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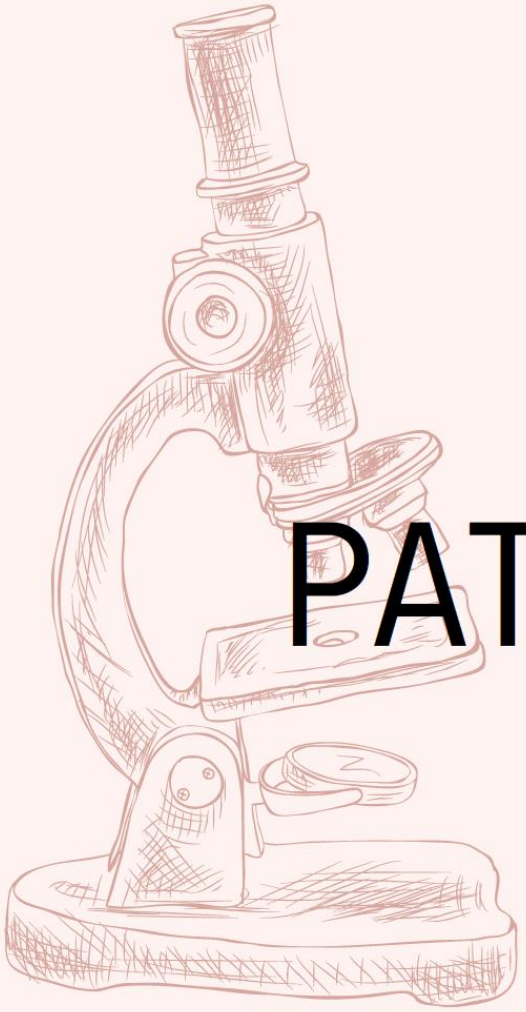


PATHOLOGY

Central Nervous System

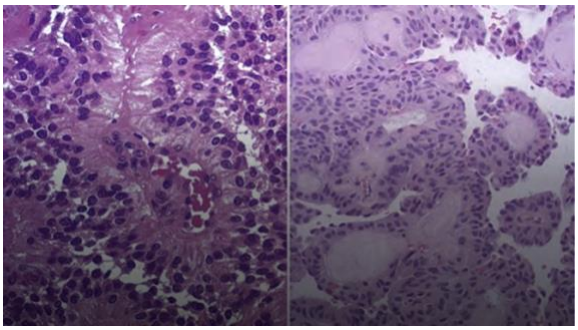
Writer: Rayyan Shtewe

Corrector: Roa'a Abuarab

Doctor: Maram Abdaljaleel

- (Note before starting our lecture: anything with black is the slides content purple is the doctor's notes, enjoy the last pathology lecture!)

- We will continue with the CNS tumors; okay this is the last glial tumor that we gonna be talking about and it's the "Ependymoma".



Ependymoma

- Are circumscribed tumors, they are graded into grade 2 and grade 3 tumors and these tumors tend to happen adjacent to ependymal-lined ventricular system, including the central canal of the spinal cord.
- Circumscribed glioma, mostly arise next to the ependyma-lined ventricular system, including the central canal of the spinal cord.

A. The most common Locations are:

1. Posterior fossa – near the 4th ventricle.
2. Supratentorial – away from the ventricular system
3. Spinal

(In our book, Robbins it only mentioned the spinal and posterior fossa.)
*In terms of the age, ependymoma affects children in the first 2 decades of life, especially in the posterior fossa near the 4th ventricle.

Ependymoma also happens in adults, in spinal and supratentorial equally.
Usually, the outcome depends on your ability to do a complete surgical excision, so you gonna expect that the outcome in spinal and supratentorial will be better than the outcome in the posterior fossa.
Why is that?
Because in posterior fossa gonna be near vital centers, near brain stem, cerebellum and ventricular system, so complete surgical excision is difficult and may end up with certain neurologic deficits.

B. Age:
- In the first 2 decades of life; near the 4th ventricle (post.Fossa)
- In adults the spinal cord and supratentorial ependymomas occur with almost equal frequency.

