presence of palisaded nuclei around necrotic area.
- Vascular proliferation in glioblastoma Manifests as tufts of cells that pile up and bulge into the lumen. The presence of double endothelial layer is enough (minimal criteria) to diagnose vascular proliferation. If it is marked and severe it forms: glumeruloid body (refer to figure 2)

Figure 1

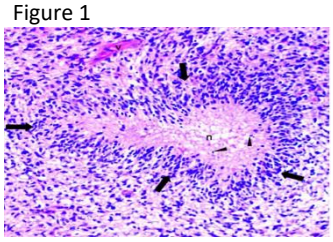
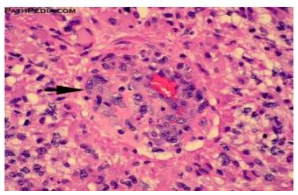
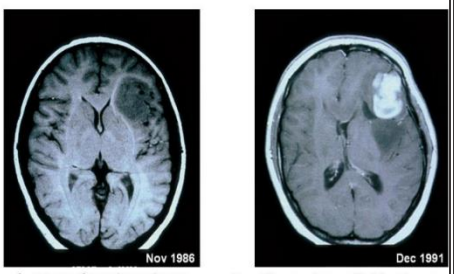


Figure 2: Glomeruloid body



Radiological Features

- High grade astrocytoma contains abnormal leaky vessels.
- This gives contrast enhancement on imaging studies.
- Contrast given before MRI scanning has limited capacity to reach the brain tissue due to blood brain barrier (BBB).
- If there is defect in BBB (like in the leaky vessels), the contrast material reaches the brain and forms obvious lesions.



Low-grade astrocytoma (WHO grade II) → 5 years → Secondary glioblastoma (WHO grade IV)

Astrocytomas and Genetics

- 80% of astrocytomas have a mutation in ***IDH 1*** and ***IDH 2*** (isocitrate dehydrogenase).
- This mutation is important in diagnosis and prognosis.
- This can be detected by immunohistochemistry and molecular studies (refer to figure 3)
- The mutations drive increased methylation in gliomas (affect the epigenetics).
- Gliomas with mutated IDH1 and IDH2 have **better** prognosis compared to gliomas with wild-type IDH.
- No drugs currently target mutated IDH, although this remains an area of active research.

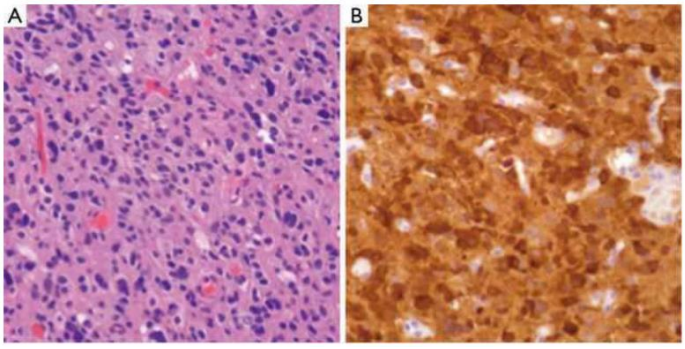
2016 classification of Glioblastoma

1. Glioblastoma, IDH-**wildtype** (about 90 % of cases), which corresponds most frequently with the clinically defined primary or de novo glioblastoma and predominates in patients over 55 years of age.
2. Glioblastoma, IDH-**mutant** (about 10 % of cases), which corresponds closely to so-called secondary glioblastoma with a history of prior lower grade diffuse glioma and preferentially arises in younger patients.

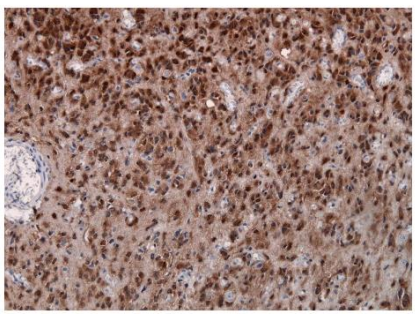
Note: Primary & secondary or IDH mutated & wild type glioblastomas are histopathologically similar

3. Glioblastoma, **NOS**, a diagnosis that is reserved for those tumours for which full IDH evaluation cannot be performed.

