Lecture Two + Three

CNS Tumors

*432 **Pathology** Team*

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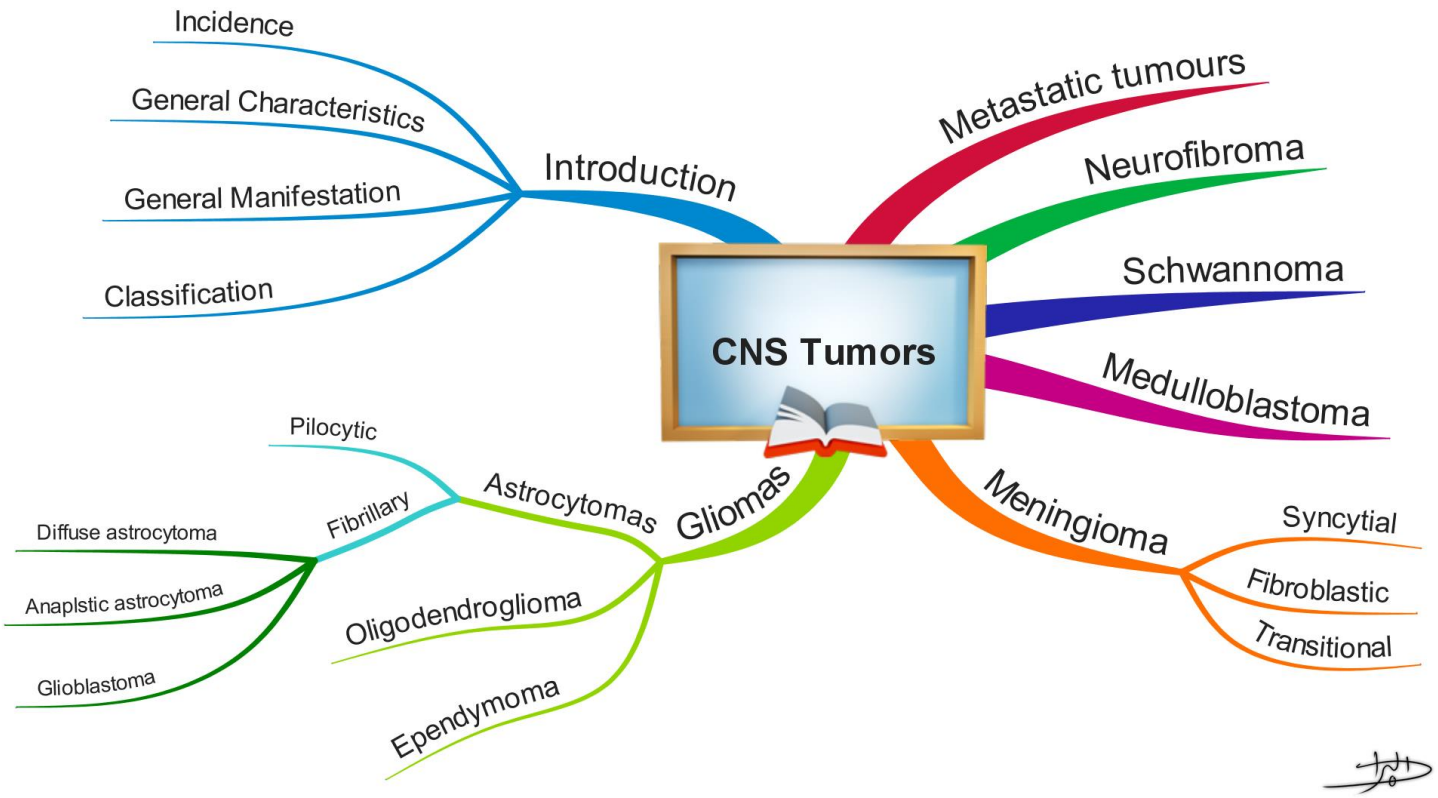
CNS Block

Color Index: female notes are in purple. Male notes are in Blue. Red is important. Orange is explanation.

