جامعة الملك سعود
King Saud University

Pathology
Teamwork 438

Lecture 2&3: CNS 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 peripheral nervous system.

Black: original content
Red: Important
Blue: only found in boys slides

Dark orange: Doctor notes
Grey: extra/Robbins
Pink: Only found in girls slides

Reviewed by Razan AlRabah & Ibrahim AlBakhiti

Editing file

Lecture Content

- Incidence
- childhood
- General characteristics
- General manifestation
- Classification

Introduction

- Astrocytoma
  - Fibrillary
  - Pilocytic
- Oligodendrogliomas
- Ependymomas

Gliomas

CNS Tumors

Meningioma and Medulloblastoma

- Origin
- Epidemiology
- Histopathology
- Prognosis

Peripheral nervous system tumors

- Schwannoma
- Neurofibroma
- Metastatic tumors

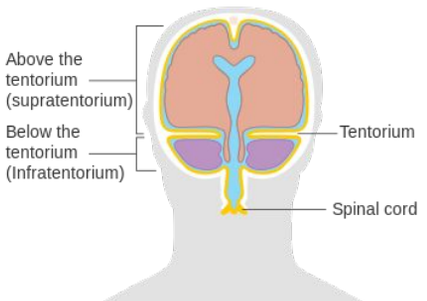
Introduction

Incidence:

- The annual incidence of tumors of the CNS ranges from:
  - 10 to 17 per 100,000 persons of 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.

Childhood:

- Tumors of the CNS are a large proportion of cancers of childhood, accounting for as many of 20% of all tumors.
- CNS tumors in childhood differ from those in adults both in histologic subtype and location.
- CNS Tumors location are likely to be:
  - In adults → **supratentorial**
  - In children → **infratentorial**; in posterior fossa.



General Characteristics:

- CNS tumors do not have morphologically evident premalignant or in situ stages compared to carcinomas.
- The pattern of spread of primary CNS neoplasms:
  - Rarely metastasize outside the CNS.
  - The subarachnoid space does provide a pathway for spread.
  - What are the layers that surround subarachnoid space?
    → Arachnoid and pia layers
- Even low-grade lesions may infiltrate large regions of the brain, leading to serious clinical deficits, non-resectability, and poor prognosis.

General Manifestation:

1. Seizures, headaches, vague symptoms.
2. Focal neurologic deficits **(related to the anatomic site of lesion).**
   - Example on such locations?
     → Benign meningioma may cause cardiorespiratory arrest from compression of the medulla.
3. Rate of growth may correlate with history.

Classification:

CNS tumors may arise from:

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

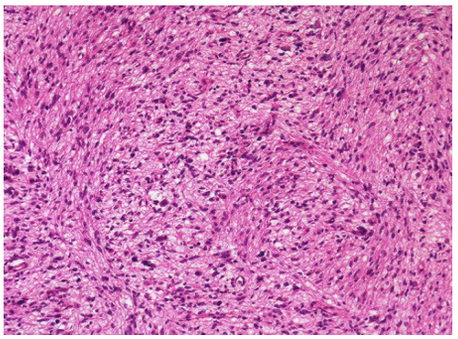
Gliomas

- **Gliomas** are tumors that arise from the glial cells of the brain or the spinal cord.
- They are divided into **3 types** based on the origin of the tumor:
  1. Astrocytoma (Astrocytes)
  2. Oligodendrogliomas (oligodendrocytes)
  3. Ependymomas (ependyma)

Astrocytoma

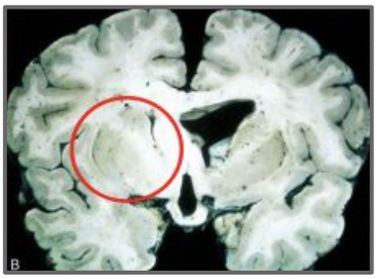
- Astrocytes are of two types thus astrocytoma can be divided into two types:

1. **Pilocytic (Grade I) Astrocytoma**
   - Epidemiology: children and young adults
   - Location: commonly affect the cerebellum
   - Type: relatively benign
2. **Fibrillary Astrocytoma** ***All malignant.**
   - Epidemiology: between 4th and 6th decades (30-59).
   - Location: commonly affect the cerebral hemisphere
   - Type: variable grades (Grade II → Grade IV)
   - Fibrillary astrocytoma can vary in grades