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

❖ Ependymoma WHO grade 2, Macroscopic:

- Solid and non-infiltrative mass.
- Moderately well demarcated from adjacent brain.
- The proximity to vital structures often makes complete removal impossible, except in the spinal cord (in the spinal cord total resection is more feasible).
-

As I told you, it's a moderately circumscribed tumor, grade 2 (at least grade 2 يعني يا grade 2 أو 3) . But why grade 2?

- Because its presence near these vital centers makes the complete surgical excision impossible, except for the ones that are located in the spinal area these have a better prognosis and we can do a complete surgical excision.
- Grossly it's a solid tumor, non-infiltrative and moderately circumscribed.
- This tumor if its location was critical the prognosis will be worse, and the more the location was easy to be reached to do surgical excision the better the prognosis is.

❖ Ependymoma WHO grade 2, microscopic:

- In terms of histology, this tumor is formed or composed of sheets of uniform small cells, with oval round nucleus, granular chromatin and they are present in a fibrillary background.
- So, they look like the glial tumors, they have the proliferative activity& mitotic index is low, so low mitotic activity, low cellularity and there is no necrosis or microvascular proliferation if we are talking about grade 2 tumors.
  If you look at these tumors under EM you see cilia and microvilli.
- **These have a characteristic, the cells in these tumors take a certain arrangement in a gland-like structure or take the shape of the spoke wheel. tumor cells are arranged on the periphery they just do like a circle around certain center and that's called a "rosette formation".**
- 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) àRosette formation: when the tumor cells are arranged around a central structure, their fibrillary processes are directed toward the center like the spoke of the wheel in the pic! & there are2 types of rosettes that happens in ependymoma:

1. Ependymal rosettes: diagnostic hallmark of ependymoma (25%). (If we see them, they are diagnostic, but if they don't exist this does not rule out the Dx, so they are specific, but they are not present in every single case).
2. Perivascular pseudorosettes: not specific (but sensitive) for ependymoma (seen in glioblastoma and medulloblastoma). Which means they are present in most of the cases, but they are not specific for ependymoma.

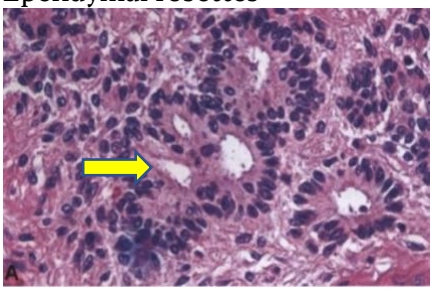
Ependymal rosettes:

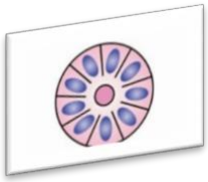
- Tumor cells arranged around central canal or lumen (patent lumen\canal which is made by the tumor cells themselves) that resemble the embryologic ependymal canal, with long, delicate processes extending into a lumen.

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. (Native vessel= vessel from existing tissue, and the tumor cells just arranged themselves around it). That's why it's called pseudorosette, it's around a structure that's not neoplastic it's around a BV).

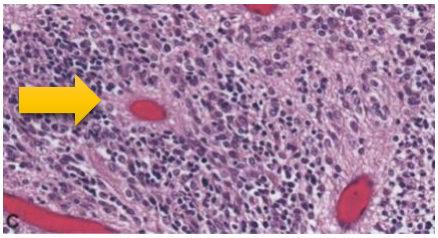
Ependymal rosettes

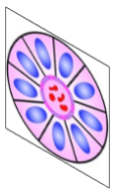




This figure shows you the ependymoma, as you can appreciate here, cells are uniform, round to oval, have finely granular chromatin with a fibrillary background made of these thin long astrocytic processes.

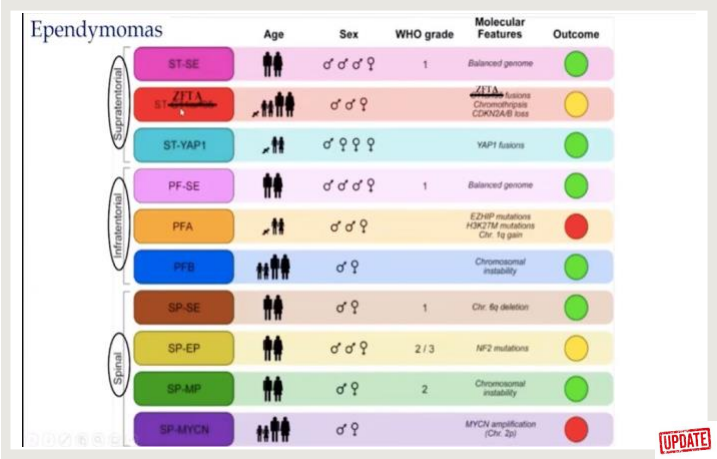
Notice the yellow arrow: we have a central lumen, and the tumor cells are just arranged around this central lumen where their processes are directed toward the center. (True ependymal rostte)





