Revised & Approved

Abdullah Alsubaihi
Rania Almutiri

02 03

Pathology

(CNS Tumors)

439

Color index

- Important
- Doctor's note
- Extra info
- Main text

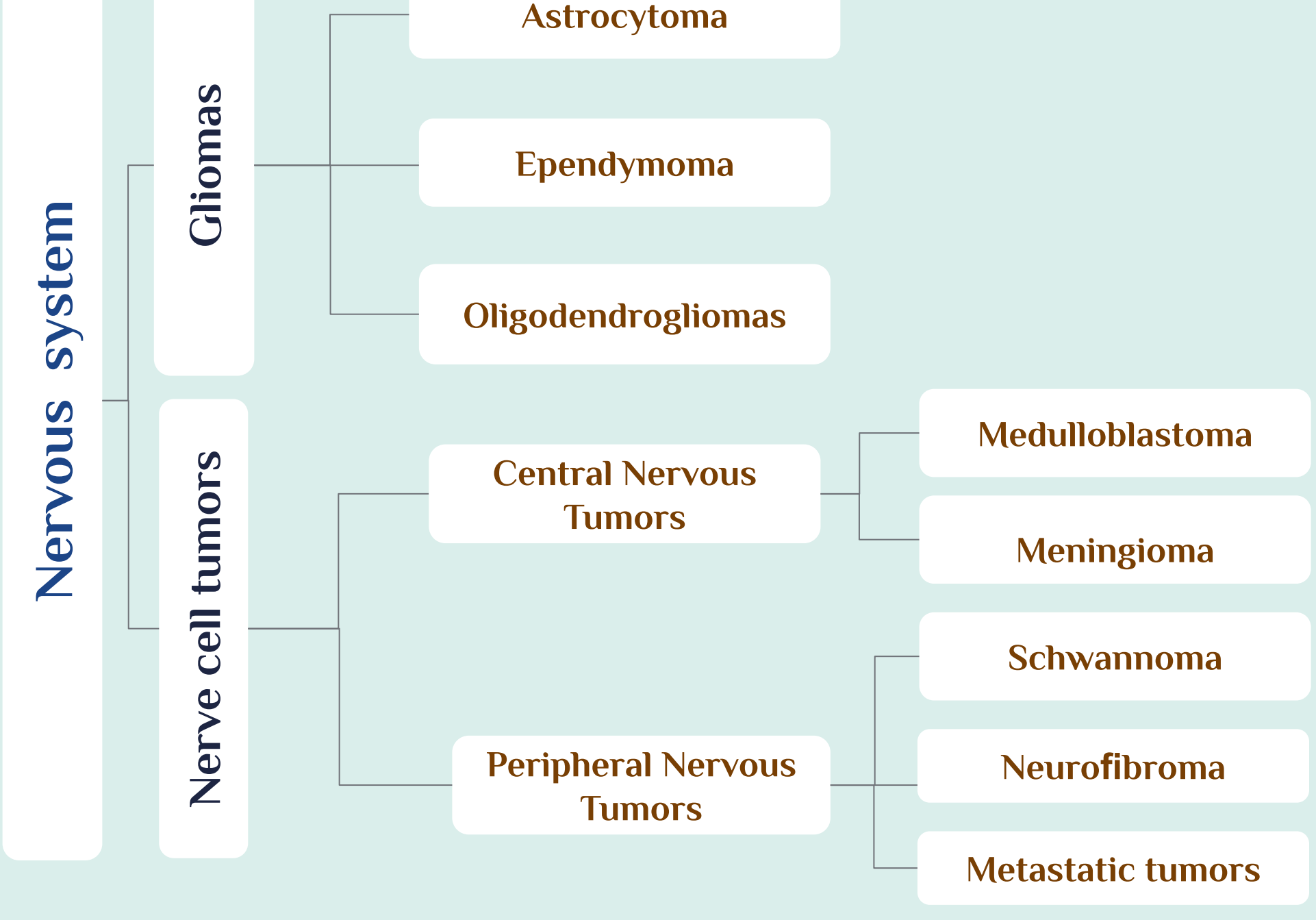
" اللهم لا سهل الا ماجعلته سهلا و انت تجعل الحزن إذا شئت سهلا "

Objective

01 Appreciate how the anatomy of the skull and the spinal column influences the prognosis of both benign and malignant primary CNS tumors

02 List the principal clinicopathological features of some of the main types of tumors that can arise within the central and peripheral nervous system

Overview



Introduction

Tumors of the CNS make up a larger proportion of childhood cancers, accounting for as many of 20% of all pediatric tumors.

