PATHOLOGY

SHEET NO. 8

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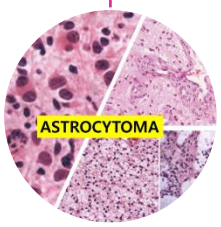
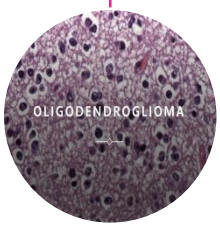


ASTROCYTOMA



OLIGODENDROGLIOMA

EPENDYMOMA

Doctor: In this lecture we will continue with the introduction to CNS tumors last lecture we talked about one class of Gliomas (Gliomas are the most common type of CNS tumors) which is the most common one Astrocytoma which account for 80% of Gliomas, then we have Oligodendrogliomas which account for 5-15% of Gliomas and Ependymomas which are much less common. All those tumors are parenchymal brain tumors, and the cells here have morphological similarities with glial cells this why we call them Astrocytoma, Oligodendroglioma, Ependymoma.

Oligodendroglioma

Info from the slides is highlighted with

Any thing in red is from the doctor

- Accounts for 5-15% of gliomas.
- Age at diagnosis: 40-50.

Doctor: Your patient is usually an adult just like we said in astrocytoma, between 4^{th}-5^{th} decade.

- Location: mostly in the cerebral hemispheres, mainly in the frontal or temporal lobes, white matter.

Doctor: The location: any place in the brain can be affected but most commonly the white matter of the frontal or temporal lobes. For a long time, the frontal lobe was considered the most common location but WHO said that the frontal and temporal lobes are affected almost at similar frequency.

Diagnosis

- The presence of IDH mutation and 1p & 19q co-deletion is diagnostic for oligodendroglioma.

Doctor: The diagnosis of oligodendroglioma requires certain molecular findings which are: the presence IDH (Isocitrate dehydrogenase) mutation **and** the presence of 1p & 19q co-deletion. So, if you have an infiltrating glial cell tumor with the presence of IDH mutation and 1p & 19q co-deletion then this is definitely an oligodendroglioma. So, the diagnosis of the tumor has a molecular requirement and doesn't just depend on the phenotype of the tumor.

Treatment and prognosis

- The combination of surgery, chemotherapy, and radiotherapy yields an average.

survival of:

- 10-20 years for WHO grade 2. Doctor: Because of infiltration.
- 5-10 years for WHO grade 3. Doctor: Because of anaplastic features which we will talk about shortly.
- Grade 3 is more aggressive than grade 2 oligodendroglioma
- NO grade 1 OR 4 oligodendroglioma
- **Better prognosis than astrocytoma of the same grade! (The doctor focused on this point)**

Oligodendroglioma, WHO grade 2:

- infiltrative tumors
- +/- cysts, focal hemorrhage, and calcification.

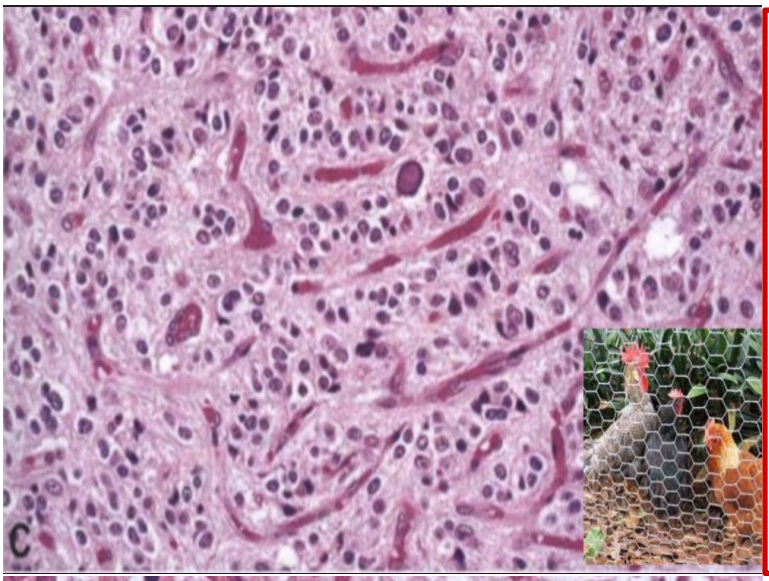
Doctor: As we all agreed in the previous lecture these are infiltrative tumors, which means they have poorly identified boundaries, they infiltrate the adjacent normal appearing tissues, they may form cyst like structures and calcifications are considered common (Calcification in 90% of tumors). That's why when we talked about radiographic findings, I told you that if you saw calcifications with a diffuse infiltrating tumor in the radiograph this can guide you to the diagnosis of Oligodendroglioma, but of course we need histology and molecular testing.