Perivascular pseudorosettes

(not specific& can be seen in other tumors)
Again, we have like moderately cellular proliferation of these round- oval cells, they have fine granular chromatin& fibrillary Background. Tumor cells accumulating just around this BV where we have a zone here (the pink area) that's free of nuclei which is called 'nuclear free zone'

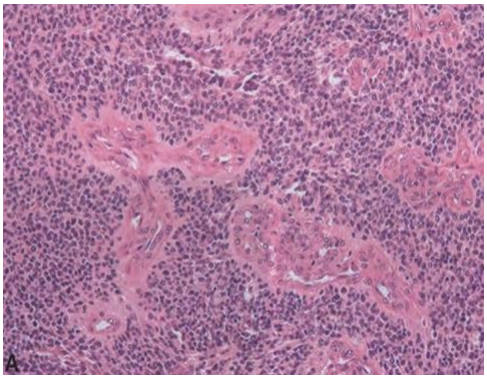


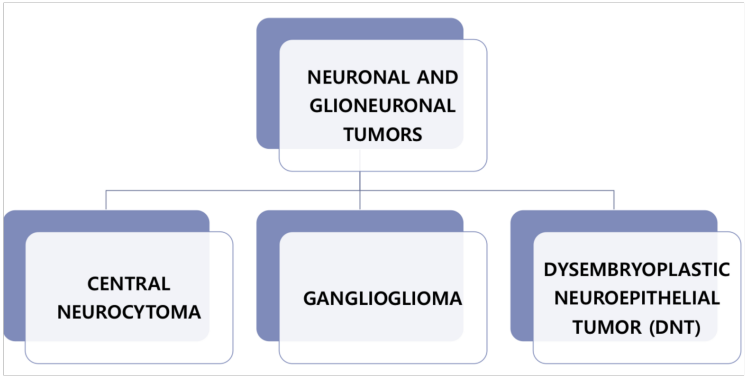
- In the 5th edition of the WHO book, ependymoma are further classified into more than 9 classes according to their molecular background. They have different epidemiologic data, incidence, gender, histology & different outcome. The idea behind this is to show you that all these tumors have different molecular background, different prognosis, management and so we treat everyone separately.

❖ Anaplastic ependymomas, WHO grade 3:

- Show less evident ependymal differentiation. (So, I expect to see less ependymal rosettes).
- Brisk mitotic rates, and microvascular proliferation carry more prognostic impact than necrosis and atypia.

In this figure we have cellular proliferation of these Hyperchromatic cells& abnormal vessels, the walls of these vessels are made of 2 or more layers (more than 5 or 6 layers). And if we see this slide on higher power, we can see frequent mitotic figures.





Okay, now we'll have a brief intro to the neuronal and neuroglial tumors.

Neuronal Tumors

- Less frequent than gliomas
- Composed of cells with neuronal characteristics and express neuronal markers, such as synaptophysin and neurofilaments.
- Typically, lower-grade lesions. (Grade 1 or grade 2)
- Often present with seizures. – (is the most common presentation for your patient, who may be a child or young adult).