CNS Tumors

Mind Map:



Introduction

1. 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.

While metastatic tumor of brain rarely metastasize to the rest of the body, because:

1. Metastatic tumor kills before the metastasis.
2. Blood-brain barrier plays a role in direction from the brain to outside (its role in the opposite direction is less regard to high rate of metastatic tumor in the brain).

In children:

- 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
- In childhood, tumors are likely to arise in the posterior fossa (infratentorial or cerebellum), while in adults they are mostly supratentorial (cerebral hemisphere).

2. General characteristics:

- The anatomic site of the neoplasm can have lethal consequences irrespective of histological classification (i.e. benign tumors can be fatal in certain locations) *(Small channels of the ventricular system- at cardio respiratory center on medulla) could cause cardio respiratory arrest from compression of the medulla by the tumor.*
- These tumors do not have detectable premalignant or in situ stages comparable to those of carcinomas
- The pattern of spread of primary CNS neoplasms differs from that of other tumors:
    - Rarely metastasize outside the CNS.
    - The subarachnoid space does provide a pathway for spread.

What are the layers that surround subarachnoid space?

Pia matter → subarachnoid space → arachnoid membrane.

- Even low-grade lesions may infiltrate large regions of the brain, leading to serious clinical deficits, nonresectability, and poor prognosis.

REMEMBER:
WHO grades the brain tumor (grading based on the histology of the tumor):

i. Benign
ii. Low-grade malignancy
iii. High-grade malignancy
iv. The most malignant

3. General manifestations:

- Seizures, headaches, vague symptoms
- Focal neurologic deficits related to the anatomic site of involvement
- Rate of growth may correlate with history

4. Classification:

- May arise from (basically on the type of the cells):
  - Cells of the coverings (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) from: lung, kidneys and breast tumors.

Gliomas

a) Astrocytomas

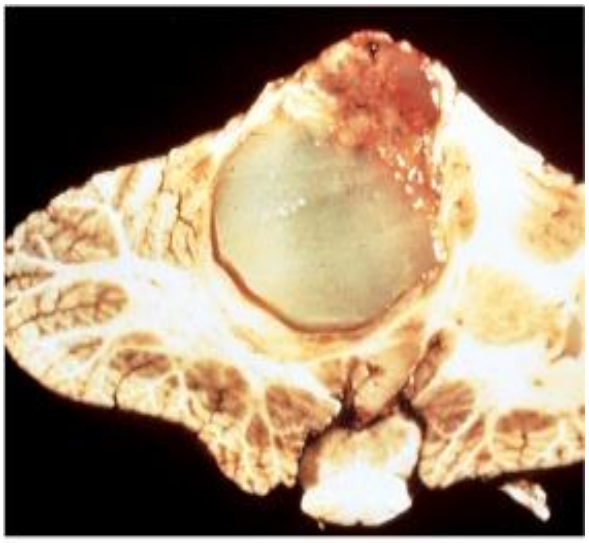
b) Oligodendrogliomas

c) Ependymomas

NOTE: There is nothing called microglioma.

a) Astrocytomas:

1. Pilocytic Astrocytoma: (Grade I)



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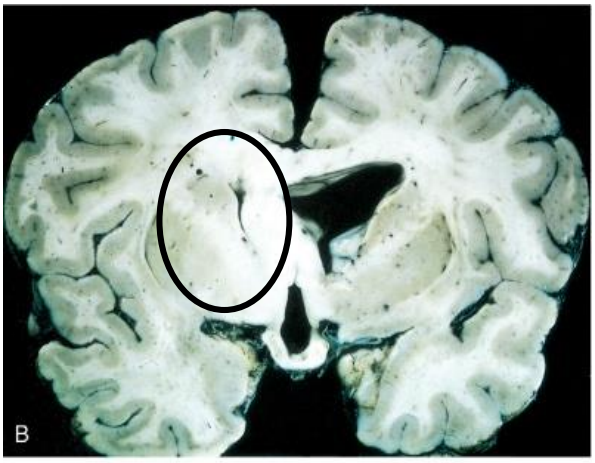
- Children and young adults (infratentorial)
- Commonly cerebellum
- Relatively benign
- Often cystic, with a mural nodule in the wall of the cyst.
- Well circumscribed
- Pilocytic processes "hair =pilo" (hair-like process) that are GFAP[1] positive
- Rosenthal fibers & hyaline granular bodies are often present
- Necrosis and mitoses are typically absent.