Microscopy of diffuse astrocytoma

Type	Diffuse Astrocytoma	Anaplastic Astrocytoma	Glioblastoma
Differentiation	Well	Less	Less
Grade	2 (low)	3 (high)	4 (high)
Progress	Slow	Fast	Fast
Cellularity	Moderate	High	High
Pleomorphism	Variable	Great	Great
Survival	>5 years	<5 years	8-10 months (with treatment)
Notes		Mitosis is seen in morphology	**Necrosis, mitosis and vascular cells proliferation**

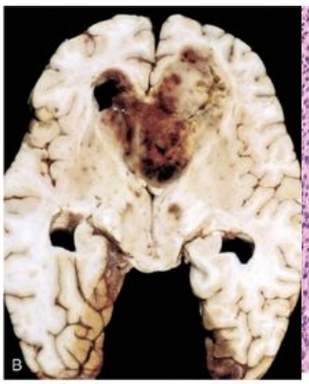


Poorly demarcated diffuse astrocytoma

Gliomas

In GBM **(Glioblastoma Multiforme)** we'll find:

1. Pseudopalisading necrosis marginal deadzone between tumors.
2. Vascular proliferation increase in vessels.
   * If you have one of this two findings or both, the tumor will be Grade IV instead of Grade III.



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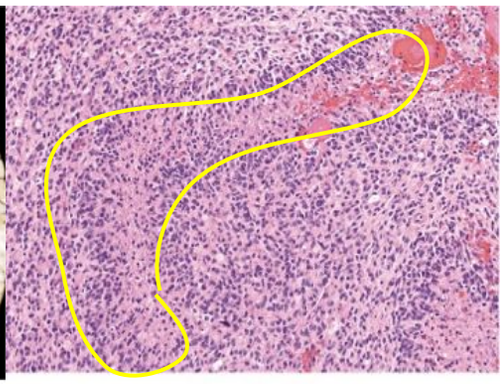
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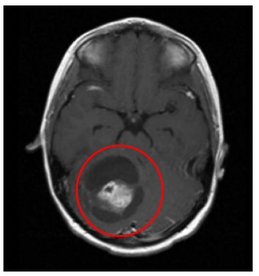
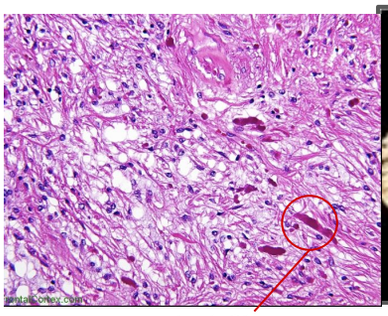
Genetic role in Astrocytoma

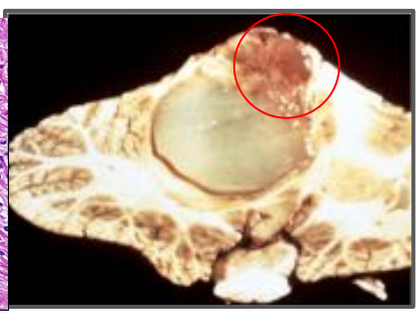
Low grade astrocytoma	Secondary[1] glioblastoma	Primary glioblastomas
Is linked to mutations that alter the activity of two isoforms of the metabolic enzyme **isocitrate dehydrogenase (IDH1 and IDH2)**	Is linked to **p53** mutations that characterize low-grade gliomas	Are characterized by amplification of **epidermal growth factor receptor (EGFR)** gene

Pilocytic Astrocytoma

- Often cystic with a mural nodule. *in wall of nodule.
- Well circumscribed
- Hairlike = pilocytic processes that are **GFAP[2] positive**
- Rosenthal fibers and hyaline (glassy) bodies are present.
- No necrosis or mitosis present
- Infratentorial


Well demarcated Pilocytic astrocytoma


Rosenthal fibers

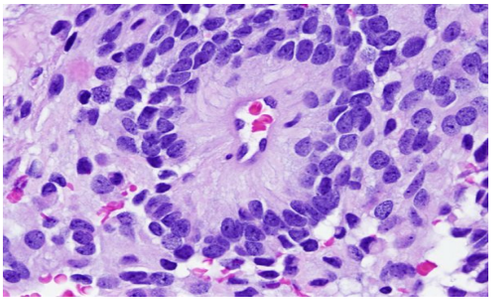


1- when we say secondary it means it was a different type of tumor that transformed into glioblastoma
2- Glial fibrillary acidic protein positive

