PATHOLOGY

☑ Sheet ○ Slide ○ Handout

Number

10

Subject

CNS Tumors 2

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بسم الله الرحمن الرحيم و به دوما نستعين

We started talking about the tumors of the brain and we classified them into:

1- primary, they were further divided into Glial tumors (Gliomas) and Non-glial tumors.

2- secondary.

Gliomas can be localized like pilocytic astrocytomas (which is relatively benign of grade 1), or diffused tumors of grade 2,3,4.

Also, we have said that tumors of grade 4 are called Glioblastomas multiforme because it has several structural ganging forms (necrosis, hemorrhagic areas, cystic formation).

Also we said that In order to diagnose Glioblastoma, two conditions must be present:

1- necrosis.

2- vascular proliferation (its responsible for the **enhancement** in the MRI -enhancement lesion-).

- Genetic changes in gliomas in general:

Changes in the IDH (Isocitrate dehydrogenase) enzyme, and the mutations affecting this enzyme are of the early changes.

Isocitrate Dehydrogenase is an enzyme involved in the dehydrogenation of Isocitrate, note that the citric acid is found in the Krebs cycle), when the citric acid is converted to Isocitrate then by normal IDH1 and IDH2 it is converted to alpha ketoglutarate.

When there are mutations; the IDH1 and 2 gain new function converting alpha ketoglutarate to 2-hydroxyglutarate, causing Gliomas.

So the normal IDH is responsible of keeping equilibrium between Isocetrate and alpha ketoglutarate, and when those enzymes are mutated we lose the equilibrium and alpha ketoglutarate is converted to 2-hydroxyglutarate which causes cancer (glioma).

- How does 2-hydroxyglutarate resulting from mutated IDH cause glioma?

Before answering let us remember the genes which when get mutated they cause cancer:

1- Tumor suppressor genes.

2- Proto oncogenes.

3- Genes responsible for apoptosis.

4- Genes regulating DNA repair.

So not any haphazard mutation can cause cancer, for example cystic fibrosis, thalassemia and down syndrome are pathological conditions with mutations without cancer. Abnormal uncontrolled proliferation must occur in order to result in neoplasia.

Returning to our question, IDH mutations cause cancer by a mechanism related to **Epigenetic changes** of the genome (methylation or acetylation).

Its thought and experiments are still working to approve that 2-hydroxyglutarate causes hyper-methylation of the promoter of tumor suppressor gene, and while I am hyper-suppressing the suppressor and then I am shifting the balance towards proliferation.

Also some theories state that 2-hydroxyglutarate affects **HIF** (Hypoxia inducible factor).

The main idea that we need to keep in mind is that: All Gliomas (low grade) start with the IDH mutation.

IDH 1 and 2 mutations are present in 90% of glioma cases. (**patients with mutated IDH have better prognosis and survival than patients with the wild type**).

Treatments must be initiated after the diagnosis of IDH mutations, **vaccine therapy** is one of these treatments. (Treatments still under research)

What is vaccine therapy?

Stimulation of the patient's T-cells to kill any cell with the IDH mutation.

In the new classification, Glioblastoma is divided into three types:

1- Glioblastoma IDH wild type, meaning that there is no mutation.

2- Glioblastoma IDH mutant.

3- Glioblastoma NOS, not otherwise specified.

As we said previously, 90% of low grade gliomas have the IDH mutation, while 90% of glioblastomas are of the wild type (don't have mutations) and only 10% have mutations.

Previously glioblastomas were classified into two categories; primary and secondary.

Low grade gliomas can progress into grade four, some patients have primarily glioma and then it progresses to glioblastoma (here its called secondary glioblastoma), while others have glioblastoma from the early beginning (here its called primary glioblastoma).

Now, secondary glioblastomas are the ones with IDH mutations.

IDH mutations are diagnosed by staining the enzyme itself, brown color indicates a positive stain. When the stain is negative we don't give up and we make other test regarding genetic analysis for the IDH1 and 2.

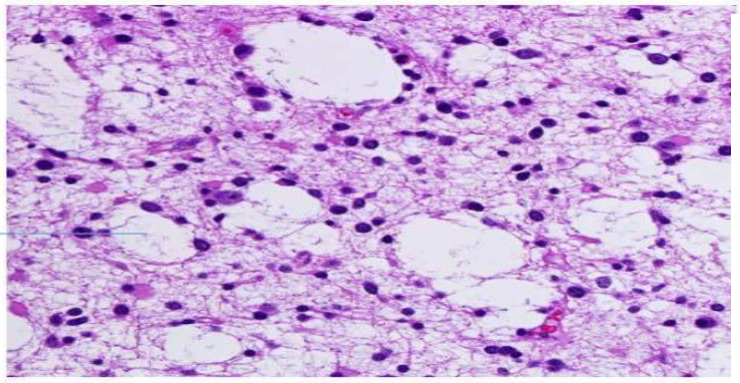
Now we have finished Diffused gliomas, and we have agreed that there is a type of gliomas considered as grade 1 called **pilocytic astrocytoma** and its benign and it has a very good prognosis, its most common location for presentation is in **The cerebellum**, and more commonly presented in children.

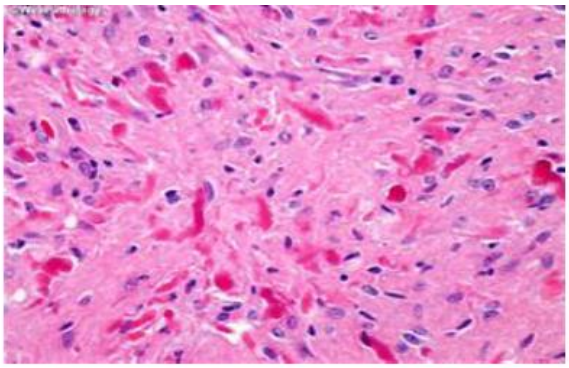
Its well circumscribed, small, rounded and localized.