Histology (for grade 2)

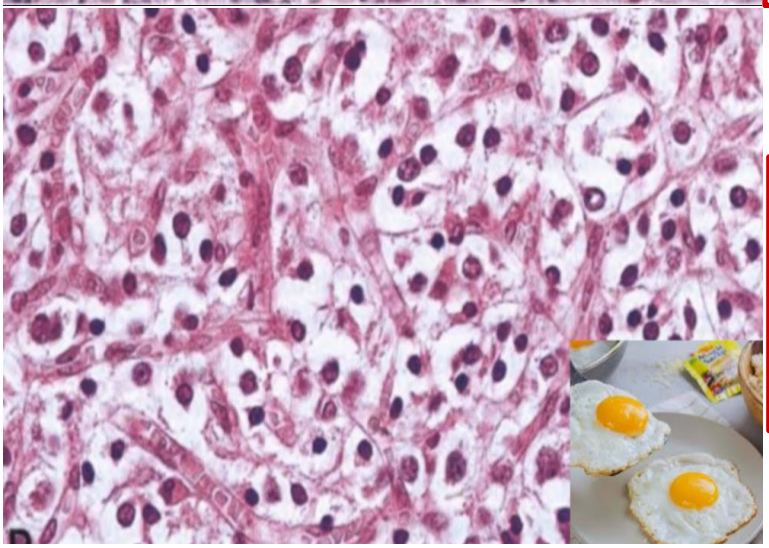
- sheets of regular cells with spherical nuclei containing finely granular chromatin
- The nuclei are surrounded by a clear halo of cytoplasm (Fried-egg appearance).
- delicate network of anastomosing capillaries "chicken-wire".

- Calcification in 90% of tumors.
- Mitotic activity usually is low.
- No spontaneous necrosis.
- No microvascular proliferation.

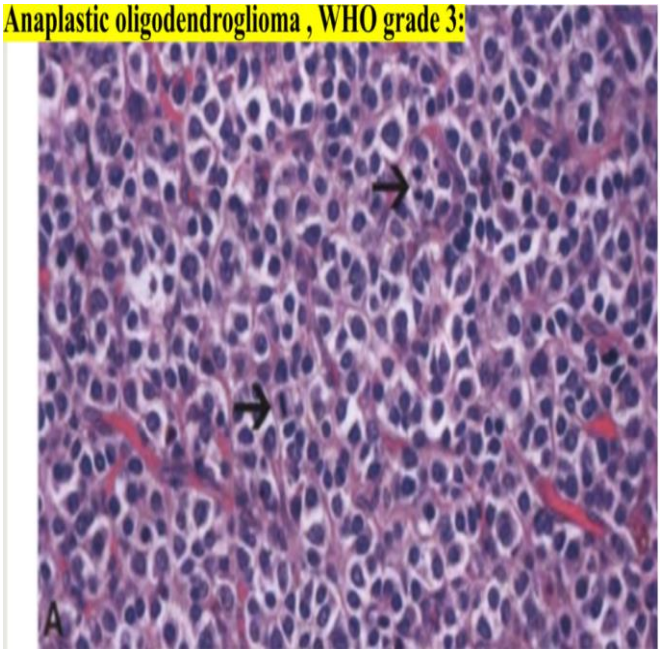
Doctor: Those cells are well differentiated cells that look like oligodendrocytes, so they are regular cells with round to oval nucleus, finely granular chromatin that looks like the chromatin of normal oligodendrocytes. And they have clear spaces surrounding the nucleus we call them perinuclear haloes, these perinuclear haloes are actually artifacts on the H&E stained slides while they are actually clear cytoplasms not real haloes (the cytoplasm appears like an empty space), and we call this appearance Fried-egg appearance. Another Characteristic feature of these tumors is the presence of a fine delicate network of anastomosing capillaries in the background just like a chicken cage ("chicken-wire" appearance), there is calcifications in 90% of the cases as we said before, because these are grade 2 tumors the mitotic index is low, no spontaneous necrosis and no microvascular proliferation.