2. Fibrillary Astrocytoma:

- 4th to 6th decade
- Commonly cerebral hemisphere (supratentorial)
- Variable grades:
  - **Diffuse astrocytoma (Grade II)**
  - **Anaplstic astrocytoma (Grade III)**
  - **Glioblastoma (Grade IV)**
  - **No grade I**

Well differentiated "diffuse astrocytoma" (WHO grade II):

- Static but at some point they progress (mean survival of more than 5 years)
- Moderate cellularity
- Variable nuclear pleomorphism
- High number of astrocyte more than gliosis (difficult to differentiate)



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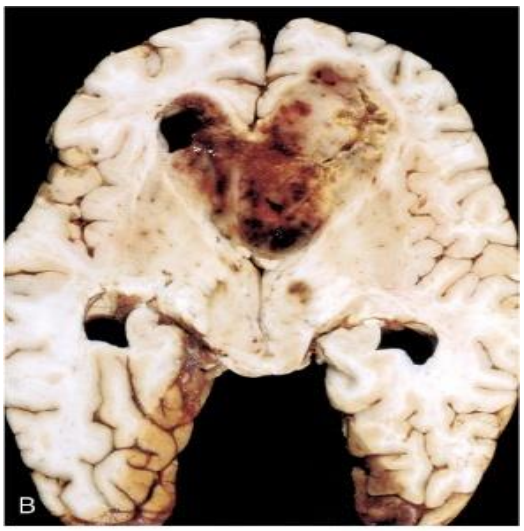
Note that diffuse astrocytoma are poorly demarcated

[1] GFAP stain: is useful for determining whether a tumor is of glial origin.

Less differentiated (higher-grade):

a) Anaplastic astrocytoma (WHO grade III)
   - More cellular
   - Greater nuclear pelomrophism
   - Mitosis
   - There is no necrosis or vascular or endothelial cell proliferation, when they exist the tumor will be grade IV

b) Glioblastoma (WHO grade IV) :
   With treatment, mean survival of 8-10 months
   All the features of anaplastic astrocytoma, plus:
   1- Pseudopalisading necrosis.
   2- AND/OR
      - Vascular proliferation
      - Edema and vascular leak
      - Endothelial cell proliferation



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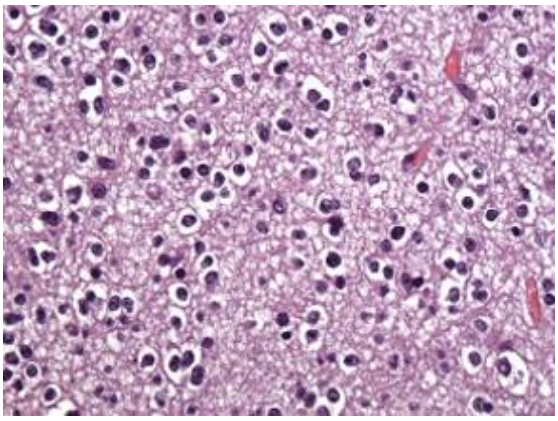
- **Secondary** glioblastomas (there is lower grade either beside or before) share ***p53*** mutations that characterized low-grade gliomas.
- While **primary** glioblastomas are characterized by amplification of the epidermal growth factor receptor **(*EGFR*)** gene.