Its name is pilocytic astrocytoma; cystic means that it has a cystic component with another solid one.

Under the microscope we see several small cysts, with minor cellularity.

This left slide is important for the exam.





The fibrillary background is stained by **GFAP** (glial fibrillary acidic protein).

In the right slide, you can see red **Rosenthal fibers** which are thick, elongated, eosinophilic protein aggregates seen in **pilocytic astocytoma and gliosis**.

- Pilocytic astrocytoma's genetics:

It doesn't have IDH mutations, instead **BRAF mutations** which is related to RAS pathway (oncogene).

- The second type of gliomas; **Oligodendroglioma:**

1. It constitutes 10% of all gliomas, rarer than astrocytomas (Gliomas are the most common brain tumor, astrocytomas are the most common of gliomas and glioblastomas are the most common of astrocytomas, so the most common brain tumor in adults is glioblastoma).
2. Presents at the age of 40-50 years, in the cerebral hemispheres (the white matter specifically).
3. It has a better prognosis than astrocytomas (patients with grade two live 10-20 years, and those with grade 3 live up to 10 years with aggressive treatment).
4. 90% of the patients with oligodendroglioma has IDH1 or IDH2 mutations, because ALL gliomas are based on this mutation (it's the molecular signature of this type of tumor), and originate from the progenitor cell.

Previously we used to classify the tumor depending on its morphology (if its shape is like astrocytmas its classified as such, if it looks like oligodendroglias it classified as such and if its hybrid of both it is classified as oligoastrocytoma), now according to the WHO's classification we do genetic analysis to classify them according to them as the following:

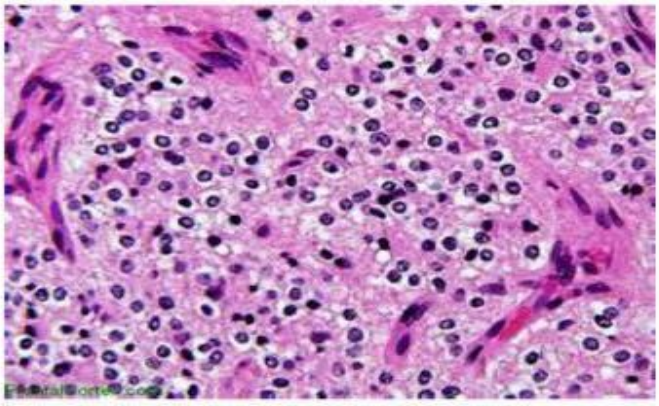
1- If IDH mutation is found with **1p and 19q** deletion it is called oligodendrogliomas regardless of their morphology and they have good prognosis.

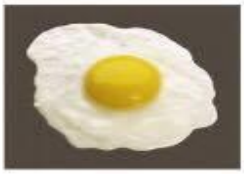
2- If IDH mutation is found without 1p and 19q deletion it is called astrocytomas regardless of their morphology and they have poor prognosis.

That's why oligoastrocytic classification is no more used now, due to genetic analysis.

- Morphology of oligodendrogliomas under the microscope:

White halo surrounding the nuclei giving the fried egg appearance.





- Grading of oligodendrogliomas:

There is grade two, three and four with NO grade one oligodendroglioma.

- Grade two is Well differentiated and low cellularity, polymorphism and mitosis.
- Grade three is Anaplastic; more cellularity, mitosis and polymorphism.
- Grade four is the one which develops to Glioblastoma (so both oligodendrogliomas and astrocytomas can develop to Glioblastomas).

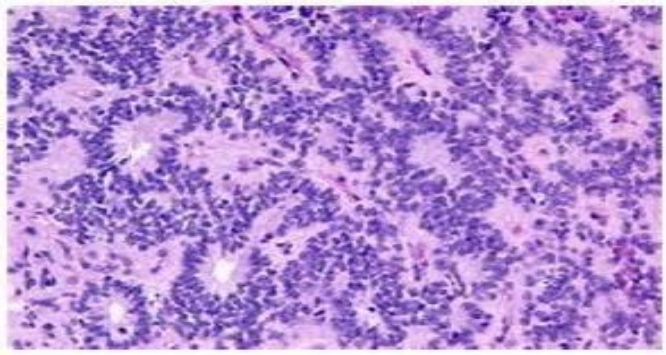
- The third type of Gliomas is the **Ependymomas:**

Located in the ventricles in children and in the spinal cord in adults (where ependymal cells are present).

They have better prognosis than the other types, specially if they are resectable.

- Morphology of ependymomas:

They form rosettes around canals (ventricles or central canal of the spinal cord), and pseudo-rosettes around the blood vessels (perivascular).



Tumors related to the ependymal cells: There are some tumors that are found below the ependymal lining or in association with the choroid plexus but they are not ependymomas, these tumors include: Subependymoma (found bellow the ependymal cells) and colloid cysts found in ventricles and choroid plexus pappiloma.

All of them are rare tumors and benign, they are important clinically because they result in hydrocephalus.

The doctor will NOT ask us about the neuronal tumors as they are very rare and we will not see them in our career, just know that there are tumors arising from neural cells like: **Central neurocytoma** and **Gangliоglioma**.

Sorry for any mistake, Good luck <3

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