Figure 3: IDH 1 staining in anaplastic astrocytoma



IDH staining



Pilocytic Astrocytoma

WHO Grade I Astrocytoma

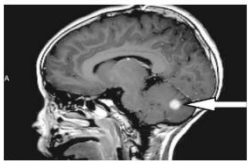
General Info

- Relatively benign (WHO grade 1).
- Slow growing tumours and can be surgically resected.
- Occurs in children and young adults.
- Location: **Mostly** In the **cerebellum**, but can also involve: third ventricle, optic pathway, spinal cord, and rarely cerebral hemispheres.
- They have different mutations than diffuse astrocytomas (no IDH mutation, and rarely TP53 mutation.)
- They have BRAF pathway mutations. So targeted therapy with BRAF inhibitors can help in treatment, especially in cases where the tumour is not resectable.

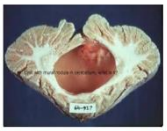
Gross Features

- Has Solid and Cystic components
- If solid, it is usually well defined.

Note the well circumscribed lesion in the cerebellum



Pilocytic astro: this example is mainly cystic but has also a solid component



Microscopic Features

- bipolar cells with long GFAP positive processes.
- **Rosenthal** fibres: thick, elongated, eosinophilic protein aggregates seen in astrocytic processes. Rosenthal fibres can also be seen with **chronic gliosis** (fig. 1)
- eosinophilic granular bodies.
- Microcyst (refer to figure 2)
- mitosis and necrosis are **rare**.

Pilocytic astrocytoma

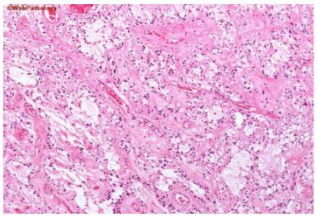


Figure 1: Rosenthal fibers

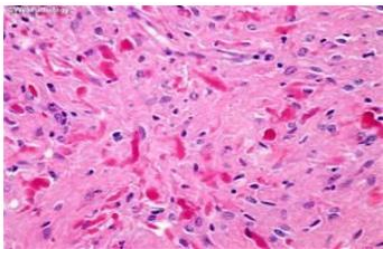
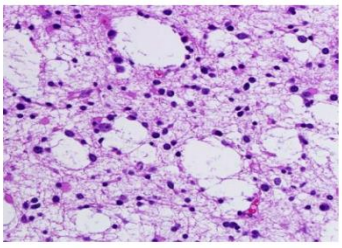


Figure 2 Pilocytic/ microcysts



LECTURE 11 | **CNS Tumors (2)**

In this lecture, we will talk about:

- Oligodendrogliomas (and how they differ from Astrocytomas)
- Ependymomas
- The tumours related to the ependymal cells.
- Some Neuronal Tumours.
- Some Embryonal neoplasm
- Medulloblastoma

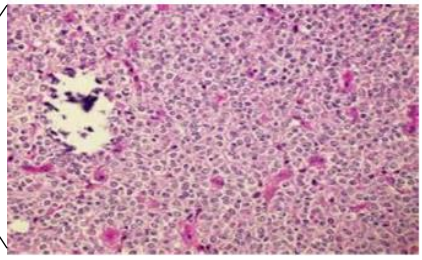
Oligodendrogliomas

WHO Grade II & III Oligodendrogliomas

General Info

- Make about 5-15% of gliomas.
- Occur most often in people **between the ages of 40-50.**
- Location: Cerebral hemispheres, mainly in the white matter.
- Has a better prognosis than astrocytoma of the same grade.
- There is **no** WHO grade 1 oligodendroglioma.
- Well differentiated oligodendrogliomas (**WHO II**): 10-20 years survival; with treatment.
- Anaplastic oligodendrogliomas (**WHO III**): 5-10 years survival; with treatment
- Anaplastic oligodendrogliomas: more cellularity, more anaplasia (& increased pleomorphism), and more mitosis=>Poorer prognosis

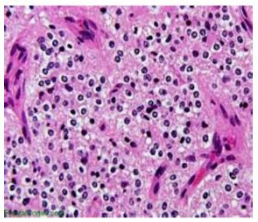
Anaplastic Oligodendroglioma



Morphology

- Infiltrative, gelatinous masses
- Can have cysts, haemorrhage, or calcifications.
- **Microscopically**:
  - ❖ Sheets of regular cells with spherical nuclei, granular chromatin, clear cytoplasm, rare mitoses
  - ❖ **Fried egg appearance** of the cells.