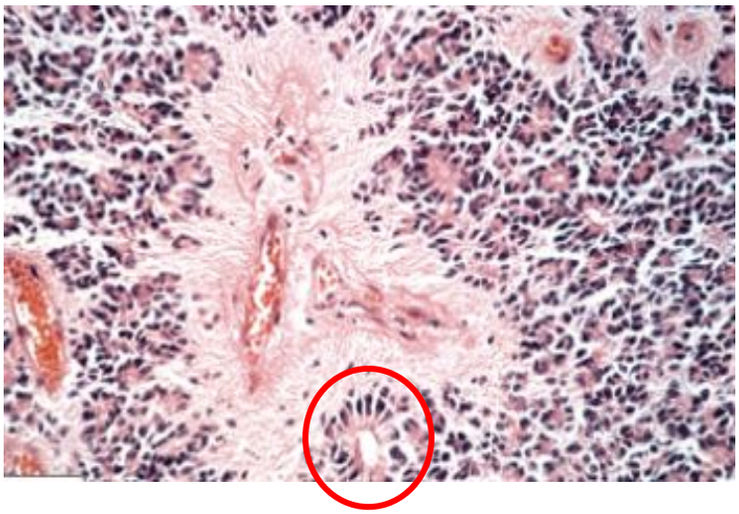
Gliomas

Ependymoma (grade II)

- Ependymoma arise next to the ependyma-lined ventricular system of the brain and the central canal of the spinal cord.
- Occurs in the first two decades of life (children & young adults)
- Typically occur near the **fourth ventricle**
- In ***adults***, it's more common in the ***spinal cord***

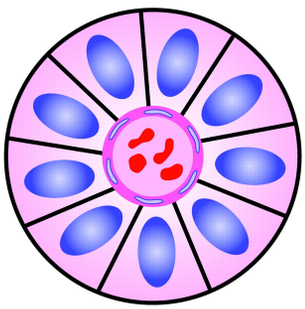


- Tumor cells may form round or elongated structures called **rosettes**
- Rosettes are round assemblage of cells around a central lumen
- In ependymoma, **perivascular pseudorosettes** are more common and are cellular assemblage around a small blood vessels
- Pseudorosettes do not have lumen



In **anaplastic ependymomas (grade III)** we find:

1. Increased cell density
2. High mitosis
3. Necrosis
4. Less ependymal differentiation



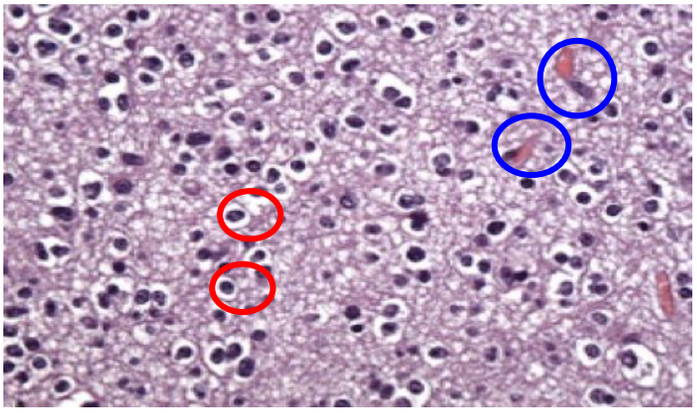
Gliomas

Oligodendrogliomas

- Oligodendrogliomas is a CNS tumor found in people between the 4th and 5th decades.
- It affects the **cerebral hemisphere** especially white matter.
- Better prognosis than patients with astrocytoma with a survival rate of 5-10 years.
- Anaplastic form has a much worse prognosis.
- The most common genetic findings are loss of **heterozygosity for chromosomes 1p and 19q** (co-deletion).

Histopathology of oligodendrogliomas (grade 2):

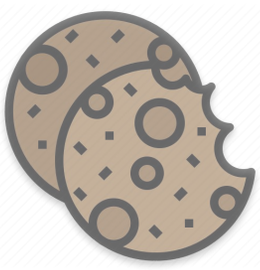
- Oligodendrogliomas cells have round nuclei with a cytoplasmic halo often referred to as **fried eggs pattern.**
- Blood vessels are thin and can form an interlacing pattern often referred to as **chicken wire pattern.**
- Calcification is also present in 90% of cases.