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

In childhood, tumors are likely to arise in the posterior fossa, whereas tumors in adults are mostly supratentorial.

Childhood CNS tumors differ from those in adults in both histologic subtype and location.

Skipped by doctors

The annual incidence of CNS tumors ranges from 10 to 17 per 100,000 individuals for intracranial tumors and 1 to 2 per 100,000 individuals for intraspinal tumors.

Unique characteristics of nervous system tumors

1. These tumors do not have morphologically evident premalignant or in situ stages comparable to those of carcinomas (like squamous cell carcinomas, they start as in situ & limited then invade)

2. Even low-grade lesion may infiltrate large lesion of the brain , leading to serious clinical deficits , inability to be resected , and poor prognosis due to the compression of a region with an important function by the tumor

3. The anatomic site of the neoplasm can influence outcome independent of histologic classification due to local effects (e.g., a benign meningioma may cause cardiorespiratory arrest from compression of the medulla).

4. The pattern of spread of primary CNS neoplasms differs from that of other tumors:
   - The subarachnoid space does provide a pathway for spread
   - Rarely metastasize outside the CNS

Symptoms of CNS tumors include:

01 Seizures, headaches, vague symptoms

02 Focal neurologic deficits related to the anatomic site of involvement like abnormal speech .

03 The rate of growth may correlate with the history and duration of symptoms.
-Mild symptoms for a long time ➞ low grade
-Rapid progression of symptoms ➞ high grade

CNS tumors may arise from

1st Cells of the coverings “meninges” (meningiomas)

2nd Cells intrinsic to the brain (gliomas, neuronal tumors, choroid plexus tumors inside ventricular system)

3rd Other cell populations within the skull (primary CNS lymphoma, germ-cell tumors “remnant germ cells”)

4th Tumor from elsewhere in the body spreading to the CNS (metastases)

Gliomas

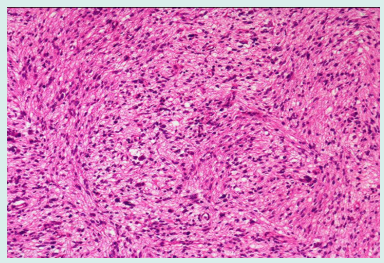
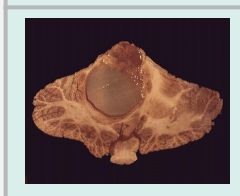
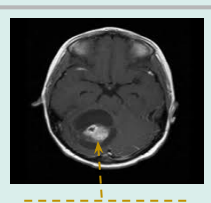
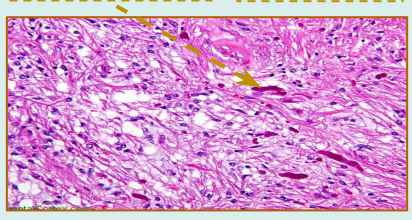
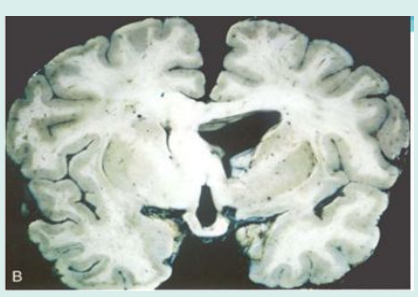
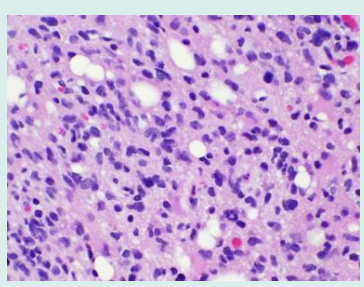
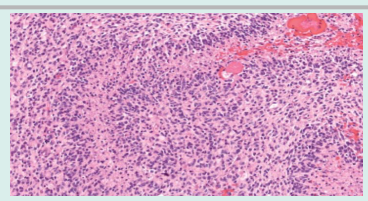
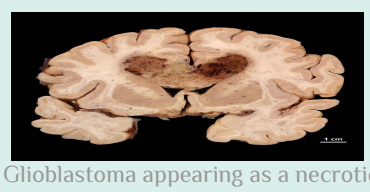
1 Astrocytomas
“Astrocytes”

