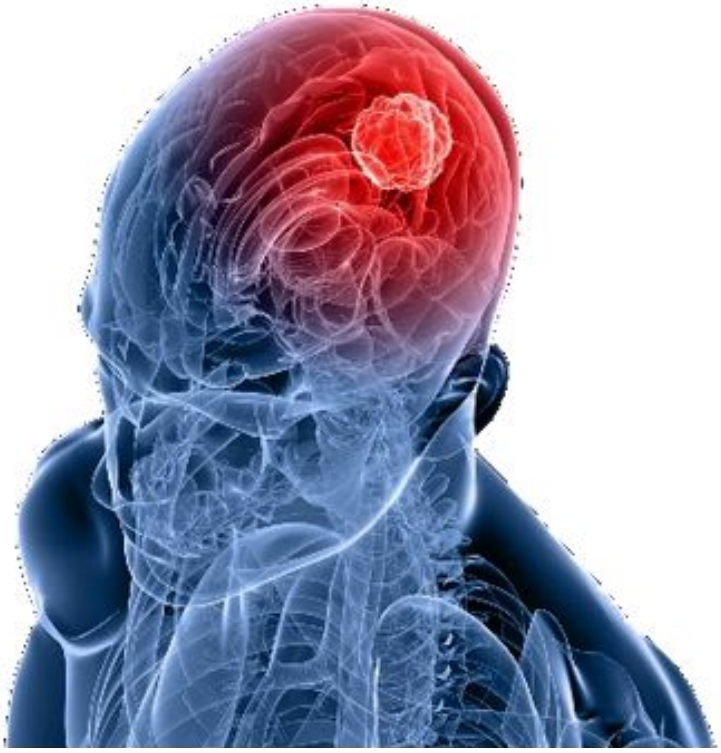
Brain Tumors



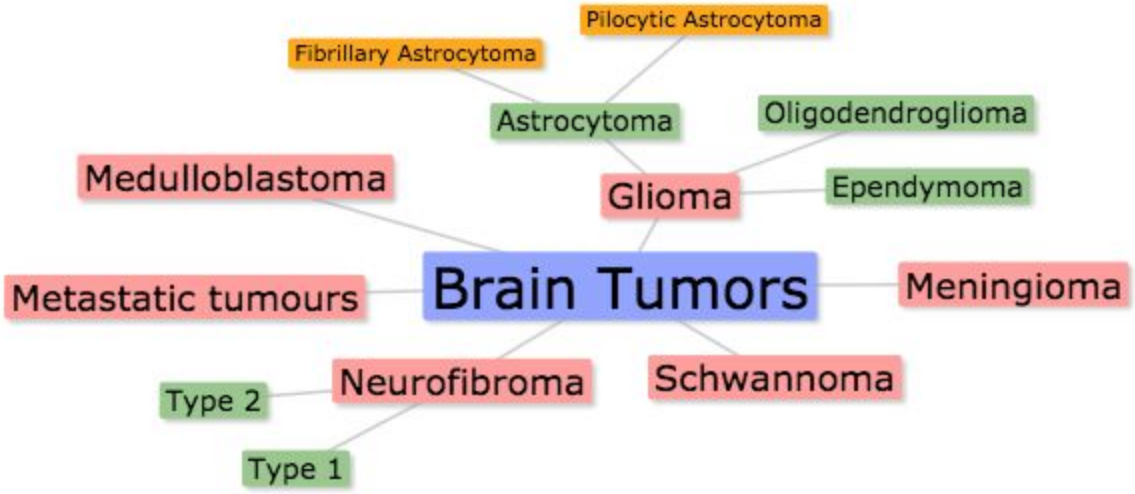
Objectives:

- Appreciate how the anatomy of the skull and the spinal column influences the prognosis of both benign and malignant primary CNS tumors.
- List the principal clinicopathological features of some of the main types of tumors that can arise within the central and the peripheral nervous systems.