NOTE from Robbins: Mutations that alter the enzymatic activity of two isoforms of the metabolic enzyme isocitrate dehydrogenase (IDH1 and IDH2) are common in lower-grade astrocytomas. As a result, immunostaining for the mutated form of IDH1 has become an important diagnostic tool in evaluating biopsy specimens for the presence of low-grade astrocytoma.

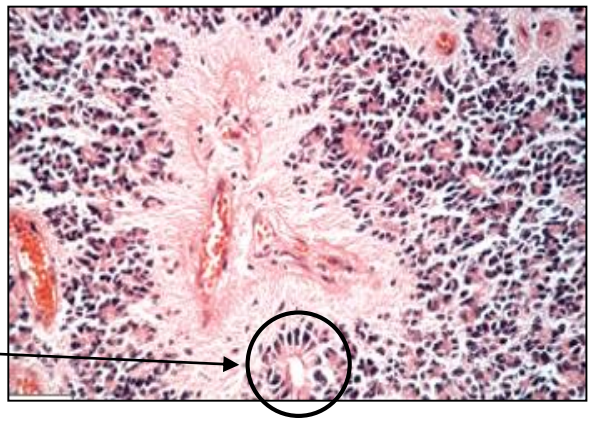
b) Oligodendroglioma:

- These cells have egg-fried appearance (whitish cytoplasm with artificial fibers).
- The most common genetic findings are loss of heterozygosity for **chromosomes 1p and 19q.**
- 4th & 5th decades (the most common).
- Cerebral hemispheres, with a predilection for white matter.
- Better prognosis than that for patients with astrocytomas of similar grade (5 to 10 years with Rx).
- Anaplastic form prognosis is worse.
- Grades: **II** and **III**, grade **III** has more mitosis, pleomorphism, necrosis and vascular cell proliferation (not like astrocytomas).
- In oligodendroglioma tumor cells have round nuclei, often with a cytoplasmic halo.
- Blood vessels in the background are thin and can form an interlacing pattern (chicken wire appearance of blood vessels but not in this picture).



c) Ependymoma:

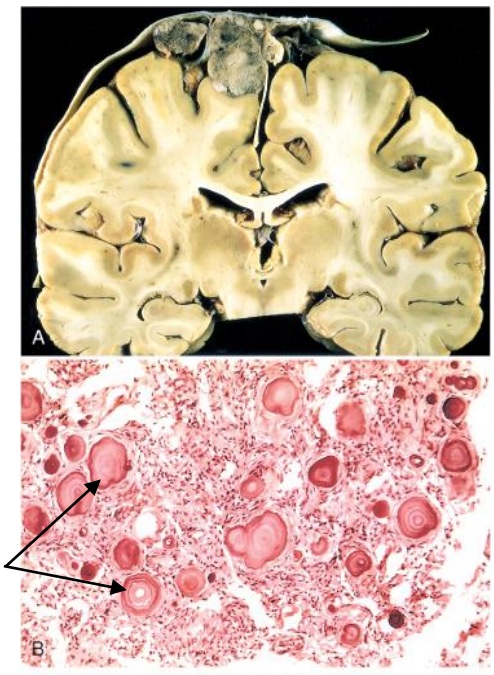
- Most often arise next to the ependyma-lined ventricular system, including the central canal of the spinal cord.
- Occurs in the first two decades of life, they typically occur near the fourth ventricle.
- In adults, the spinal cord is their most common location.
- Tumor cells may form round or elongated structures (rosettes, canals), and perivascular pseudo-rosettes.
- Anaplastic ependymomas (grade II,III) show increased cell density, high mitotic rates, necrosis and less evident ependymal differentiation.



NOTE: There are true and pseudo (false) rosettes: true rosettes have lumen while a pseudo rosette doesn't have or it form perivascular pseudo-rosettes which is more common.