1. Central neurocytoma, WHO grade2: neuronal tumor within and adjacent to the lateral ventricle(s) and/or the 3rd ventricle affecting young adults.
2. Ganglioglioma, WHO grade 1: glioneuronal tumor affecting children and young adults. Composed of a mixture of neoplastic ganglion and glial cells, most commonly in the temporal lobe.
3. Dysembryoplastic neuroepithelial tumor (DNT), WHO grade 1: glioneuronal tumor affecting the cerebral cortex of children and young adults most commonly in the superficial temporal lobe. (Low grade)

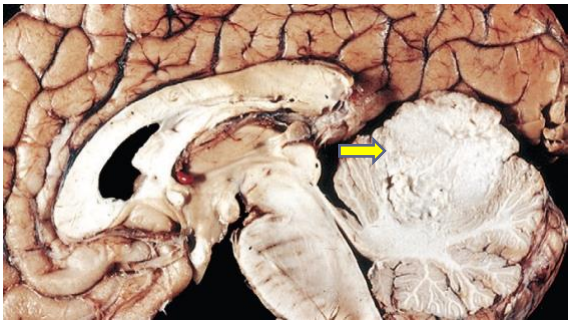
Another class of tumors that affects the CNS:

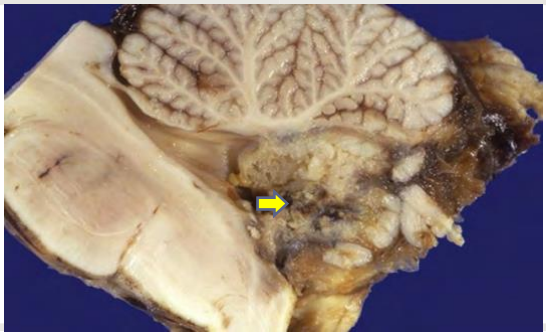
** Embryonal (primitive) neoplasms

- 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 (which we will focus on it) accounting for 20% of pediatric brain tumors.

Medulloblastoma,WHO grade 4:

- Predominantly in children, (it can affect all age groups according to the updates but most commonly children.)
- Mainly in cerebellum (regarding the location, before it was exclusively in the cerebellum, but the case reports found that this tumor exists also in other places like the brainstem. (Mainly in the cerebellum but not exclusively!)
- (If we left the patient untreated this will result in dismal outcome, but if it was treated with surgery, chemotherapy and radiotherapy the 5 years survival may exceed 75% because it's a radiosensitive!

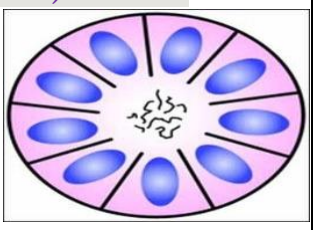




❖ Macroscopic:

- Well circumscribed (often)
- May extend to the cerebellar surface and involve the leptomeninges.
- It's associated with <u>common complication:</u>

- Medulloblastoma have tendency to spread to the subarachnoid space à Dissemination through the CSF (so seeding to other spaces like the spinal cord for ex.)
- Often there can be small fossi of necrosis, but extensive masses of necrosis as seen in glioblastoma is rare and considered uncommon.



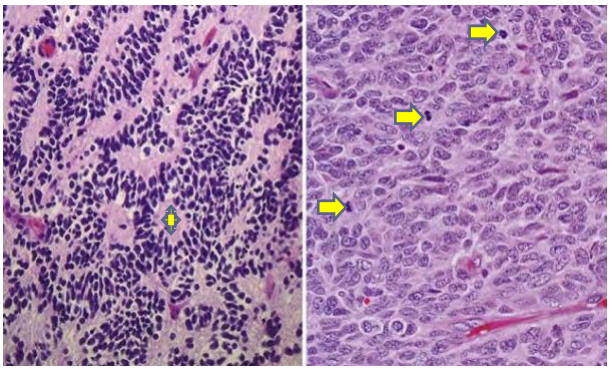
Morphology:

- Under the microscope its very cellular
- They are made of sheets of small primitive cells ("small Blue"), each cell with little cytoplasm and hyperchromatic elongated or cresent-shaped nuclei. Small cells means that the cells have little cytoplasm and high n/c ratio. Necrosis is commonly in the tumor.
- Mitoses are abundant.
- They Often express neuronal markers such as synaptophysin
- The expression of glial markers (GFAP) is less common.
- These primitive tumors, show neuronal differentiation and may show a glial differentiation, so it's not uncommon to find the synaptophysin and the GFAP are pos+ in these tumors.