Important note: **Please check out this link before viewing the file to know if there are any additions or changes. The same link will be used for all of our work: Pathology Edit**

Red: Important
Grey: Extra notes

Lecture contents:



- Check this helpful video from Pathoma about CNS tumors (12:24 min): https://drive.google.com/file/d/0B8QLRmhxZMRoUm5zUjVFTHhMd0U/view?usp=sharing

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Incidence.

The annual incidence of tumors of the CNS ranges from:

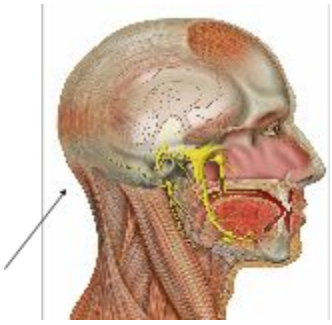
- 10 to 17 per 100,000 persons for intracranial tumors.
- 1 to 2 per 100,000 persons for intraspinal tumors.

About half to three-quarters are primary tumors, and the rest are metastatic.

In childhood.

Tumors of CNS are a large proportion of cancers of childhood, accounting for **20%** of all tumors. CNS tumors in childhood differ from those in adults both in histologic subtype and location. Most likely location:

- In childhood → **posterior fossa**. (Bottom of the skull)
- In adults → **mostly supratentorial**. (Forebrain)



General characteristics.

- Do not have detectable premalignant or in situ stages comparable to those of carcinomas.
- Even low-grade lesions may infiltrate large regions of the brain, leading to serious clinical deficits, nonresectability[1], and poor prognosis.
- The anatomic site of the neoplasm can have lethal consequences irrespective of histological classification. (i.e. benign tumors can be fatal in certain locations).

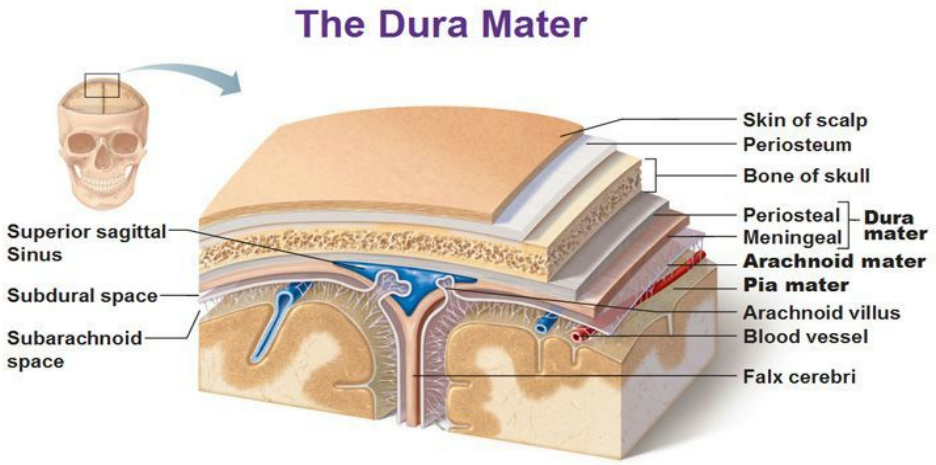
Examples of such locations? Brain stem in medulla can cause cardiorespiratory arrest.

[1] Unable to be removed by surgery.

- The pattern of spread of primary CNS neoplasms differs from that of other tumors: Rarely metastasize outside the CNS. (Because of the BBB) Although **subarachnoid space does provide a pathway for spread**

What are the layers that surround subarachnoid space?

Subarachnoid space is located between the arachnoid mater and the pia mater.
it contain blood vessels & CSF making metastases within the CNS possible (distant sites along neuroaxis[2]).



General manifestations.

- Seizures, vague[3] symptoms, headaches especially in the morning.

Why? Tumors usually compress the surrounding area and while we are sleeping more fluid will be to the brain and it can't return to the body as fast as normal due to the presence of the tumor and that's called (hydrocephalus[4]) increasing the intracranial pressure which causes headache.

- Focal neurologic deficits related to the anatomic site of involvement.
- Rate of growth may correlate with history.