Meningioma

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



Microscopic features:

Whorled pattern of cell growth (cells arranged in wool ball shape) and **psammoma** bodies (type of calcification).

Main subtypes:

1) Syncytial (cell borders is not clear)
2) Fibroblastic (spindle cell legion)
3) Transitional (both Syncytial and Fibroblastic)

Also note:

- Atypical meningiomas (grade **II**)
- Anaplastic (malignant) meningiomas (grade **III**)
- It is complicated to grade.
- Although most meningiomas are easily separable from underlying brain, some tumors infiltrate the brain → grade **II**
- The presence of brain invasion is associated with increased risk of recurrence.

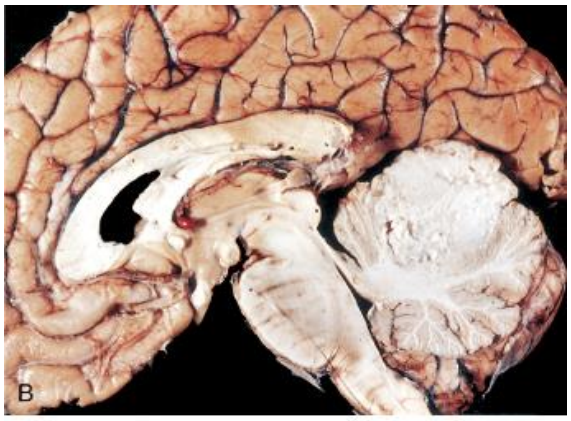
Medulloblastoma (Grade IV)

-Primitive tumor.

-Children and exclusively in the cerebellum

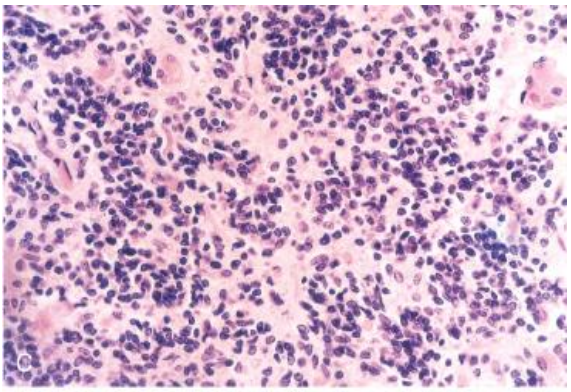
-Neuronal and glial markers may be expressed, but the tumor is often largely undifferentiated

-The tumor is highly malignant, and the prognosis for untreated patients is dismal; however, it is exquisitely radiosensitive



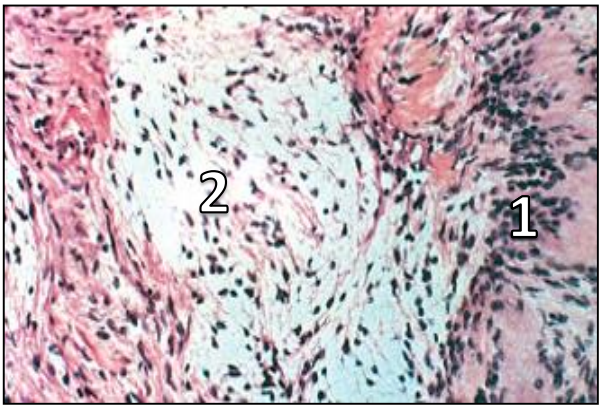
-With total excision and radiation, the 5-year survival rate may be as high as 75%

-Extremely cellular, with sheets of anaplastic ("small blue") cells
-Small, with little cytoplasm and hyperchromatic nuclei; mitoses are abundant.