oligodendroglioma;/ note the white halo around the nuclei giving the fried egg appearance



Oligodendrogliomas and Genetics

- IDH 1 and 2 mutations exist in **90%** of cases. (mutated tumors have better prognosis than wild type)
- Co-deletion of chromosomes 1p and 19q is found in **80%**
- The presence of (1p, 19q mutation) makes this tumour highly responsive to chemotherapy and radiotherapy.
- With the new WHO classification (2016) the **1p,19q co-deletion** is essential to **diagnose** oligodendroglioma.
- Glial tumour + IDH Mutation + 1p,19q co-deletion **= oligodendroglioma**
- Glial tumour + IDH Mutation = **Astrocytoma** (regardless of their morphology).

Ependymomas

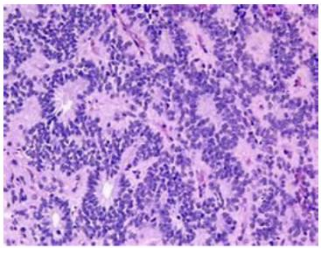
General Info

- Arise next to **ventricles** and **central canal** of spinal cord.
- If they occur in first two decades of life: mostly will arise near the fourth ventricle.
  In adults: mostly in the spinal cord
- Prognosis is better if the tumour is resectable.
- Supratentorial and spinal cord tumours are more amenable to complete surgical resection, thus they have a better prognosis than posterior fossa tumors.

Morphology

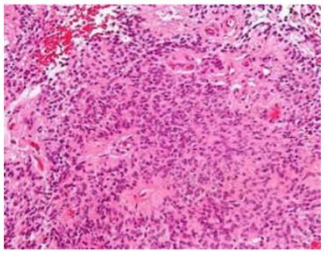
- Solid or papillary masses
- Regular round nuclei
- Granular chromatin
- Dense fibrillary background (GFAP**+)**
- **Rosette** formation around **canals** and **Pseudo-rosette** around **blood vessels.**
- Anaplastic ependymoma: cellular, mitosis, necrosis.

Ependymoma/ rosettes
note: true rosettes arise around canals



Notice the Difference.

Ependymoma/ pseudorossetes, these arise around blood vessels



Tumors related to the ependymal cells.

General Info

- There are some tumors that occur below the ependymal lining or in association with the choroid plexus.
- These tumors include *choroid plexus papilloma*, *subependymoma* and *colloid cysts.*
- All the above are **benign**! And **rare**.
- However, because of their location they cause clinical problems including hydrocephalus.
- Choroid plexus carcinoma can occur but is a rare tumour.

Neuronal Tumors

General Info

- These are rare tumors that have neuronal differentiation.
- *Central neurocytoma*: low grade neoplasm within and adjacent to ventricular system.
- *ganglioglioma*: glial elements and mature appearing neurons.
    - Usually are slow growing but the glial element can progress.

Embryonal Neoplasms

General Info

- These are tumors of **neuroectodermal origin**.
- Primitive appearance that resembles the normal progenitor cells that are found in the developing CNS: small round cells, little cytoplasm.
- Most common type of these tumors: *medulloblastoma*
- *Medulloblastoma*: 20% of paediatric brain tumors.

Medulloblastoma

WHO Grade 4 Tumour

General Info

- Occurs predominantly in **children**.
- Exclusively in the **cerebellum**
- Highly malignant if untreated
- Radiosensitive
- Surgery + chemotherapy+ Radiotherapy => 5-year survival reaches 75%
- Treatment: Medulloblastoma therapy, including craniospinal radiation and multiagent chemotherapy, results in significant long-term **toxicity** for many disease survivors, including ***neurocognitive impairment, neuropathy, endocrinopathy, impaired bone growth, impaired motor function, hearing loss,*** *and* ***secondary malignancy***.
- These side effects are closely related to **dose** of **radiation therapy** and **age** at diagnosis, the earlier the age, the worse the neurologic toxicity for the developing brain.