Classification.

Brain tumors are classified with respect to the origins they're arising from:

- Cells of the layers covering the CNS (meningiomas).
- Cells intrinsic to the brain (gliomas, neuronal tumors, choroid plexus tumors).
- Other cell populations within the skull (primary CNS lymphoma, germ-cell tumors).
- They may spread from elsewhere in the body (metastases).

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[2] ṅpaired part of the central nervous system: spinal cord, rhombencephalon, mesencephalon, and diencephalon.

[3] مبهم

[4] Accumulation of fluid in the brain.

Gliomas.

Gliomas are type of CNS tumors arising from the glial cells. They're classified as:

- Astrocytomas, arising from the astrocytes.
- Oligodendrogliomas, arising from the oligodendrocytes.
- Ependymomas, arising from the ependymal cells.

Astrocytomas.

They are classified into 2 types:

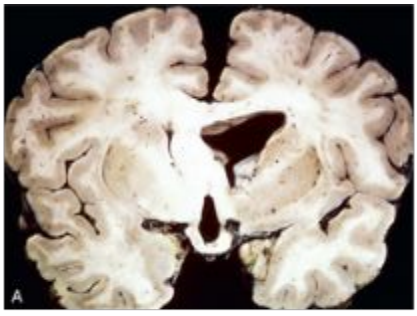
Pilocytic (Grade I)	Fibrillary
Children and young adults	4th - 6th decades of life
Commonly affects the cerebellum	Commonly affects the cerebral hemisphere
Relatively benign	Classified into 3 variable grades

Fibrillary Astrocytoma.

On the basis of histologic features, they are stratified into three groups:

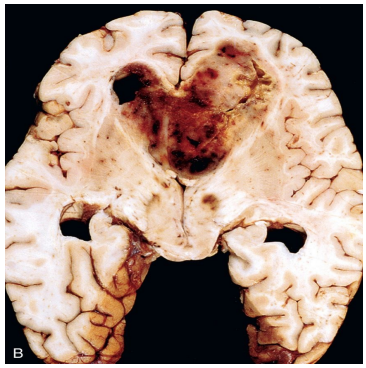
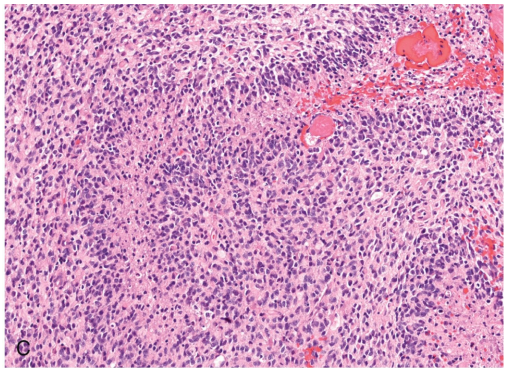
Well differentiated "diffuse astrocytoma" (WHO[5] grade II)	Less differentiated Anaplastic astrocytoma (WHO grade III)	Less differentiated Glioblastoma[6] (WHO grade IV)
Static or progress slowly (mean survival of more than 5 years)	-	With treatment, mean survival of 8-10 months
Moderate cellularity	More cellular → Mitosis	Mitosis
Variable nuclear pleomorphism	Greater nuclear pleomorphism	-
-	-	Necrosis and/or Vascular endothelial cell proliferation.

- Glioblastoma is the most common malignant CNS tumor in adults.



Note that diffuse astrocytoma (Low grade) are poorly demarcated.

[5] World Health Organization.
[6] also known as **GBM** "GlioBlastoma Multiforme"

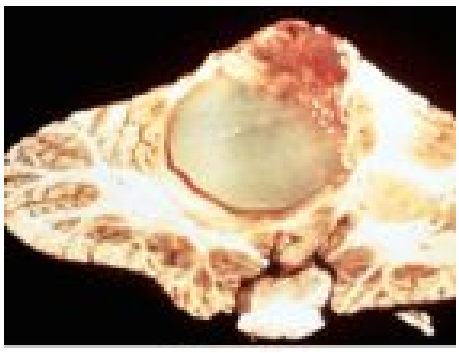
GBM "Glioblastoma Multiforme"	
	
crosses the corpus callosum (the butterfly glioma)	- Pseudopalisading[7] necrosis <u>And/Or</u> Vascular proliferation. - GFAP[8] positive.