- The microscopic appearance of IDH mutated and 1p & 19q co-deleted **Oligodendroglioma grade 2**.
- So, in this tumor we have sheets of proliferating cells similar to each other there isn't much pleomorphism or variation in the size and shape, and each cell has a rounded or oval shaped nucleus, finely granular or stabled chromatin and a perinuclear halo or clear space.
- If we zoom out a little bit in the background there is a delicate network of anastomosing delicate capillaries that looks like chicken wire, at the center of this field we have a center of calcification, low mitosis, no necrosis and no microvascular proliferation.



- Here is another figure showing **Oligodendroglioma grade 2 tumor.**
- Notice the haloes which surround each nucleus, this space (the halo) is made by a clear cytoplasm which gives the Fried-egg appearance.



- Here we have an **Oligodendroglioma grade 3 tumor or Anaplastic Oligodendroglioma.**
- The differences between grades 2 and 3 are that grade 3 has increased cellularity, easily identifiable mitotic figures (notice the black arrows), and microvascular proliferation, ± necrosis.
- If we see necrosis, can we call it grade 4? No there isn't a grade 4 oligo, and necrosis is not a requirement for grade 3, increased mitosis and microvascular proliferation are enough to call this tumor Anaplastic Oligodendroglioma.

From 8:40 to 11:56 the doctor explained some extra information that isn't required.

Ependymoma

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

• Location: posterior fossa (60%), supratentorial (30%), spinal (10%)

Doctor: The third type of Gliomas is Ependymoma, the 2021 book say that these tumors by definition are circumscribed Gliomas, that is the first difference. And they tend to happen near areas that is lined by ependymal cells such as the ventricular system, the central canal of the spinal cord but after that they found that some of them are supratentorial, spinal and even extra-CNS (which we are not going to talk about). The most common locations are above.

• Age:

- In the first 2 decades of life; near the 4th ventricle (post. Fossa)
- In adults, the spinal cord and supratentorial ependymomas occur with almostequal frequency

Doctor: If we combined the location with the age group, we are going to find that in children most commonly the tumor will be in the posterior fossa, and in adults intraspinal or supratentorial ependymomas. If we are going to talk about classification, in past we knew two

ependymomas, ependymoma grade 2 and the anaplastic ependymoma and that's it but in 2016 they added supratentorial ependymomas which were called RELA fusion positive ependymomas this entity was cancelled in 2021. Now we have 10 classes according to the molecular background of ependymomas.

• The clinical outcome for completely resected supratentorial and spinal

ependymomas is better than for those in the posterior fossa.

Morphology

• A composed of uniform small cells with round to oval nuclei and granular chromatin in a fibrillary matrix and characterized by:

Rosettes

• Rosette formation:

- Ependymal rosettes: diagnostic hallmark of ependymoma (25%)
- perivascular pseudorosettes: not specific for ependymoma.

Doctor: A proliferation of uniform small cells with round to oval nuclei and granular chromatin in a fibrillary matrix(background). We differentiate them from other types with something characteristic called rosettes, rosettes (or rosette formation) are tumor cells arranged like a circle around a central structure and if the central structure is a central canal or lumen forming then they are called ependymal rosettes, and ependymal rosettes are actually specific and characteristic and diagnostic for Ependymoma despite that they are not present in all Ependymomas but only in fourth. So, if they are present, they are diagnostic but if they aren't that doesn't mean it's not ependymoma it still can be. Another type of rossete apearence is around a blood vessel which are called Perivascular Pseudorosettes which we can see in ependymomas, but they are not specific, because we can see them in other tumors like: glioblastoma, medulloblastoma and neuroblastoma, but they help alongside the age of the patient, location, the immune stains and the presence of rosettes (ependymal rosettes).