Microscopic Features

- Highly cellular.
- Sheets of small blue cells (small, rounded hyperchromatic nuclei, scanty cytoplasm)
- Many mitoses.
- Homer Wright Rosettes= primitive tumour cells surrounding central neuropil (pink material formed by neuronal processes) *Refer to figure* **2**

Genetics

- The presence of MYC amplification indicates poor prognosis.
- The presence of **WNT signalling** pathway mutations indicates **better** prognosis. (long term survival exceeds 90%)
  - Beta catenin stain can be used to help in determining the type of mutation in medulloblastoma. So, if it was (+) then we have a better prognosis (**WNT signalling** pathway mutations are present)
    Refer to figure **1**
- WNT tumors arise exclusively in an older age group of children over the age of three years.
- These can help in developing new therapy because it is better to avoid radiotherapy in young patients.
- Activating mutations in beta-catenin in approximately 10% of medulloblastoma represent the WNT subtype.
- The identification of nuclear beta-catenin has been demonstrated to be nearly 100% specific and sensitive for the presence of mutation and makes it possible to reliably identify WNT pathway tumors using routine immunohistochemistry.

Figure 1

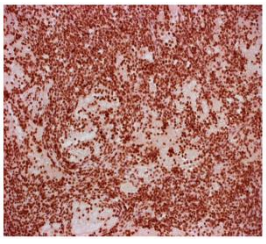
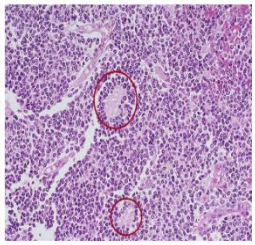


Figure 2



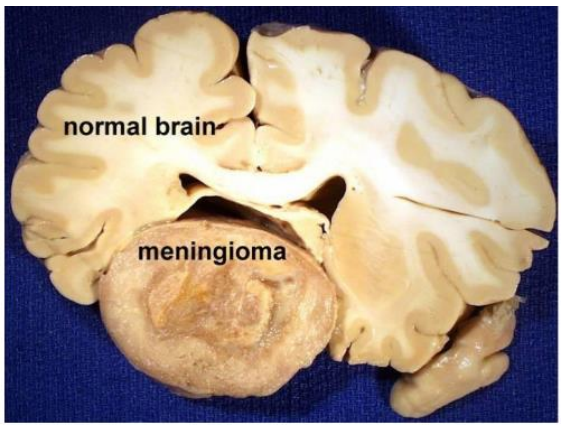
LECTURE 12 | **CNS Tumors (3)**

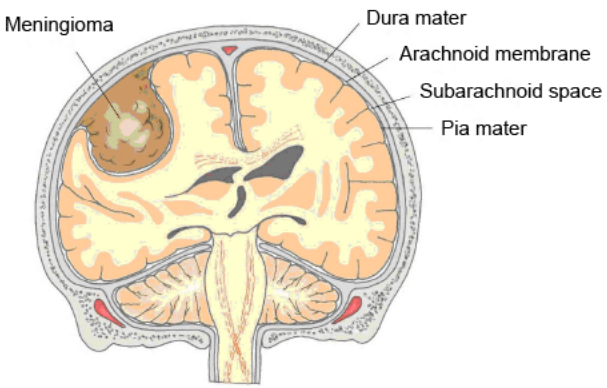
In this lecture, we will talk about:

- Meningiomas
- CNS Lymphoma
- Metastatic Tumours
- Paraneoplastic Syndrome
- Familial tumour syndromes
  - Tuberous sclerosis
  - Von Hippel Lindau syndrome

Meningiomas

- Arise from arachnoid meningothelial cells.
- Arise in adults.
- Attached to the dura.
- Can be seen at external surfaces of the brain or within the ventricular system.
- Majority can be easily separated from brain, but some are infiltrative.
- Behaviour: **benign** but infiltrative lesions recur
- Outcome depends on size, location, histological grade.
- Histological Grades:
  - WHO I: (**well diff**) meningioma.
  - WHO II: **atypical** meningioma.
  - WHO III: **anaplastic** (malignant) meningioma





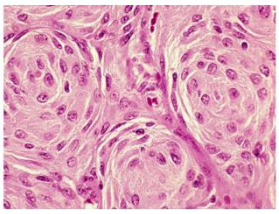
Grade I Meningiomas

Morphology

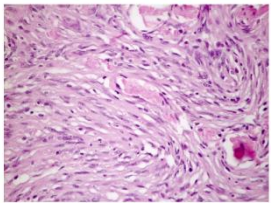
- Well defined, dura-based masses.
- May compress but do not invade brain.
- Can extend to overlying bone.
- Histological Types