In anaplastic oligodendrogliomas (grade 3) we find:

1. High mitotic activity
2. High cellularity
3. Vascular proliferation
4. Necrosis (with or without palisading)

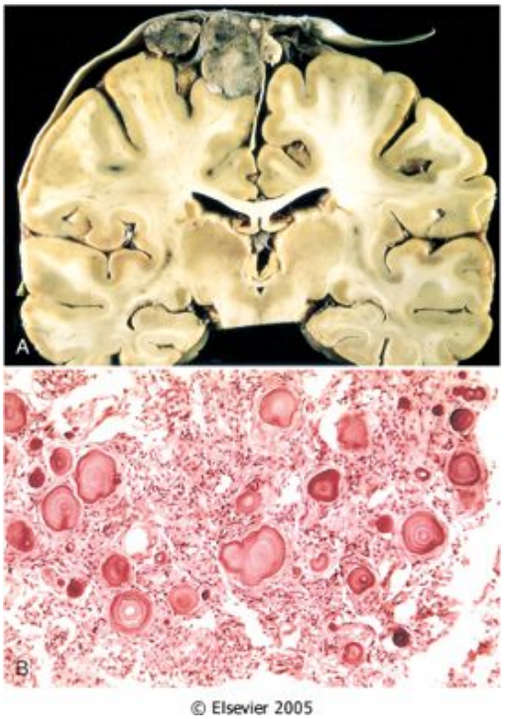
Study break...



Let's hope this covers up
our poor judgment of space

Central Nervous System Tumors

Meningioma



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- Predominantly **benign** tumors of adults.
- **Origin:** meningothelial cell of the arachnoid.
- Well demarcated.
- Attached to the dura with compression of underlying brain.

Histopathology

- **Whorled pattern** of cell growth.
- **Psammoma bodies;** laminated calcification.

- Although most meningiomas are easily separable from underlying brain, some tumors infiltrate the brain.
- The presence of brain invasion is associated with increased risk of recurrence.

Main subtypes: (Grade I)

- Syncytial "meningothelial" = multiple whorls
- Fibroblastic = spindle shaped cells
- Transitional = show both features
- Psammomatous & secretory

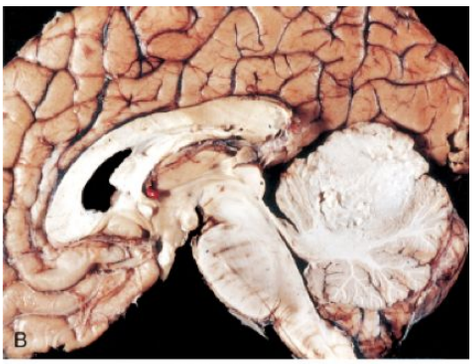
Also Note:

- Atypical meningiomas; increased cellularity and prominent nucleoli. (Grade II)
- Anaplastic (malignant) meningiomas; mitotic rate higher than atypical meningioma and more aggressive. (Grade III)

Central Nervous System Tumors

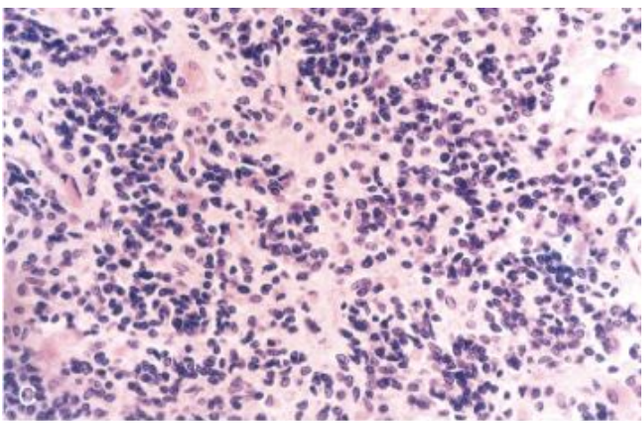
Medulloblastoma (Grade IV)

- Occurs in Children and <u>always in the cerebellum.</u>
- Neuronal and glial markers may be expressed, but the tumor is often largely undifferentiated.
- The tumor is **highly malignant,** and the prognosis for untreated patients is dismal; however, it is exquisitely radiosensitive.
- With total excision and radiation, the 5-year survival rate may be as high as 75%.