• low cell density and a low mitotic count. Doctor: If we are talking about grade 2

• Cilia and microvilli are seen on ultrastructural examination.

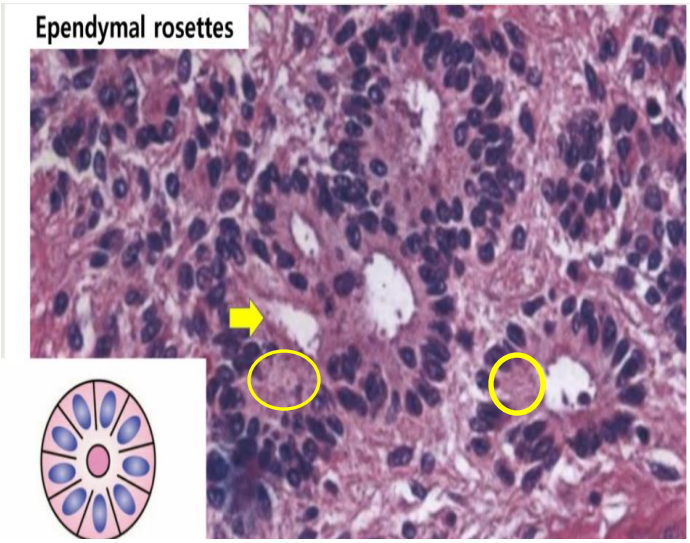
Doctor: Ependymal cells are epithelioid cells cuboidal to low columnar cells, they have cilia and microvilli that aren't visible under light microscopy we need an electron microscope.

Ependymal rosettes:

- tumor cells arranged around central canal or lumen that resemble the embryologic ependymal canal, with long, delicate processes extending into a lumen. Doctor: The embryologic ependymal canal is a true lumen. The long processes are between the canal and cells on the periphery.

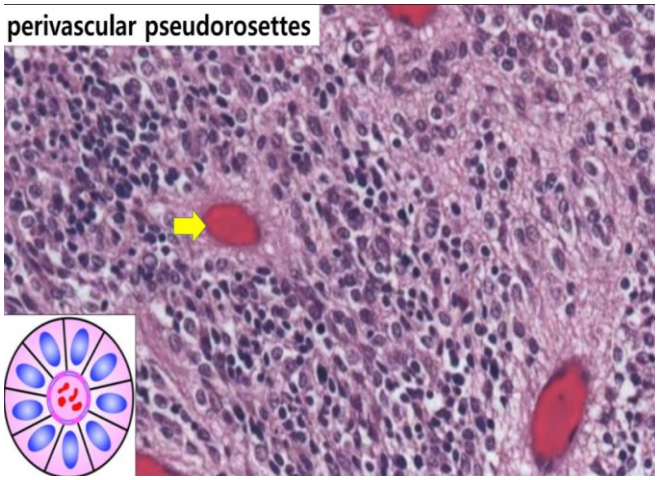
Perivascular Pseudorosettes:

• composed of tumor cells radially arranged around vessels with an intervening anucleated zone containing thin ependymal processes.



- Here we have ependymoma grade 2 tumor cells arranged in circles around central lumen or a true canal
- The yellow arrow is pointing into an empty space or a true central canal there is no blood.
- Yellow circle: The delicate processes making the pink material.
- The lumen is made by the tumor cells themselves

True or Ependymal Rosettes



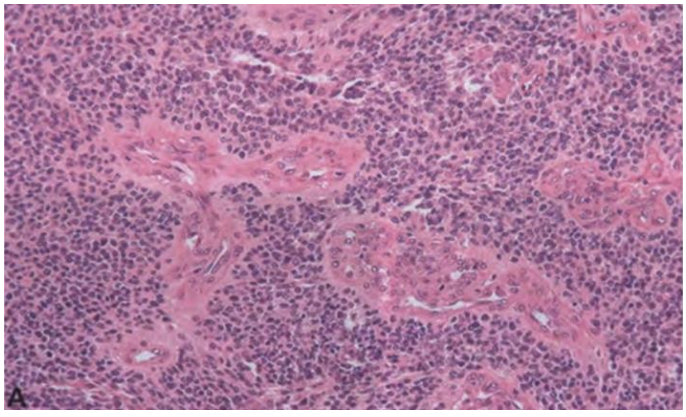
- Here we have ependymoma grade 2 tumor cells arranged around a central blood vessel which is a common finding in this tumor.
- The lumen was there before the tumor cells, and it is not empty

Perivascular pseudorosettes

• Anaplastic ependymomas: increased cell density, high mitotic rates, necrosis, microvascular proliferation, and less evident ependymal differentiation.