Mutations:

- Mutations that alter the enzymatic activity of two isoforms of the metabolic enzyme **isocitrate dehydrogenase** (**IDH1** and **IDH2**) are common in lower-grade **<u>astrocytomas</u>.**
- Secondary glioblastomas share **p53** mutations that characterized low-grade **<u>gliomas.</u>**
- **Primary glioblastomas → Amplification of the epidermal growth factor receptor (EGFR)** gene.

Pilocytic Astrocytoma.

- Benign tumor of astrocytes.
- Most common CNS tumor in children (usually arises in the cerebellum).
- Often **cystic**, with a mural[9] nodule.
- Well circumscribed.
- "hairlike" = pilocytic processes that are **GFAP** (Glial Fibrillary Acidic Protein) positive.
- **Rosenthal fibers** & hyaline granular bodies are often present.
- Necrosis and mitoses are typically ***<u>absent</u>***.

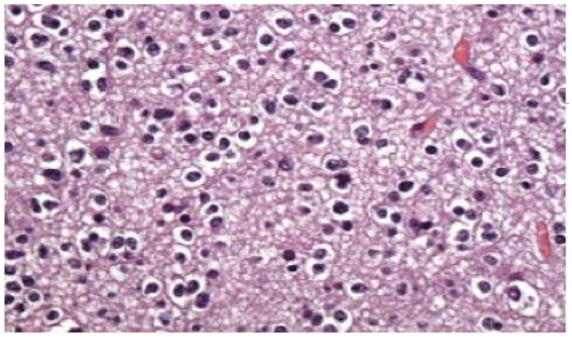


[7] Characterized by an accumulation of tumor cells around central necrosis.

[8] Glial fibrillary acidic proteins are the intermediate filaments present in the glial cells.

[9] A mural nodule is a small mass of solid tissue on the inner wall of a cyst.

Oligodendroglioma.



Malignant tumor. Usually affects adult in Fourth and fifth decades. Lesions are found mostly in **cerebral hemispheres** mainly in frontal and temporal lobes and usually affect white matter (because oligodendrocytes are present in white matter).

Genetic findings: loss of heterozygosity for **chromosomes 1p and 19q**
Imaging reveals: Calcified tumor in white matter. may present with seizures.
Morphology:

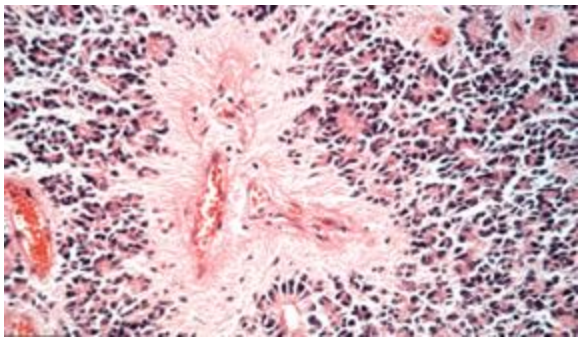
- Round nuclei often with a cytoplasmic halo. (**Fried egg pattern**)
- Blood vessels are thin and can form an interlacing pattern. (Chicken wire pattern)

Ependymoma.

Malignant tumor of ependymal cells and usually seen in children and first two decades of life. (usually from ependymal in **ventricular system** including the **central canal of the spinal cord.** So, may present with **hydrocephalus**). In adults, the spinal cord is most common location.