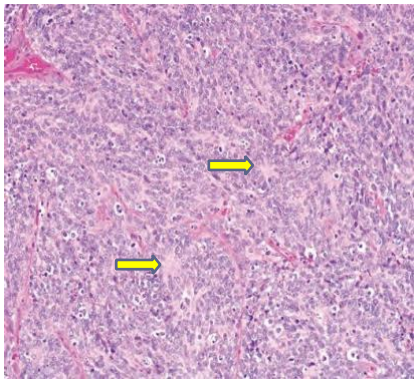
- Homer Wright Rosettes:

These small round blue cells sometimes they show a certain degree of neuronal differentiation &they arrange themselves in a gland-like structure called Homer Wright Rosettes.

- Primitive tumor cells surrounding central neuropil (delicate pink material formed by neuronal processes).
- Represents focal neuronal differentiation. And make neuropil.
- Not specific; seen also in neuroblastoma and pineablastoma.



Yellow arrows point the mitotic



Sheets of primitive small blue cells that form homer wright rosettes with central neutrophils

Oncogenic pathways in medulloblastoma:

*There are 3 important oncogenic pathways that will help in classification later on:

- Wnt pathway activation: will result in gain of function mutations in the gene encoding for β-catenin; have the most favorable prognosis of all the genetic subtypes.(the outcome will be better for the patient).
- MYC overexpression: due to MYC amplification; these tumors have the poorest prognosis.
- Hedgehog pathway activation: associated with loss of function mutations in PTCH1 (one of the tumor suppressor genes) and this affects the the Hedgehog pathway by a negative regulator); these tumors have an intermediate prognosis, but the concomitant presence of P53 mutation (they do the worst) confers a very poor prognosis.

- Medulloblastomas are classified according to molecular characteristics in addition to histopathological features into: According to these molecular pathways this tumor is further classified into 4 main classes:

1. Medulloblastoma, WNT activated
2. Medulloblastoma, SHH activated and P53 wildtype
3. Medulloblastoma, SHH activated and P53 mutant
4. Medulloblastoma, non-WNT/non-SHH

*This classification is beneficial, it will give us further classification of these tumors according to their morphology, so their outcome will be completely different, it ranges between very good prognosis and very bad prognosis. (If molecular classes and histology were combined, we will have better prediction for prognosis and management.)

Table 8.01 Medulloblastoma subtypes characterized by combined genetic and histological parameters

Genetic profile	Histology	Prognosis
Medulloblastoma, WNT-activated	Classic	Low-risk tumour; classic morphology found in almost all WNT-activated tumours
	Large cell / anaplastic (very rare)	Tumour of uncertain clinicopathological significance
Medulloblastoma, SHH-activated, TP53-mutant	Classic	Uncommon high-risk tumour
	Large cell / anaplastic	High-risk tumour; prevalent in children aged 7-17 years
	Desmoplastic/nodular (very rare)	Tumour of uncertain clinicopathological significance
Medulloblastoma, SHH-activated, TP53-wildtype	Classic	Standard-risk tumour
	Large cell / anaplastic	Tumour of uncertain clinicopathological significance
	Desmoplastic/nodular	Low-risk tumour in infants; prevalent in infants and adults
	Extensive nodularity	Low-risk tumour of infancy
Medulloblastoma, non-WNT/non-SHH, group 3	Classic	Standard-risk tumour
	Large cell / anaplastic	High-risk tumour
Medulloblastoma, non-WNT/non-SHH, group 4	Classic	Standard-risk tumour; classic morphology found in almost all group 4 tumours
	Large cell / anaplastic (rare)	Tumour of uncertain clinicopathological significance

UPDATE

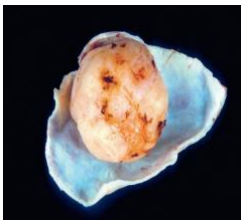
Meningiomas

- Tumors that arise from meningothelial cells of the arachnoid matter and usually attached to the dura.
- Age at presentation: Adults (women>Men)
- Location: intracranial, intraspinal or orbital attached to the dura.
- Usually, they are circumscribed tumors.
- Presentation: Most common, headache, seizures, weakness/neurologic deficit (depends on location)
- Prognosis: determined by the lesion size and location, surgical accessibility, and histologic grade (they are graded into 1,2,3)
- Usually solitary, but multiple sites can be affected.
- Meningiomas express progesterone receptors and may grow more rapidly during pregnancy, only to regress after delivery. (Return to their normal sites was before pregnancy),{يعني بعد الولادة برجعوا لحجمهم الطبيعي الي كان قبل الحمل

Pathogenesis

- The most common cytogenetic abnormality is the loss of chromosome 22, especially the long arm (22q). (If we knew that this region is the same region of neurofibromatosis 2 gene, so meningiomas then are considered common lesion in the setting of the neuroF2).
- The deletions include the region that harbors the NF2 gene.
- Meningiomas are a common lesion 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. (Attached to the dura, usually not infiltrative, but in some cases, it may have infiltration of the adjacent brain).