1) ***Syncytial***: whorled clusters without visible cell membranes.
2) ***Fibroblastic***: elongated cells and abundant collagen
3) ***Transitional***: features of both, syncytial and fibroblastic
4) ***Psammomatous***: numerous psammoma bodies

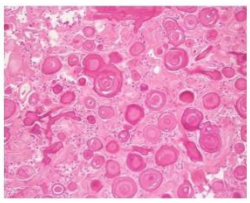
syncitial



fibroblastic



pasammomatous



Grade II Meningiomas

General Info

- Atypical Meningioma=WHO grade II
- More aggressive than grade 1
- Recur

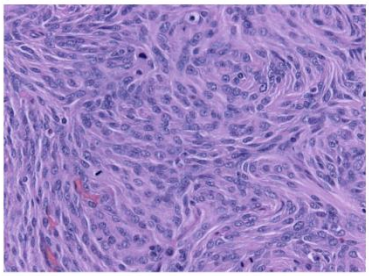
Anaplastic meningioma = WHO grade 3

- Highly aggressive
- Resemble sarcomas

Morphology

- High cellularity
- Prominent nuclei
- High mitotic rate

Atypical meningioma



Primary CNS Lymphoma

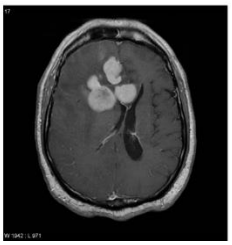
General Info

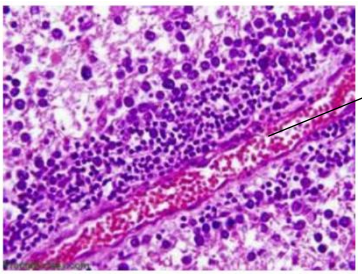
- Majority: *diffuse large B cell lymphomas*.
- 1% of intracranial tumors.
- Most **common** CNS neoplasm in the immunocompromised… in this situation they are almost always positive for EBV (Epstein – Barr virus).
- Location: Involves deep grey matter, white matter, cortex. Periventricular spread is **common**.
- Aggressive disease with poor prognosis
- Poor response to chemotherapy as compared to peripheral lymphomas.
- Spreading outside the brain happens **rarely** and **at late stages.**
- Peripheral lymphoma rarely spreads to the brain. if it does, there is usually associated meningeal and CNS involvement.

Morphology

- Usually, *multiple nodules* are present within the brain parenchyma.
- Tumour nodules more defined than gliomas but less than metastases
- EBV positive tumors usually have extensive areas of necrosis.

lymphoma: note the multiplicity of the lesions





Metastatic tumors

- 25% - 50% of intracranial tumors
- Most common primary sites: lung, breast, melanoma, kidney, and GIT.
- Form discrete well-defined masses, can be multiple.

Paraneoplastic syndromes

- CNS and peripheral nerves can be affected in disseminated cancer as part of the paraneoplastic syndromes.
- These include several manifestations including dementia, ataxia, sensory neuropathy and psychosis

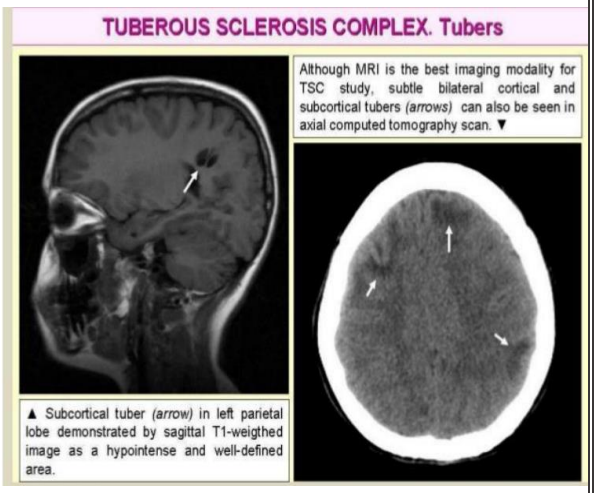
Familial tumour syndromes

- Inherited syndromes
- Mutations in several tumour suppressor genes
- Associated with increased risk of certain types of cancer.
- 2 syndromes with CNS involvement: **Tuberous sclerosis** and **von Hippel - Lindou**