This is way different from grade 2 which had no mitosis, low cellularity, no necrosis, no microvascular proliferation.

Also, this tumor (The anaplastic) can be poorly differentiated sometimes.



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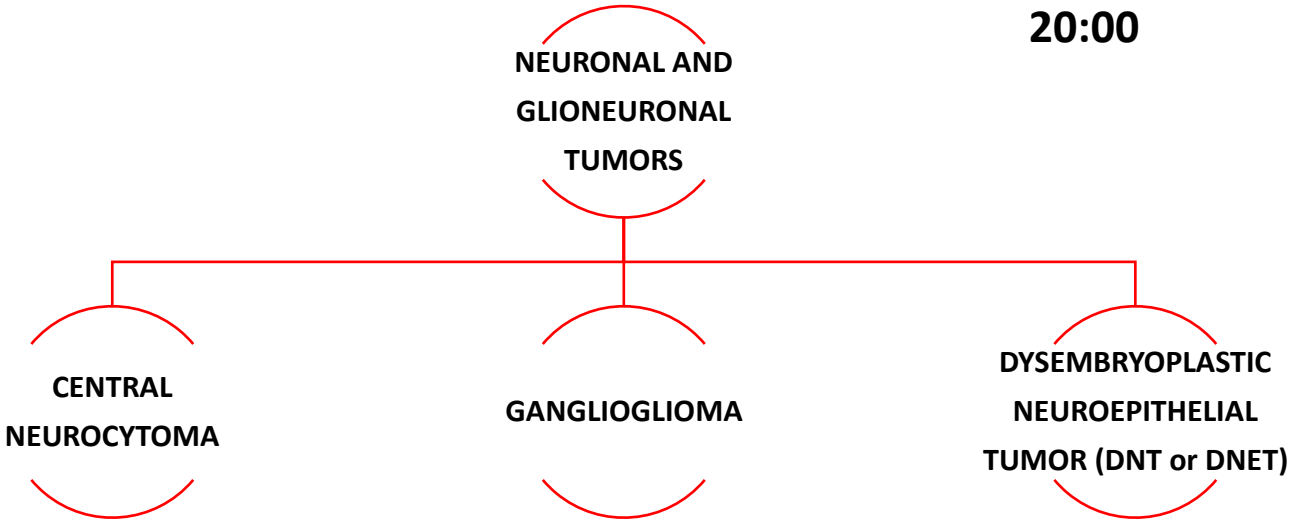


The shared thing between these tumors is that all of them show neuronal differentiation, which means when you stain them with immune stains for neurons, they are going to be positive (synaptophysin positive and neurofilament positive). They are less common than glial tumors and are usually present in children and young adults and the most common presentation is seizures. Most tumors under this umbrella are grade 1 or 2, so they have really good prognosis.

The usual scenario: A child with a new onset of seizures and a tumor in the temporal lobe, a frozen biopsy will be given to you to determine if it is a tumor or a focal cortical dysplasia that can cause a seizure.

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
- often present with seizures.

• Central neurocytoma, WHO grade 2: low-grade neuronal tumor within and adjacent to the lateral ventricle(s) and/or the third ventricle affecting young adults.

Doctor: From the name neurocytoma there is no glial component in this tumor. Patient presented with seizures.

• Gangliogliomas, WHO grade 1: Well differentiated glioneuronal tumor affecting children and young adults. composed of a mixture of neoplastic ganglion and glial cells, most commonly in the temporal lobe.

• Dysembryoplastic neuroepithelial tumor (DNT), WHO grade 1: low-grade (well differentiated) glioneuronal tumor affecting the cerebral cortex of children and young adults most commonly in the superficial temporal lobe.