2 Oligodendrogliomas
“Oligodendrocytes”

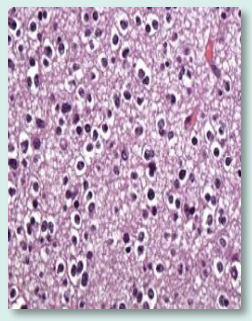
3 Ependymomas
“Ependymal cells”

Astrocytoma

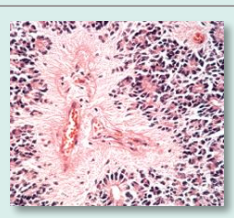
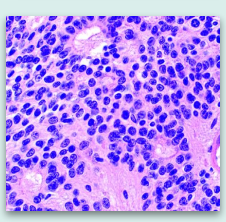
The World Health Organization (WHO) classifies astrocytomas into four grades depending on how fast they are growing and the likelihood that they will spread (infiltrate) to nearby brain tissue

Types	Pilocytic Astrocytoma	Fibrillary Astrocytoma		
Grades	Grade I	Diffuse Astrocytoma (Grade II)	Anaplastic Astrocytoma (Grade III)	Glioblastoma (Grade IV)
Overview In each tumor, we should describe its : 1- cellularity 2- pleomorphism 3- Necrosis 4- Mitoses	-Relatively benign tumor It is actually a low grade tumor not benign, but its behavior is close to benign tumors .	Usually an infiltrating tumor -Differentiation : Well - Progress : Slowly - Cellularity : Moderate - Pleomorphism : Variable - Survival : >5 years -Necrosis isn't seen	More progressive tumor than grade II -Differentiation : less - Progress : Fast - Cellularity : High - Pleomorphism : Great - Survival : <5 years	Most aggressive type of nervous system tumor -Differentiation : less - Progress : Fast - Cellularity : High - Pleomorphism : Great - Survival : 8-10 months (with treatment)
Epidemiology	**Affects children and young adults**	people in their 4th to 6th decade		
Location	most commonly found in cerebellum, optic nerve pathway, and brainstem	commonly found in cerebral hemisphere Variable grades based on histological features		
Morphology	Radiology: Cystic with a mural nodule. well circumscribed. "hairlike" pilocytic processes that are GFAP positive **Rosenthal fibers** & hyaline granular bodies are often present Necrosis and mitoses are typically absent	 Moderate Hypercellularity Variable pleomorphism	**Mitosis** is seen in morphology	All the features of anaplastic astrocytoma, plus **necrosis** and/or (vascular or endothelial cell proliferation)
	  Rosenthal fibers Mural nodule  Hair like processes arranged in bundles Rosenthal fibers that are mainly Eosinophilic	 Poorly demarcated. Grade II astrocytoma appears as expanded white matter of the left cerebral hemisphere and thickened corpus callosum and fornices	 Anaplastic Astrocytoma shows a greater extent of pleomorphism, an increased cellular component than lower grade astrocytomas also mitosis present	 Densely cellular tumor with necrosis present and **pseudopalisading necrosis** of tumor cell nuclei.  Glioblastoma appearing as a necrotic , hemorrhagic , infiltrating mass
Marker	- Marker of astrocytoma : is linked to mutations that alter the activity of two isoforms of the metabolic enzyme isocitrate dehydrogenase **(IDH1 and IDH2)** which are common in **lower grade astrocytomas** .			
	Marker of Glioblastoma : - **Primary glioblastomas** (started as 4th grade): Are characterized by amplification of epidermal growth factor receptor **(EGFR) gene** - **Secondary' glioblastoma** (started as low grade then changed to higher grades): Is linked to **p53 mutations** that characterize low-grade gliomas			