Morphology:

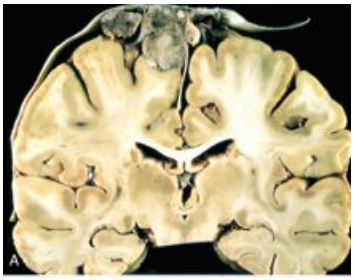
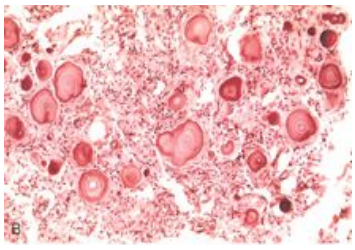
- Tumor cells may form round or elongated structures (**rosettes[10], canals**)
- **perivascular pseudo-rosettes[11].**
- Anaplastic ependymomas show increased cell density, high mitotic rates, necrosis and less evident ependymal differentiation



Rosettes Pattern

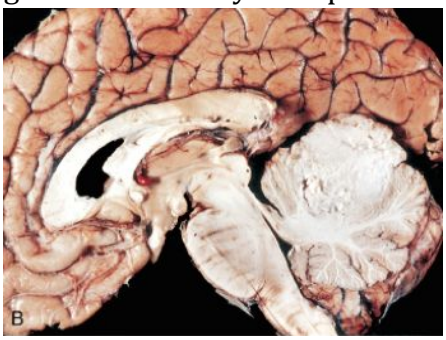
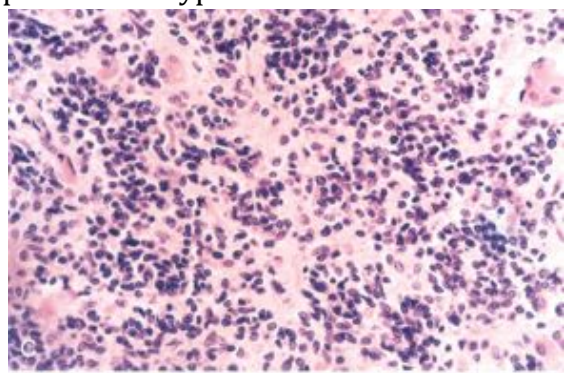
[10] that resembles the embryologic ependymal canal with long delicate process extending into lumen.
[11] which tumor cells are arranged around blood vessels with intervening zone containing thin ependymal process.

Meningioma.

common in	Benign Tumor usually in Adults (women)
Origin	Meningothelial cell of the arachnoid. (Layers of meninges are: Dura, Arachnoid and pia maters.)
Invasion	Easily separable from underlying brain, but some tumors infiltrate the brain. The presence of brain invasion → increased risk of recurrence. (may present with seizure)
Gross appearance	● Well demarcated ● mass in the dura with compression of underlying brain 
Microscopic appearance	● Whorled pattern of cell growth (.حلزوني) ● Psammoma bodies. ● Atypical meningiomas (more pleomorphism, mitosis and increased cellularity). 
Main subtypes	1-Syncytial. Cluster of cells without visible cell membrane. 2-Fibroblastic. Elongated cells with collagen deposition between them. 3-Transitional. Combination of the two previous types.

When a person has **multiple meningiomas**, especially in association with **eighth-nerve schwannomas** or **glial tumors**, the diagnosis of **neurofibromatosis type 2 (NF2).** (Check the Homework page)

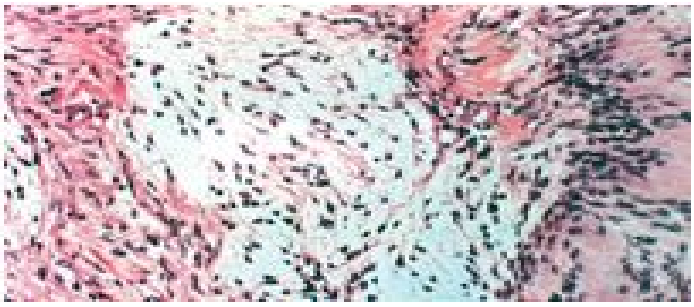
Medulloblastoma.