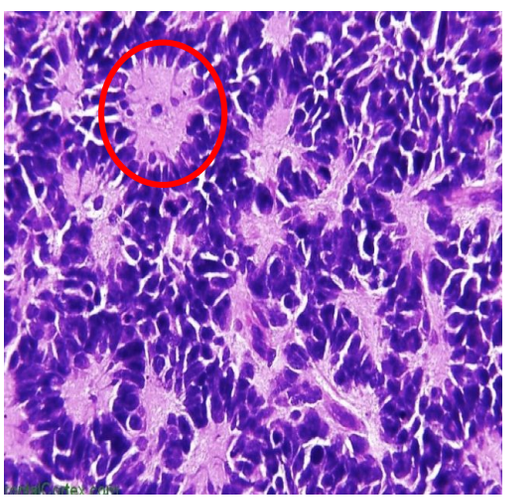
Histopathology:

- Extremely cellular
- Sheets of anaplastic ("small blue")
- Cells small with little cytoplasm and hyperchromatic nuclei
- Mitoses are abundant



Histopathology: only found in female's slides

- Often, focal neuronal differentiation is seen in the form of the Homer Wright or **neuroblastic rosette.**
- They are characterized by primitive tumor cells surrounding central neuropil (delicate pink material formed by neuronal processes).



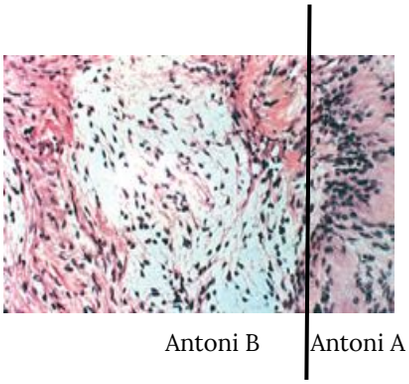
Peripheral Nervous System Tumors

Schwannoma

- **Benign,** encapsulated tumors that can occur in soft tissues, internal organs, or nerve roots
- In the CNS, they are often encountered within the cranial vault in the **cerebellopontine angle**
- where they are attached to the vestibular branch of the **eighth nerve** (tinnitus and hearing loss)
- **Sporadic** schwannomas are associated with mutations in the **NF2** gene
- Bilateral acoustic schwannoma is associated with NF2 syndrome (neurofibromatosis type 2)
- Attached to the nerve but can be separated from it

Histopathology:

- 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.**



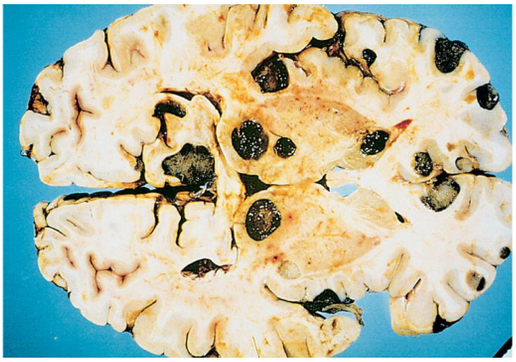
Antoni B Antoni A

Neurofibroma

- Benign peripheral nerve sheath tumors
- Examples:
  1. *Cutaneous neurofibroma*
  2. *Solitary neurofibroma* **(** in peripheral nerve).
- These arise sporadically or in association with: **type 1 neurofibromatosis**, rarely malignant
- plexiform neurofibroma, mostly arising in individuals with NF1[1] have potential malignancy.
- Neurofibromas cannot be separated from nerve trunk (in comparison to schwannoma).

Metastatic tumors

- About half to three-quarters of brain tumors are primary tumors, and the **rest are metastatic**
- Lung, breast, skin (melanoma), kidney and gastrointestinal tract are the commonest.
- Sharply demarcated masses with edema.



1- neurofibromatosis type 1

Homework!

Homework: Familial Tumor Syndromes.

Q1: Describe the inheritance pattern and the main features of:

- Type 1 Neurofibromatosis.
- Type 2 Neurofibromatosis.