Embryonal (Primitive) Neoplasms

Doctor: In general, Embryonal (Primitive) Neoplasms are primitive small round blue cell that resemble the progenitor cells of the system that they originate from.

• Primitive small round cell tumor of neuroectodermal origin resembling normal progenitor cells in the developing CNS.

Doctor: So, if you look at normal embryonic CNS cells you will see the same morphology of these neoplasms but without atypia (neoplasms have atypia).

• **Medulloblastoma, WHO grade 4:** (Prototype of the CNS primitive neoplasms group)

• The most common CNS embryonal tumor.

• 20% of paediatric brain tumors.

Doctors: We have other tumors affecting the paediatrics such as the ATRT (Atypical Teratoid Rhabdoid Tumor), embryonal tumor with multi-layered rosettes and other tumors.

• predominantly in children

• mainly in cerebellum

• All are highly malignant, WHO grade 4

• the prognosis for untreated patients is dismal

Doctor: Can happen in adults and outside the cerebellum but we say mainly in cerebellum and children.

• radiosensitive. (Treatment includes surgery, chemotherapy and radiation)

• With total excision, chemotherapy, and irradiation, the 5-year survival rate may be as high as 75%.

Morphology:

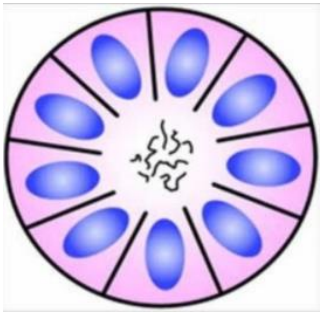
• densely cellular, with sheets of anaplastic ("small blue") cells with little cytoplasm and hyperchromatic nuclei

• mitoses are abundant.

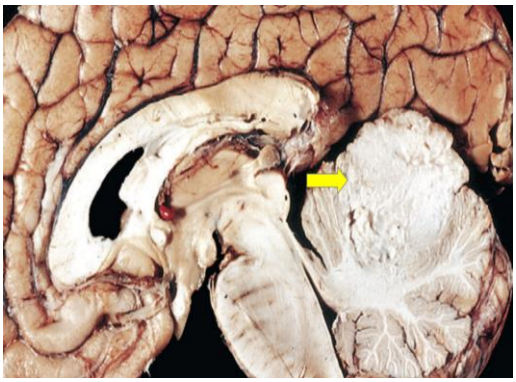
Doctor: We are talking about a grade 4 tumor, so we expect high cellularity. Made of small round blue cells with little rim of the cytoplasm and large nucleus that shows atypia and hyperchromasia, there is pleomorphism, variation in the nuclear size and shape and a high mitotic index (because it is a grade 4 tumor). We can see microvascular proliferation but it is not needed, and necrosis if it happened it is going to be small and focal (the excessive areas of necrosis that are seen in glioblastoma are absent in this tumor).

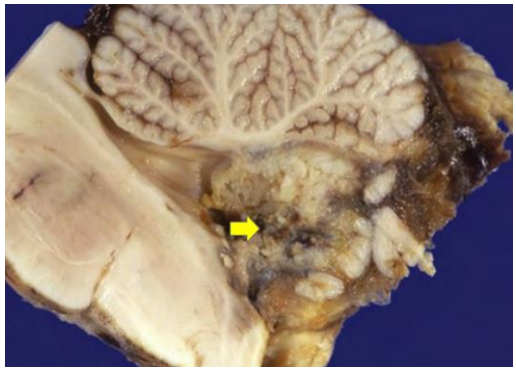
• **Homer Wright Rosettes:**

- primitive tumor cells surrounding central neuropil (delicate pink material formed by neuronal processes).
- Represents focal neuronal differentiation.
- seen also in neuroblastomas.



Doctor: Homer Wright Rosettes are Psuedorosettes. Neuropil (which is seen under the light microscope) reflects that the tumor has some degree of focal neuronal differentiation but this won't change the grade it is still a grade 4 tumor, and it's not specific for medulloblastoma because it can be seen in some neuroblastomas and other tumors.