Age and site	Children, exclusively in the cerebellum.
Type and prognosis	The tumor is highly malignant derived **from granular cells of cerebellum**. Prognosis is poor for untreated patients because its rapid growth and spreads by CSF. ● With total excision and radiation, your patient could has 5-year survival rate.
Gross appearance	● showing medulloblastoma with **destruction of the superior midline cerebellum..** ● largely undifferentiated. ● Neuronal and glial markers may be expressed 
Microscopic appearance	● Small, round and blue cell ● little cytoplasm with hyperchromatic nuclei 

Schwannoma. Robbins p. 806

Benign tumor of schwann cells, can involved both **cranial** or **spinal nerve** (most commonly involves the **8th cranial nerve** at cerebellopontine angle producing **tinnitus and hearing loss**).

- **10%** of **Sporadic schwannomas** are associated with mutations in the **NF2 gene**.
- **ALL Bilateral acoustic schwannoma** is associated with **NF2.**




Gross appearance: Circumscribed & usually encapsulated.
Histology:

- Cellular Antoni A pattern and less cellular Antoni B.
- nuclear-free zones of processes that lie between the regions of nuclear palisading are termed **Verocay bodies.**

What Are Antoni A and Antoni B Patterns?

- **Antoni A:** Highly cellular, fibrillary, intensely polar, elongated appearing tissue type.
- **Antoni B:** distinct loose microcystic tissue adjacent to the Antoni A regions.

Neurofibroma. Robbins p. 806

Neurofibromas are benign tumors of peripheral nerve.

Examples:

- **Cutaneous (diffuse) neurofibroma** or in (**solitary neurofibroma** These arise sporadically or multiple lesion in association with **type 1 neurofibromatosis (NF1)**, **rarely malignant.**
- **plexiform neurofibroma**, mostly arising in individuals with NF1, and associated s**mall real malignant transformation**

Neurofibromas cannot be separated from nerve trunk (in comparison to schwannoma which can be supperated), therefore it's difficult to be removed surgically.

Metastatic tumours.

About 50% of CNS tumors. Lung, breast, skin (melanoma), kidney, and gastrointestinal tract are the commonest primary sites.
Gross appearance:

- **multiple**, **well circumscribed.**
- Sharply demarcated lesion at **gray matter with edema.**

Homework! (Familial Tumor Syndromes) Robbins p. 806

1. **Describe the inheritance pattern and the main features of:**
   - **Type 1 Neurofibromatosis**
   - **Type 2 Neurofibromatosis**

Neurofibromatosis (**NF**) refer to a number of inherited conditions that are clinically and genetically distinct and carry a high risk of tumor formation, particularly in the brain. Thy are autosomal dominant disorders. **They have 2 types:**

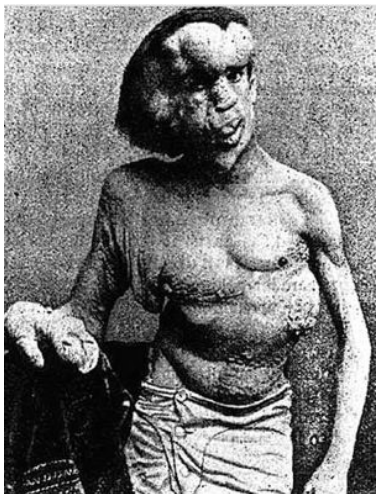
1. Type 1 Neurofibromatosis.
2. Type 2 Neurofibromatosis.
3. Schwannomatosis.

- NF2 patients are at risk of developing multiple schwannomas, meningiomas, and ependymomas.
- The presence of bilateral vestibular schwannomas is a hallmark of NF2.