Oligodendroglioma

	Grade II (conventional type)	Grade III (anaplastic type)
Epidemiology	4^{th} and 5^{th} decades (Age is important)	
Location	Cerebral hemispheres, with a predilection for the white matter	
Most common genetic findings	The most common genetic findings are loss of heterozygosity for chromosomes **1p and 19q.**	
Prognosis	- Better prognosis than astrocytomas (5 to 10 years with treatment) - The prognosis of the anaplastic type is worse than the conventional type.	
Morphology **Fried EGG appearance**	- In oligodendroglioma tumor cells have round nuclei, often with a cytoplasmic halo (clear) - Blood vessels in the background are thin and can form an interlacing pattern 	show increased cell density, high mitotic rates, necrosis and less evident ependymal differentiation Mitosis

Ependymoma

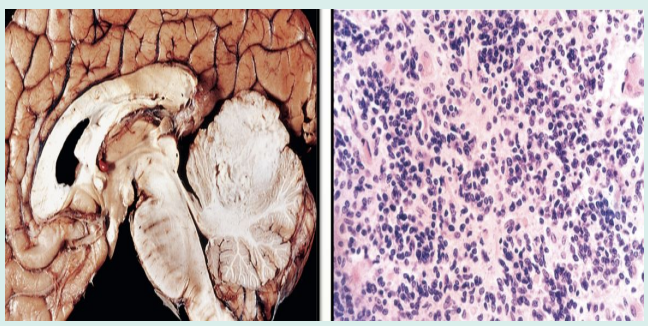
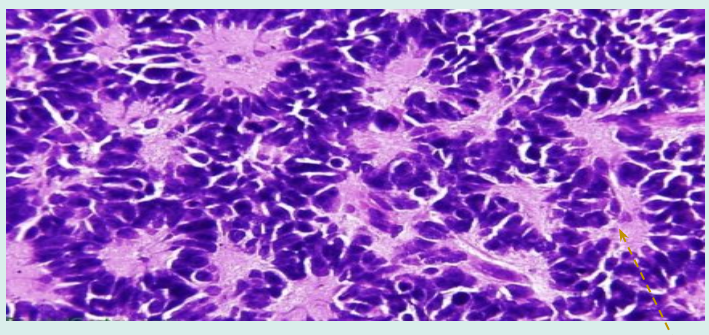
	Grade II Conventional ependymomas	Grade III Anaplastic ependymomas
Epidemiology	They occur in the first two decades of life (Children)	
Location	- They most often arise next to the ependyma-lined ventricular system, including the central canal of the spinal cord. - In children, They typically occur near the fourth ventricle "in the posterior fossa" - In adults, the spinal cord is their most common location.	
Morphology	Tumor cells may form round or elongated structures **(rosettes, canals)** more frequently present are **perivascular pseudorosettes** in which tumor cells are arranged around vessels with an intervening zone containing thin ependymal processes.  	Show increased cell density, high mitotic rates, necrosis and less evident ependymal differentiation

Nerve cell tumors

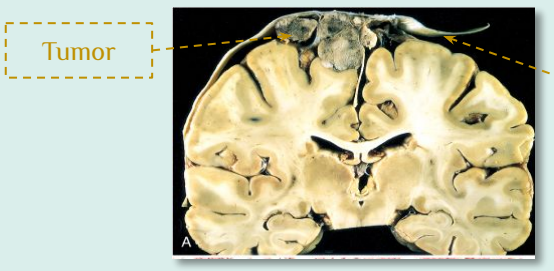
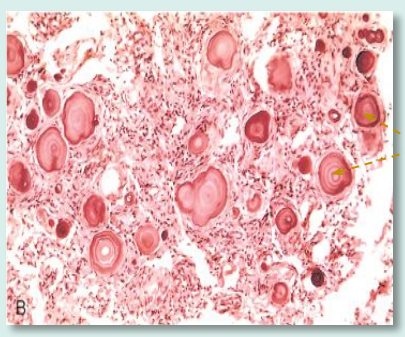
We already discussed Gliomas

- **Peripheral Nervous Tumors**
  - Metastatic tumors
  - Neurofibrma
  - Schwannoma
- **Central Nervous Tumors**
  - Medulloblastoma
  - Meningiomas