Neurofibromatosis	Type 1	Type 2
Inheritance pattern	An **autosomal dominant** disorder caused by mutations in the **tumor suppressor neurofibromin**, encoded on the long arm of chromosome **17** (17q).	A **dominant** loss of function mutation of the **merlin gene** on chromosome **22**.
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)

Q2: 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

CNS Tumors

Gliomas	❑ **Astrocytoma:** **<u>1. Fibrillary Astrocytoma:</u>** adults, Cerebral hemisphere "supratentorial", **types:** **A. Diffuse astrocytoma (Grade II) ----->** Variable nuclear pleomorphism. **B. Anaplastic astrocytoma (Grade III) ----->** Greater nuclear pleomorphism, mitosis. **C. Glioblastoma (Grade IV) ----->** Necrosis, vascular or endothelial cell proliferation. **<u>2.Pilocytic Astrocytoma:</u>** Children and young adults, Benign in cerebellum "infratentorial". **Gross:** cystic, with a mural nodule, Well circumscribed. **Histology:** Rosenthal fibers, hyaline granular. *GFAP positive. ❑ **Oligodendroglioma:** Adults, Malignant tumor mainly in Cerebral hemispheres, loss of heterozygosity for chromosomes **1p** and **19q.** **Morphology:** fried egg pattern, Chicken wire pattern. ❑ **Ependymomas:** Malignant tumor, children and first two decades of life, Ventricular system (4th ventricle) & central canal, in adults (spinal cord). **Morphology:** perivascular pseudorosettes, Rosettes canals, high mitotic, necrosis.
Meningioma	• Benign tumor in subarachnoid in adults (mainly women). **Microscopic:** Psammoma bodies, whorled pattern. **Main types (Grade I):** 1. Syncytial. 2. Fibroblastic. 3. Transitional. **Subtypes:** 1. Atypical meningiomas (Grade II). 2. Anaplastic meningiomas (Grade III).

PNS Tumors

Medulloblastoma	• Children. • Highly malignant tumor in the cerebellum. (Grade IV). **Morphology**: small, round and blue cells, little cytoplasm & hyperchromatic nuclei.
Schwannoma	• Sporadic benign tumor. • Bilateral, within the cranial vault in the cerebellopontine angle (8th nerve). • Associated with NF2 gene. **Microscopic:** Biphasic pattern (Antoni A and little Antoni B), Verocay bodies.
Neurofibroma	• Benign tumors of peripheral nerve. • With type 1 neurofibromatosis. • Plexiform neurofibroma: NF1 syndrome.
Metastatic tumors	• lung , breast, skin (melanoma), kidney and gastrointestinal tract are the commonest. • Sharply demarcated masses with edema.

Quiz

Q1: Which of the following isn't correct:

A) CNS tumors in adults most likely arise from supratentorial.
B) CNS tumors in children most likely arise from posterior fossa.
C) intracranial tumors are more common than intraspinal tumors.
D) Intraspinal tumors are more common than intracranial tumors.

Q2: Most common site of Fibrillary astrocytoma:

A) Cerebellum.
B) Diencephalon.
C) Cerebral hemisphere.
D) Red nucleus of the brainstem.

Q3: Secondary Glioblastomas share which of the following mutations?

A) EGFR
B) WEDO
C) p53
D) BRCA1

Q4: In Oligodendroglioma, the most common genetic findings are loss of heterozygosity in:

A) Chromosome 1q and 19p.
B) Chromosome 1p and 19p.
C) Chromosome 1p and 19q.
D) Chromosome 1q and 19q.

Q5: one of the histopathological findings in Ependymoma:

A) Verocay bodies.
B) rosettes.
C) Psammoma bodies.
D) Kamino bodies

Q6: Medulloblastoma exclusive site in children:

A) Cerebral hemisphere.
B) Cerebellum.
C) Medulla.
D) Pons.

Q7: One of the histopathological findings in Meningioma:

A) Kamino bodies.
B) rossetts.
C) Psammoma bodies.
D) Verocay bodies.

Q8: Sporadic Schwannoma and Bilateral acoustic schwannoma is associated with which of the following gene mutations?

A) BRCA1.
B) EGFR.
C) NF2.
D) p53.

Q9: after ending this lecture, what is the most dangerous and invasive brain tumor?

A) Medulloblastoma.
B) Ependymoma.
C) Meningioma.
D) Glioblastoma.

1D 2C 3C 4C 5B 6B 7C 8C 9D

Team Leaders

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Thank you