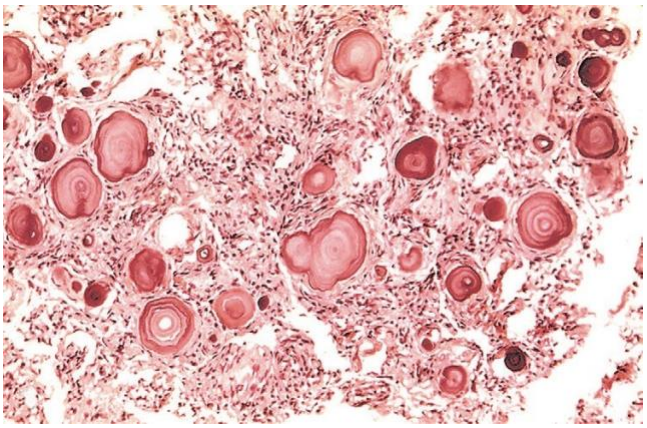
❖ Meningiomas (WHO grade 1):

- well-defined dura-based masses that may compress the brain but do not typically invade it +/- overlying bone extension. (No brain infiltration)
- They are made of Epithelioid polygonal cells with abundant cytoplasm arranged in whorlyدوّامات (syncytial) pattern ,where the boundries between cells are blurred +/- psammoma bodies (concentric rings made of calcified material).
- Many histologic patterns, with no prognostic difference
- meningothelial (most common pattern)---clusters of epithelioid cells with fuzzy blurred margins between cells or indiscernible cell membranes.

- Other patterns include fibroblastic (tumors cells are spindled with collagen deposition in between) , transitional.(when the tumor shows meningothelial and fibroblastic differentiation in the same tumor), and psammomatous (when it shows abundant psammoma bodies).

This figure shows you, a grade 1 meningioma, proliferation of epithelioid cells that form whorls/ syncytial pattern with abundant cytoplasm.

Cell membranes of cells are indistinct, they appear mixed together, making this whorly pattern with concentric rings of calcific deposits in between (psammoma bodies, are common in meningiomas but not specific).



Psammoma bodies are concentric rings of calcification deposited

Psammoma bodies are not specific, seen in other tumors like:

1. PTC
2. Serous carcinoma of the ovary.

❖ ATYPICAL MENINGIOMAS, WHO grade 2: high risk of recurrence

- recurrence and aggressive local growth (may require radiation & surgery)
  1. 4 ≥ mitoses/10 HPF; or
  2. (presence of 3 features out of 5): increased cellularity, small cells with a high N/C ratio, prominent nucleoli, patternless growth , or necrosis (3/5 is enough to upgrade your meningioma into grade 2-atypical meningioma)
  3. Special histologic type of meningioma ,2types clear cell or chordoid subtypes of meningioma.

ANAPLASTIC MENINGIOMAS, WHO grade 3 (malignant):

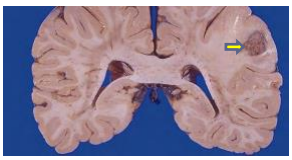
• highly aggressive(sometimes we need immune stains ,t's hard to diagnose on histology , because they look like carcinoma or sarcoma), resemble a high-grade sarcoma or carcinoma morphologically.

1. >20 mitoses/ 10HPF; or
2. Papillary; or rhabdoid meningioma.

Metastatic Tumors:

- 25-50% of intracranial tumors.
- mostly , metastasis is from carcinomas
- The most common primary sites are lung, breast, skin (melanoma), kidney, and gastrointestinal tract (80% of cases).
- sharply demarcated masses, often at the grey-white matter junction, and elicit local edema (as a response from the tissue, grossly edema& or radiology also).
- The boundary between tumor and brain parenchyma is sharp at the microscopic level with surrounding reactive gliosis.