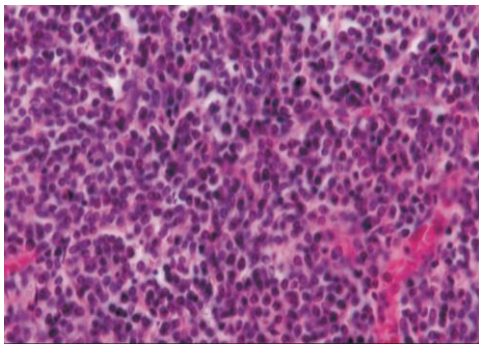




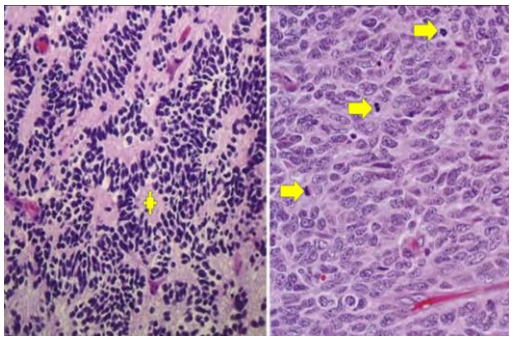
The picture above: A sagittal section through the brain for a case of Medulloblastoma involving the superior part at the midline of the cerebellum. There is no hemorrhage or necrosis, the color is yellow to gray, the margins are not that definite, but we can almost put a margin to the tumor not a well-defined one.

The picture below: Medulloblastoma involving the cerebellum and the 4th ventricle with areas of hemorrhage and necrosis.

So there is variation from one case to case depending on the neuronal differentiation but all of them are grade 4 tumors.



In terms of histology, we have a highly cellular tumor with frequent mitotic figures and made of small round blue cells with little rim of the cytoplasm and large nucleus that shows atypia and hyperchromasia, there is pleomorphism, variation in the nuclear size and shape, sometimes you can find foci of necrosis in this tumor.in figure we can't see the Homer Wright Rosettes.



The yellow star points to an area of central neuropilalistic material called central neuropil, tumor cells arrange themselves to form a circle surrounding the neuropil, and this is what we call Homer Wright Rosettes which reflects focal neuronal differentiation, but it won't change the grade for the tumor.

Pathogenesis

• medulloblastomas are classified according to molecular characteristics in addition to histopathological features.

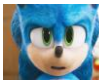
Doctor: Classification according to the above will help you give the right treatment to the patient, for example you will use radiology only to the patients that have tumors that are radiosensitive.

• Clinical trials are ongoing that seek to tailor therapy targeted to molecular alterations, with the goal of avoiding radiation therapy when possible.

Oncogenic pathways in Medulloblastoma:

Three pathways:

• Wnt pathway activation: associated with gain of function mutations in the gene for β-catenin; have the most favourable prognosis of all of the genetic subtypes.



• Hedgehog (sonic hedgehog) pathway activation: associated with loss of function mutations in PTCH1 (a negative regulator of the Hedgehog); these tumors have an intermediate prognosis, but the concomitant presence of P53 mutation confers a very poor prognosis.

• MYC overexpression: due to MYC amplification; these tumors have the poorest prognosis.

30:00

OTHER PARENCHYMAL TUMORS

Primary Central Nervous System Lymphoma

- aggressive disease, poor response to chemotherapy.
- most common subtype: diffuse large B-cell lymphomas.
- it is the most common CNS neoplasm in immunosuppressed individuals
- Presentation:
  - multiple tumor nodules within the brain parenchyma (the surgeon is will ask you is this a lymphoma or metastasis because of the multiple nodules)
  - relatively **well defined** as compared with glial neoplasms (compared to diffuse glioma but it won't be as discrete as the masses made by metastasis)
  - not as discrete as metastases.
- lymphoma originating outside the CNS rarely spreads to the brain parenchyma

Germ Cell Tumors

- Can be primary or metastatic
- Primary brain germ cell tumors:
  - Locations: along the midline, most commonly in the pineal and the suprasellar regions.
  - 90% during the first 2 decades of life.
  - The most common primary CNS germ cell tumor is germinoma, testicular seminoma.