	Type 1 Neurofibromatosis	**Type 2 Neurofibromatosis**
inheritance pattern	Mutation on chromosome 17 coding for neurofibromin	Mutation on chromosome 22 coding for merlin
main features	1. learning disabilities. 2. seizures. 3. skeletal abnormalities. 4. vascular abnormalities with arterial stenoses. 5. pigmented nodules of the iris (*Lisch nodules*). 6. pigmented skin lesions (axillary freckling and café au lait spots) in various degrees.	1. Benign tumor 2. Bilateral acoustic neuromas (schwannoma; >90% of cases) 3. CN VIII tumor 4. Sensorineural hearing loss, tinnitus 5. Meningiomas 6. Spinal schwannomas 7. Juvenile cataracts (~80% of cases)

2. **Which one of these two syndromes, has a propensity for the neurofibromas to undergo malignant transformation at a higher rate than that observed for comparable tumors in the general population?**

   Neurofibromatosis Type 1.



Summary.

Tumor	Type	Gene/ Mutation	incidence	Gross & Clinicle	Histology	Notes
Pilocytic Astrocytoma	benign	IDH1 & IDH2	Children & young adults	In cerebellum cystic, mural[12] nodule, Well circumscribed.	Rosenthal fibers	GFAP
Fibrillary Astrocytoma	diffuse astrocytoma (II)	-	4th - 6th decades	In cerebral hemisphere	pleomorphism	>5 years
	Anaplastic astrocytoma (III)	-			Mitosis & pleomorphism	
	Glioblastoma (IV)	1ry: EGFR 2ry: p53			Mitosis, Necrosis & vascular prolifration	8-10 months, GFAP
Oligo-dendroglioma	Malignant	chromosomes 1p and 19q	4th - 5th decades	cerebral hemispheres (frontal & temporal) white matter seizures	Fried egg pattern & interlacing pattern	
Ependymoma	Malignant		children and first two decades	Ventricles & central canal → hydrocephalus	rosettes[13], canals + Mitosis + Necrosis	Adults → SC
Meningioma	Benign		Adults (women)	Well demarcated	Whorled pattern Psammoma bodies	
Medullo-blastoma	Highly malignant		Children	cerebellum & destruction of the superior midline cerebellum	Small, round and blue cell	
Schwannoma	Benign	Bilateral: NF2		tinnitus and hearing loss & encapsulated	Antoni A > Antoni B Verocay bodies	
NF1	benign	**CH 17**		Pigment of iris & skin		
NF2	benign	**CH 22**		tinnitus and hearing loss		
Metastatic	-	50% of CNS		multiple, well circumscribed, gray matter, edema		

[12] A mural nodule is a small mass of solid tissue on the inner wall of a cyst.

[13] that resembles the embryologic ependymal canal with long delicate process extending into lumen.

MCQ's.

1-The neoplasm that most frequently occurs in the fourth ventricle is:
A- Oligodendroglioma
B- Ependymoma
C- Medulloblastoma
D- Neuroblastoma
Ans B

2- Loss of heterozygosity for chromosomes 1p and 19q is the most common genetic finding in:

A- Medulloblastoma B- Astrocytoma
B-Meningioma
C- Oligodendroglioma
Ans D

3- A biopsy was taken from a patient and it showed whorled pattern of growth and psammoma bodies. What is the most likely diagnosis:
A- Medulloblastoma
B- Glioblastoma
C- Meningioma
D- Pilocytic astrocytoma
Ans C

4- Bilateral acoustic schwannoma is associated with :
A- V600E
B- NE2
C- NF2
D- IDH1
Ans C

5- In meningioma presence of brain invasion is associated with :
A- Decreased risk of recurrence
B- Increased risk of recurrence
C- It has no effect
Ans B

6-psammoma bodies are found in:

A-meningioma
B-glioblastoma
C-schwannoma
D-neurofibroma
Ans A

For any suggestions or questions please don't hesitate to contact us on: Pathology434@gmail.com

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Ask us: www.ask.fm/Pathology434

Examine yourself in pathology:
http://library.med.utah.edu/WebPath/EXAM/MULTORG/examidx.htm

Good Luck! :)

"YOU CAN HAVE IT ALL. JUST NOT ALL AT ONCE"

مها الربيعة
ريما الرشيد
ريما الناصر
هديل السلمي
سارة السلمان

حسين الكاف
سعد الخريجي
عبدالعزيز الطويل
عبدالرحمن الكاف