Medulloblastoma

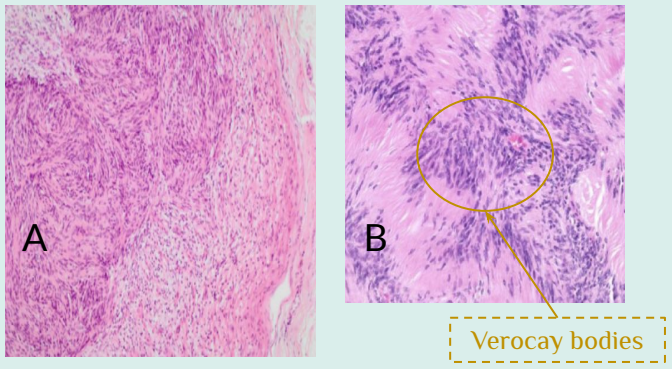
Epidemiology	occur in children and exclusively in the cerebellum (primitive usually becomes blastoma
Markers	Neuronal and glial markers may be expressed, but the tumor is often largely undifferentiated
Prognosis	The tumor is highly malignant, and the prognosis for untreated patients is dismal; however, it is exquisitely radiosensitive (better prognosis with radiotherapy)
Survival	With total excision and radiation, the 5-year survival rate may be as high as 75%
Morphology	 The tumor is extremely cellular, with sheets of anaplastic ("small blue") cells with little cytoplasm and hyperchromatic nuclei; **mitoses are abundant.** Medulloblastoma. (A) Sagittal section of a brain showing medulloblastoma involving the superior vermis of the cerebellum. (B) Microscopic a ance of medulloblastoma, showing mostly small, blue, primitive-appearing tumor cells.  1- Often, focal neuronal differentiation is seen in the form of the **Homer Wright or neuroblastic rosette.** 2-they are characterized by primitive tumor cells surrounding central **neuropil** (delicate pink material formed by neuronal processes). Medulloblastoma has a special type (characteristic) of rosettes which is homer wright .

Meningioma

	Grade I	Grade II Atypical meningiomas	Grade III Anaplastic (malignant) meningiomas
Epidemiology	They are often low grade tumors of adults can be high grade rarely .		
Location	- They originate from the meningothelial cell of the arachnoid - Although most meningiomas are easily separable from underlying brain, some tumors infiltrate the brain. When infiltration become type 2		
Prognosis	The presence of brain invasion is associated with increased risk of recurrence. So in case of meningioma, it is very important to evaluate the brain invasion to know if recurrence will happen .		
Subtypes	- Meningothelial/syncytial→ classical type - Fibroblastic → elongated - Transitional → both types -Psammomatous → ↑↑ psammoma bodies - Secretory → cells with secretions	-	-
Morphology Well demarcated	 A parasagittal multilobular meningioma attached to the dura with compression of the underlying brain. Called : dura based tumor  Meningioma with a **whorled pattern of cell growth and psammoma bodies**	**Features** : prominent nucleoli, increased cellularity, pattern-less growth and often have a higher mitotic rate. These tumors demonstrate more aggressive local growth and a higher rate of recurrence. **We call it atypical if :** 1- It contains 3 out of 5 features . **Or** 2- Has specific number of mitoses .	Are highly aggressive tumors that may resemble a high grade sarcoma or carcinoma (there is mitosis, necrosis and pleomorphism).

Schwannoma

Prognosis:	-Benign -They are attached to the nerve but can be separated from it
Site of the tumor	May occur in soft tissues, internal organs, or spinal nerve roots.
the most commonly affected nerve	he most commonly affected cranial nerve is the vestibular portion of the eighth nerve. Tumors arising in a nerve root or the vestibular nerve may be associated with symptoms related to nerve root compression, which includes hearing loss in the case of vestibular schwannomas.
the tumor occur in association with	Sporadic(not hereditary)schwannomas are associated with mutations in the **NF2** gene,however bilateral acoustic schwannoma is associated with NF2 (neurofibromatosis 2) syndrome. "Having mutation in NF2 does not mean you have NF2 syndrome"
Microscopically	A-Biphasic pattern: cellular **Antoni A** pattern and a less cellular **Antoni B** pattern. B-Nuclear-free zones of processes that lie between the regions of nuclear palisading and termed **Verocay bodies**



Neurofibroma

Definition	Neurofibromas are benign tumors of peripheral nerves and they cannot be separated from the nerve trunk (in comparison to schwannoma)
Examples	-Cutaneous neurofibromas or in peripheral nerve solitary neurofibroma. -Plexiform neurofibromas (specific form with lobules), mostly arise in individuals with **NF1** syndrome with a potential malignant transformation.
the tumor occur in association with	These arise sporadically or in association with type 1 neurofibromatosis.