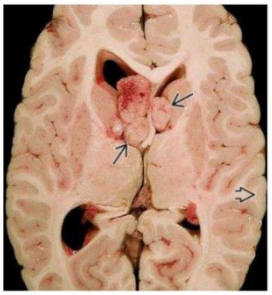
Tuberous sclerosis

General Info

- Autosomal dominant
- Hamartomas and benign neoplasms in brain and other sites
- CNS tumors: cortical tubers and subependymal hamartomas
- **Cortical tubers**: Hamartomas composed of haphazardly arranged large neurones.
- Mixture of glial and neuronal cells.
- Cause **seizures**.
- Subependymal tubers: Similar to cortical tubers
- Can cause hydrocephalus.
- Tuberous sclerosis/Extracerebral lesions
  - Renal angiomyolipoma
  - Retinal glial hamartomas
  - Pulmonary lymphangiomatosis
  - Cardiac rhabdomyoma
  - Cysts in liver, kidney, pancreas
  - Skin lesions: angiofibroma, hypopigmented areas, thickened patches.



Tuberous sclerosis.. potatoes in the brain!



Von Hippel Lindau syndrome

- Autosomal dominant
- Mutation in VHL tumor supressor gene.
- Hemangioblastomas mainly in cerebellar hemispheres, retina.
- Cysts in pancreas, liver kidney
- Increase risk of renal cell carcinoma

The Table below Summarizes what we previously discussed.

	Most common age	most common location	main histologic criteria	Genetic mutations	Prognosis	Notes
Pilocytic astrocytoma	Children	Cerebellum	Micro cysts Rosenthal fibers low cellularity	BRAF	Excellent, grade I tumour	
diffuse astrocytoma	adults 40-60	Cerebral hemispheres	Astrocytic cells in fibrillary background GFAP positive	IDH 1 or 2 Mutation	Mean survival more than 5 years	to be called grade III: increased cellularity, mitosis and polymorphism.
Glioblastoma	Adults Primary: over 55 years Secondary : younger: 50	cerebral hemispheres	Necrosis, usually palisading OR vascular proliferation	IDH mutated have better prognosis than IDH wild type	mean survival 15 months	Enhancing lesions on radiology. Can be primary (90%) or secondary (10%)
oligodendroglioma	Younger than astro 40-50	white matter	Rounded nuclei surrounded by a clear halo (fried egg appearance)	IDH PLUS 1p 19 q cpdeletion.	grade II: 10-20 years survival grade III : 5-10 years	grade III: same histological criteria of grade III astro
Ependymoma	adults and children	Adults: spinal cord <20 years: near fourth ventricle	True rosettes around empty spaces (canals) Pesudoreosettes around blood vessels		better if resectable Spinal tumors easily resectable, so better prognosis than posterior fossa ones	
Medulloblastoma	Children	Exclusively in the cerebellum	Primitive cells(small round blue cells) Homer Wright rosettes around neuropil	Myc : poor prognosis WNT: beter prognosis	grade IV tumors highly aggressive Can metastasise to bone	WNT mutation can be tested by B catenin stain.
meningioma	Middle age	Dura based lesions	Meningeal cells Psammoma bodies		generally good Depends on grade	

Past Paper Questions

1- Which of the following is correct regarding astrocytoma:

a. IDH (isocitrate dehydrogenase) mutation is a late event in the pathogenesis of gliomas.

b. Pseudo- rosettes are seen in low grade astrocytomas.

c. The presence of necrosis within a glioma indicates a high grade and a bad prognosis.

d. Contrast enhancing lesions are usually low-grade lesions.

e. Gliomas are negative with GFAP (glial fibrillary acidic protein)

2- Which of the following combinations is correct?

a. Tuberous sclerosis and increased risk of renal cell carcinoma

b. Von Hipple Lindau syndrome and autosomal recessive inheritance.

c. Medulloblastoma and Homer Wright rosettes.

d. 1p 19 q codeletion and poor prognosis in oligodendroglioma

e. WNT mutation in medulloblastoma and poor prognosis

3- A 6-year-old boy suffered from ataxia and frequent falls. MRI scan showed a well circumscribed lesion in the cerebellum which was partly cystic. histologic examination showed a tumour containing microcysts and Rosenthal fibres. what is your diagnosis?

a. Low grade oligodendroglioma

b. Pilocytic astrocytoma

c. Cerebellar ependymoma

d. Medulloblastoma

e. Glioblastoma

Answers:

1- C

2- C

3- B

GOOD LUCK!