Schwannoma

- Benign
- 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), it called acoustic schwannoma.
- Sporadic (random collection of people) schwannomas are associated with mutations in the *NF2* gene
- Bilateral acoustic schwannoma is associated with NF2 (Neurofibromatosis Type 2 syndrome), however bilateral acoustic schwannoma are diagnostic of NF2 syndrome.
- Attached to the nerve but can be separated from it.
- Cellular Antoni A pattern (1) and less cellular Antoni B (2)
- Nuclear-free zones of processes that lie between the regions of nuclear palisading are termed Verocay bodies (pseudopalisade)

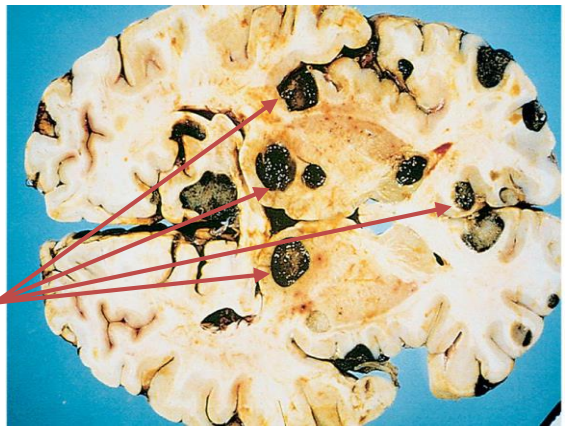


Neurofibroma

- Examples: (cutaneous neurofibroma) or in peripheral nerve (solitary neurofibroma)
- These arise sporadically or in association with type 1 neurofibromatosis, rarely malignant
- plexiform neurofibroma, mostly arising in individuals with NF1, potential malignancy
- Neurofibromas cannot be separated from nerve trunk (in comparison to shcwannoma)
- Patient may die from the tumor and may because of the pressure of the tumor on the chest.
-

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
- Feature to diagnose the tumor: multiple lesions and sharply demarcated masses with edema.



NOTE: A **colloid cyst** is a cyst containing gelatinous material in the brain. It is almost always found just posterior to theforamen of Monro in the anterior aspect of the third ventricle, originating from the roof of the ventricle. Because of its location, it can cause obstructive hydrocephalus and increased intracranial pressure. These cysts account for approximately 1% of all intracranial tumors.

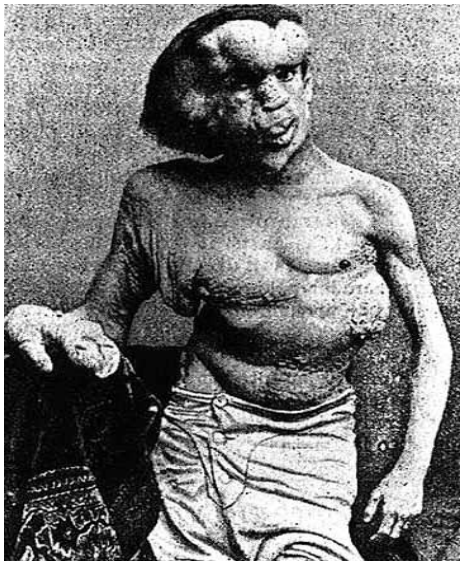
About 85% of ependymomas are benign **myxopapillary ependymoma** (MPE).MPE is a localized and slowly growing, low-grade tumor. Although some ependymomas are of a more anaplastic and malignant type, most of them are not anaplastic. Well-differentiated ependymomas are usually treated with surgery.

Homework!

FAMILIAL TUMOR SYNDROMES

Describe the inheritance pattern and the main features of:

- Type 1 Neurofibromatosis
- Type 2 Neurofibromatosis
- 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?



For further information see Robbins Basic Pathology (Page 808)

- In most peripheral nerve sheath tumors, the neoplastic cells show evidence of Schwann cell differentiation.
- Peripheral nerve sheath tumors are important features of the familial tumor syndromes neurofibromatosis type 1 (NF1) and type 2 (NF2).
- Schwannomas and neurofibromas are benign nerve sheath tumors.
- Schwannomas are circumscribed, usually encapsulated tumors that abut the nerve of origin and are a feature of NF2.
- Neurofibromas may manifest as a sporadic subcutaneous nodule, as a large, poorly defined soft tissue lesion, or as a growth within a nerve. Neurofibromas are associated with NF1.
- About 50% of malignant peripheral nerve sheath tumors occur de novo in otherwise normal persons, while the remainder arises from the malignant transformation of a preexisting NF1-associated neurofibroma.