Metastatic Tumors

Overview	-About half to three-quarters of brain tumors are primary tumors (like glial, neuronal and meningiomas), and the rest are metastatic
Origin	Lung, breast, skin (melanoma), kidney, and gastrointestinal tract are the most common primary sites for metastases
Morphology	**The metastatic deposits are usually sharply demarcated with a surrounding edema**

MCQs

QUIZ!

01 | 15-A 79-year-old man presents to the emergency room with severe right-sided weakness. He has noticed increasing difficulty using his right hand over the past several months and now walks with great difficulty. His past medical history is significant for colon cancer that was resected 5 years ago. He has poorly controlled hypertension and admits to smoking two packs of cigarettes a day for the past 50 years. A CT scan of the brain reveals a discrete globoid lesion in the frontal lobe with a prominent halo of edema. A CT-guided biopsy reveals neoplastic cells. Which of the following is the most likely diagnosis?

A)Craniopharyngioma	B)Meningioma	C)Metastatic cancer.	D)Glioblastoma multiforme

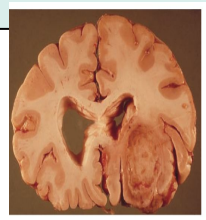
02 | 10 years old came to the hospital with headache and episodes of seizures and Shortness of breath with no history of epilepsy and asthma , MRI showed mass in the **cerebellum , under the examination of the brain biopsy showed pseudopalisading necrosis and mitosis, what is the diagnosis?**

A)anaplastic astrocytoma	B)glioblastoma	C)Meningioma	D)metastatic

03 | A 7 year old boy presents to the pediatric emergency department for lethargy,nausea, and vomiting. Medical history is unremarkable. Physical examination is notable for papilledema (optic nerve swelling) and right sided dysmetria (type of ataxia; inability to judge distance and scale) . An MRI brain without contrast demonstrates a cerebellar cystic mass.

A)meningioma	B)Schwannoma	C) Glioblastoma	D)Pilocytic Astrocytoma

04 | A 65 year old woman presents with a 3 week history of intractable headaches. Her vital signs and CBC are normal. Two weeks later, the patient develops left sided hemiparesis.
MRI reveals a large,n necrotic tumor in the right hemisphere of the cerebrum, extending across the corpus callosum into the left hemisphere. A coronal section of the patient's brain at autopsy is shown in the image.
This tumor is most likely derived from which of the following cell types?



A)Ependymal	B)Microglia	C)Astrocytes	D)Neurons

05 | 35 years old came with dizziness and headache , loss of balance with weakness of hearing of both eyes and ataxia and the last few months suffered from facial muscle deformity with history of no smoking or medication , what is the possible diagnosis?

A)A)Ependymal	B)Microglia	C)schwannoma	D)metastatic

06 | Secondary Glioblastomas share which of the following mutations?

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

MCQs Answer key	01	02	03	04	05	06
	C	B	D	C	C	C

QUIZ!

MCQs

07 | 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.

08 | Most common site of Fibrillary astrocytoma:			
A) Cerebellum	B) Diencephalon	C)Cerebral hemisphere	D)Red nucleus of the brainstem

09 | 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

10 | one of the histopathological findings in Ependymoma:			
A)Verocay bodies	B)rosettes	C)Psammoma bodies	D)Kamino bodies

11 | Medulloblastoma exclusive site in children:			
A)Cerebral hemisphere	B)Cerebellum	C)Medulla	D)Pons

12 | One of the histopathological findings in Meningioma:			
A)Kamino bodies.	B)rossetts	C)Psammoma bodies	D)Verocay bodies

13 | Sporadic Schwannoma and Bilateral acoustic schwannoma is associated with which of the following gene mutations:			
A)BRCA1	B)EGFR	C)NF2	D)p53