*This is a coronal section in the brain and as you can appreciate here the yellow arrow points to a Red-Brown tumor which is sharply defined, discrete tumor at the gray-white matter junction.



- Other parenchymal Tumors We will talk about 2 types briefly:

1. Primary Central Nervous System Lymphoma:

- The most common CNS neoplasm in immunosuppressed individuals
- In non-immunosuppressed populations, the frequency increases after 60 years of age.
- aggressive disease , poor response to chemotherapy (especially if compared with comparable histology that occur at non-CNS site)
- The most common type: diffuse large B-cell lymphomas
- Usually, the primary CNS lymphoma are multifocal, (to spread to Lymph nodes or BM this considered a rare and late complication, so this is not the most common scenario).
- Relatively usually well defined (not infiltrative like astrocytoma) as compared with glial neoplasm but not as discrete as metastases.

The other parenchymal tumor that affects the CNS is:

2. Germ Cell Tumors

- Can be primary or metastatic Primary brain germ cell tumors:
- Locations: mostly along the midline, most commonly in the pineal and the suprasellar regions (post. Pituitary and infundibular stalk). 90% during the first 2 decades of life. (May happen in young adults but mostly in the 1st 2 decades of life).
- The most common primary CNS germ cell tumor is germinoma, closely resembles testicular seminoma.
- Other germ cell tumors include: teratoma (mature and immuture), embryonal carcinoma, yolk sac tumor, chriocacinoma and mixed germ cell tumors.

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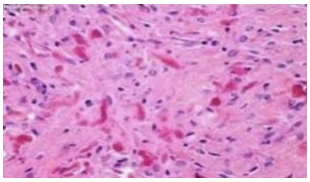
❖ **Be ready and let the fun begin! let's solve some questions beautiful Doctors!**



1. **This picture shows a feature of pilocytic astrocytoma which is:**

   a. Rosenthal fibers
   b. Microcysts
   c. High cellularity
   d. palisaded necrosis
   e. GFAP positivity

2. **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 tumor containing microcysts and Rosenthal fibers. what is your diagnosis?**

   a. Low grade oligodendroglioma
   b. Pilocytic astrocytoma
   c. Cerebellar ependymoma
   d. Medulloblastoma
   e. Glioblastoma

3. **all of the following can metastasize to brain except?**

   a. lung
   b. breast
   c. kidney
   d. melanoma
   e. bone

4. **all of the following are grade 2 meningioma except?**

   a. high mitotic rate
   b. high cellularity
   c. recurrence
   d. more aggressive than grade 1
   e. resembles sarcomas

5. **all of the following are true regarding grade 2 meningiomas Except:**
   a. high mitotic rate
   b. recurrence
   c. well defined
   d. small cells, prominent nuclei and necrosis
   e. more aggressive than grade 1
6. **True about primary CNS lymphomas Except:**
   a. the most common CNs neoplasm in the immunocompromised
   b. aggressive disease with poor prognosis
   c. common spread outside CNS
   d. Mostly: Diffuse large B-cell lymphoma.

7. **one of the following is wrongly paired:**

   a. Wright Homer rosettes- meningioma
   b. Necrosis- glioblastoma
   c. Psammoma bodies – meningioma
   d. fried egg appearance -oligodendroglioma

8. **the most common primary brain tumor:**
   a. glioblastoma
   b. meningioma
   c. gliomas
   d. germ cell tumors
9. **All of the following are true regarding grade II meningiomas EXCEPT:**
   a. Clear variant
   b. Brain invasion
   c. Choroid variant
   d. Small cells, prominent nuclei and necrosis
   e. More than 19 mitotic figures/10 HPF

10. **Choose the INCORRECT combination:**

a. Oligodendroglioma : Ip 19q codeletion .
b. Pilocytic astrocytoma : cerebellar location . c. Ependymoma : pseudorosettes
d. Medulloblastoma : low cellualrity
e. Glioblastoma : palisaded necrosis

Answers:

1. a. 2. b 3. e. 4. e. 5.c 6.c 7.a 8.c 9. e 10. d