Summary (from Robbins Basic Pathology)

Tumors of the Central Nervous System

- Tumors of the CNS may arise from the cells of the coverings (meningiomas), the brain (gliomas, neuronal tumors, choroid plexus tumors), or other CNS cell populations (primary CNS lymphoma, germ cell tumors), or they may originate elsewhere in the body (metastases).
- Even low-grade or benign tumors can have poor clinical outcomes, depending on where they occur in the brain.
- Distinct types of tumors affect specific brain regions (e.g., cerebellum for medulloblastoma, an intraventricular location for central neurocytoma) and specific age populations (medulloblastoma and pilocytic astrocytomas in pediatric age groups, and glioblastoma and lymphoma in older patients).
- Glial tumors are broadly classified into astrocytomas, oligodendrogliomas, and ependymomas. Increasing tumor malignancy is associated with more cytologic anaplasia, increased cell density, necrosis, and mitotic activity.
- Metastatic spread of brain tumors to other regions of the body is rare, but the brain is not comparably protected against spread of distant tumors. Carcinomas are the dominant type of systemic tumors that metastasize to the nervous system.

Questions from Pathology Recall book

1/ are the majority of intracranial neoplasms above or below the tentorium, in adults and children?
In adults: Supratentorial (above). In children: Infratentorial (below).

2/ where do most primary malignant CNS tumors metastasize?
They usually don't metastasize.

3/ Describe the histology of glioblastoma multiforme (GBM)?
Marked anaplasia and pleomophism; vascular changes with endothelial hyperplasia; many mitosis.

4/ what pattern of tumor cells encompass areas of necrosis and hemorrhage?
Pseudo-palisade arrangement at the periphery.

5/ describe the typical morphology of oligodendroglioma.
Large round nuclei surrounded by a halo of clear cytoplasm, often called (fried egg appearance) and foci of calcification.

6/ what is the pattern of the histology in ependymoma?
Rosettes with cells encircling vessels.

7/ what is the proliferating cell type of meningioma?
Arachnoid cell

8/ characterize meningioma?
Commonly benign and slow growing.

9/ what is the appearance under the microscope in meningioma?
Whorled pattern spindle cells, ovoid nuclei, intranuclear vacuoles, and calcified psammoma bodies.

10/ what are psammoma bodies?
Microscopic concentric laminated mass of calcified material.

11/ what is meant by a pseudoreosette?
Perivascular arrangement of tumor cells.

12/what 2 patterns of histology are seen?

a. Antoni type A neurilemoma: elongated cells with palisade nuclei, grouped in bundle
b. Antoni type B neurilemoma: less cellularity, similar pattern.

Case 1/ a 9-year-old girl is evaluated for headaches and clumsiness with walking (ataxia) over the last month. A CT scan reveals a midline, partially cystic cerebellar mass. The tumor is removed surgically, and microscope examination shows elongated bipolar astrocytes with fibillar processes and Rosenthal fibers. What is the most likely diagnosis?

A. Pilocytic astrocytoma.
B. Glioblastoma multiforme.
C. Medulloblastoma.
D. Acoustic neuroma.

Case 2/ A 65-year-old man develops new-onset seizures and headaches. A CT scan reveals a 6-cm left-sided intracerebral mass. Which of the following is the most likely diagnosis?

A. Meningioma
B. Glioblastoma multiforme
C. Shwannoma
D. Metastatic testicular carcinoma

The cases from case files Pathology book

Answers:

- Case 1 / A
- Case 2 / B

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*Good Luck ^_^*