MCQs Answer key	07	08	09	10	11	12	13
	D	C	C	B	B	C	C

Homework

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

- Type 1 Neurofibromatosis.
- Type 2 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

In boys slide only

Cases

Extra

A 42-year-old woman presents to your office complaining of headaches and vomiting over the past 4 months. Upon further questioning, you learn that she also feels as if she trips more than usual when she is walking and she has recently had more trouble remembering things. A physical examination reveals bilateral papilledema and reduced strength and hyperreflexia in both of her legs. A CT scan reveals a parasagittal mass compressing the brain and a CT-guided brain biopsy demonstrates a whorled pattern of tumor cells with psammoma bodies. You tell the patient that she will most likely need surgery to remove the tumor.

Meningioma	
Etiology and Epidemiology	Benign, slow-growing tumor arising from meningothelial cells of the arachnoid; therefore, it is external to the brain Multiple meningiomas can be present in patients with neurofibromatosis type 2 Occurs most often in women after the age of 30
Pathology	Gross: Usually round encapsulated mass with dural base; usually occurs in the convexities of the cerebral hemispheres or the parasagittal region; usually does not infiltrate brain Microscopic: Whorled pattern of tightly packed tumor cells; psammoma bodies (laminated calcifications)
Clinical Manifestations	Symptoms associated with compression of underlying brain, including seizures, headaches, nausea, vomiting, and other signs of increased intracranial pressure
Treatment and Prognosis	Surgical removal of tumor Prognosis is good
Notes	Meningiomas are the second most common primary brain tumors.

A 49-year-old man presents to the emergency department with a seizure. When he has been stabilized, he tells you that he has had several severe headaches over the past couple of months. A CT scan of his head reveals a large mass in the frontal lobe of his brain that demonstrates areas of calcification. You admit him to the neurology service and you suspect that he will need surgery to treat his condition.

Oligodendroglioma	
Etiology and Epidemiology	Relatively rare benign tumor derived from oligodendrocytes Commonly affects middle-aged people
Pathology	Gross: Circumscribed, slow-growing gray mass often with cysts; usually occurs in white matter of cerebral hemispheres (especially frontal lobe) Microscopic: Sheets of uniform cells with round nuclei with clear cytoplasm (fried egg appearance); often calcification is present; increased vascularity
Clinical Manifestations	Seizures; headaches; papilledema; other signs of increased intracranial pressure Imaging: Calcification of tumor is detected on CT scan
Treatment and Prognosis	Surgical resection, followed by radiotherapy and chemotherapy Average survival time is 5–10 years after diagnosis

A 58-year-old woman presents to your clinic complaining of hearing loss and a ringing in her left ear. The Weber and Rinne hearing tests help you to determine that the hearing loss is caused by a sensory disturbance and not a conduction deficit. You send the patient for an MRI of her head, which reveals a mass at the left cerebellopontine angle, impinging on cranial nerve VIII. You refer this patient to a neurosurgeon for a biopsy and likely removal of the mass.

Schwannoma	
Etiology and Epidemiology	Usually benign tumors arising from Schwann cells Bilateral acoustic schwannomas are associated with neurofibromatosis type 2
Pathology	Gross: Encapsulated masses, often with cystic areas; usually occur in the cerebellopontine angle, where it can compress cranial nerve VIII (acoustic schwannoma) Microscopic: Two growth patterns: (1) Antoni A: tightly packed elongated cells with palisading nuclei; (2) Antoni B: loose arrangement of cells with microcysts
Clinical Manifestations	Presents with symptoms associated with compression of involved nerve (cranial nerve VIII compression leads to patients presenting with ipsilateral hearing loss, tinnitus, and vertigo), seizures, headaches, nausea and vomiting, and other signs of increased intracranial pressure
Treatment and Prognosis	Surgical resection of tumor Prognosis is good
Notes	Pineal tumors usually occur in young men between the ages of 10 and 40. They present with Parinaud syndrome (paralysis of upward gaze caused by pretectal and superior colliculus damage, obstructive hydrocephalus [owing to compression of aqueduct of Sylvius], and endocrine abnormalities [owing to compression of hypothalamus]).