Meningiomas

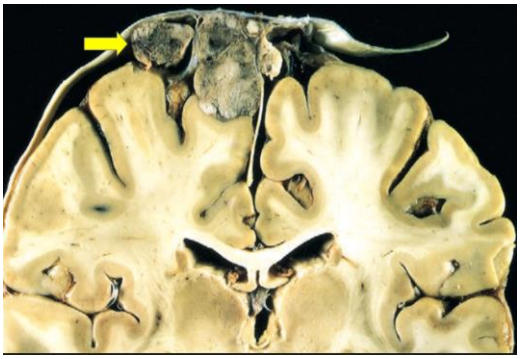
- tumors that arise from meningothelial cells of the arachnoid matter
- Age at presentation: adults (women>men) (3^{rd} to 4^{th} decade)
- Location: intracranial, intraspinal or orbital attached to the dura.
- Presentation: Most common headache, seizures, weakness (depends on location)

• Mostly separable from underlying brain, but some tumors are infiltrative, a feature associated with an increased risk for recurrence.

• Prognosis: determined by the lesion size and location, surgical accessibility, and histologic grade. (we have grades 1,2 and 3)

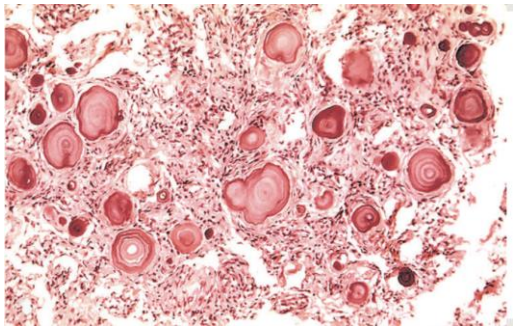
- Meningiomas (WHO grade 1):
  - well-defined dura-based masses that may compress the brain but do not typically invade it +/- overlying bone extension.
  - Epithelioid cells arranged in whorly (syncytial) pattern +/- psammoma bodies

Doctor: Proliferation of meningothelial cells, which have epithelioid shape, abundant cytoplasm indistinct cell border between cells and they form whorls (syncytial like pattern) and mostly there are calcifications called psammoma bodies because they are laminated calcifications. Meningiomas (WHO grade 1) these tumors don't have increased mitosis, don't have atypical features and don't have any feature that qualify them to be grade 2 or 3. **They don't reach the brain only compress it.**



The gross appearance of Meningiomas which is dura based.

It is easy to separate it from the underlying brain tissue it's just causing pressure.



The histological appearance we have proliferation of those epithelioid cells, whorls (syncytial like pattern), indistinct cell border, abundant cytoplasm and laminated calcifications called psammoma bodies (its not a must to have psammoma bodies but if we have them it will help us diagnose the tumor).

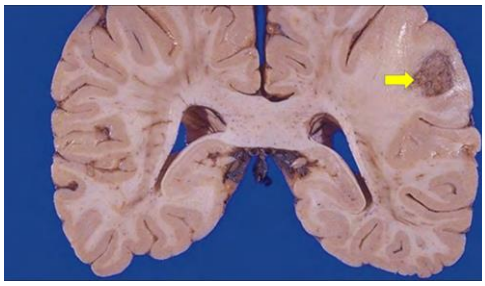
ATYPICAL MENINGIOMAS	ANAPLASTIC MENINGIOMAS
WHO grade 2 -recurrence and aggressive local growth and may require radiation therapy + surgery.	**WHO grade 3 (malignant)** -highly aggressive, resemble a high-grade sarcoma or carcinoma morphologically.
1-4 > mitoses/10HPF; **or**	**1**->20 mitoses/ 10HPF; or
2-(3 out of 5): increased cellularity, small cells with a high N/C ratio, prominent nucleoli, patternless growth, or necrosis; **or**	2-Papillary; or rhabdoid meningioma.
3-clear cell or chordoid subtypes of meningioma	

Doctor: In Atypical Meningiomas 1 of the 3 is enough to consider it Atypical and not grade 1

Doctor: In Anaplastic Meningiomas 1 of the 2 is enough regardless of the other features.

Metastatic Tumors:

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



An example of a metastatic tumor this nodule is present exactly in the junction between the gray and white matter, a discrete nodule involving this area (yellow arrow).

A common scenario is having more than one nodule but here we have only one. 40:00

Goodluck!!!!!