A 6-year-old boy presents to his pediatrician's office complaining of frequent falls. Upon further questioning, you learn that the boy has also been suffering from nausea and vomiting, which is usually associated with headaches. During physical examination, you note that the boy has an ataxic gait and bilateral papilledema. You send the boy for a CT scan, which reveals a mass in the cerebellum and dilated third and lateral ventricles. You immediately refer the patient to a neurosurgeon.

Medulloblastoma	
Etiology and Epidemiology	Highly malignant tumor arising in cerebellum; associated with deletion on short arm of chr 17 (17p-) Occurs mostly in children and accounts for 20% of all brain tumors in children
Pathology	Gross: Gray, well-circumscribed tumor located at midline of cerebellum Microscopic: Hypercellular sheets of anaplastic cells, demonstrating many mitoses, scant cytoplasm, and hyperchromatic nuclei; cells are often arranged in a rosette or perivascular pseudorosette formation
Clinical Manifestations	Unsteady gait; obstructive hydrocephalus (tumor may obstruct flow of CSF by compressing fourth ventricle); seizures, headaches; nausea and vomiting; other signs of increased intracranial pressure
Treatment and Prognosis	Surgery with radiation and chemotherapy With total excision and radiation, 5-year survival rate is 75%

An 8-year-old girl presents to your clinic complaining of blurry vision. During physical examination, you note bilateral papilledema. A CT scan of the head demonstrates a mass extending from the floor of the fourth ventricle and dilated lateral and third ventricles. You suspect that a biopsy of the mass would demonstrate cells with blepharoplasts in a perivascular pseudorosette arrangement.

Ependymoma	
Etiology and Epidemiology	Tumor arising from ependyma of the ventricular system Most commonly occur in children (usually in the fourth ventricle), but can occur in the spinal cord of adults
Pathology	Gross: Solid, papillary masses extending from floor of fourth ventricle Microscopic: Uniform cells with round nuclei set in a fibrillary stroma and arranged in a perivascular pseudorosette formation; tumor cells often have blepharoplasts (rod near nucleus, which represents basal ciliary bodies)
Clinical Manifestations	Obstructive hydrocephalus (tumor may obstruct flow of CSF through compression of fourth ventricle); seizures; headaches; nausea and vomiting; other signs of increased intracranial pressure
Treatment and Prognosis	Surgical excision (difficult owing to proximity of brainstem nuclei) Prognosis is poor with average survival time of 4 years

"اللهم علمنا ماينفعنا ، وانفعنا بما علمتنا وزدنا علما يارب العالمين"

Team leaders

Hamad Almousa — **Fatimah Alhilal**

Team members

- Hadi Alhemsi
- Abdurahman Addweesh
- Abdulrahman Barashid
- Mansour Albawardy
- Ibraheem Altamimi
- Abdulelah Saad
- Nasser Alsunbul
- Khalid Alkublan
- Abdulrahman Almebki
- Saleh Al Garni

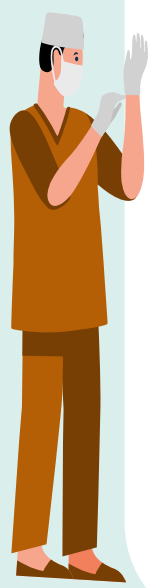
Team members

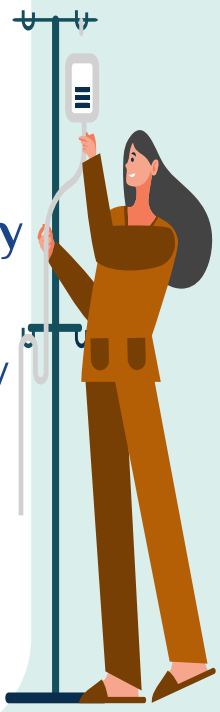
- Mariam Alruhaimi
- Renad Alhomaidi
- Ghaida Almarshoud
- Nada Bin Obied
- Ghada Alabdi
- Sarah Alaidarous
- Rania almutiri
- Abeer awwad
- Ghaida Alassiry
- Mona Alabdely
- Sara Alharbi

Any future corrections will be in the editing file , Click

This Lecture done by

- Organizer
- Member
- Note taker
- Reviser





Contact us through :
Pathology439@Gmail.com