Hashemite University
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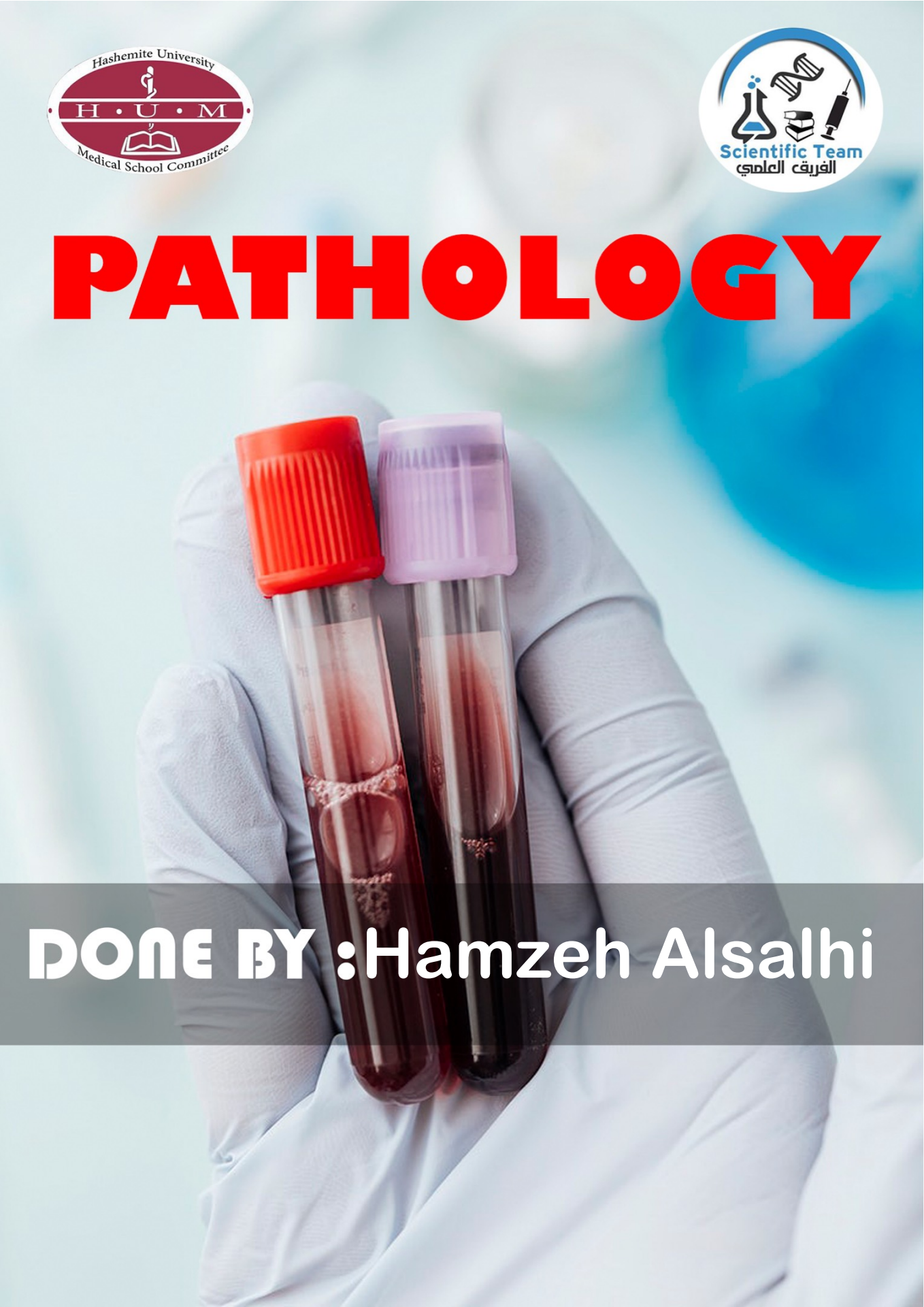
Medical School Committee

Scientific Team
الفريق العلمي

PATHOLOGY



DONE BY :Hamzeh Alsalhi

TUMORS OF THE CNS

- The annual incidence of **T** of the CNS ranges from 100 to 170/ per Million persons for **intracranial** Tumors **(T)** & 10 to 20/ per Million persons for **intraspinal T**; of which 50% are primary **T** & 50% are metastatic **T**. are more common بالعادة secondary الـ
- **20% of all childhood cancers are CNS T** & those differ from those in adults both in histologic subtype & location: **T** in **childhood** are likely to arise in the **posterior fossa**, while in **adults** they are mostly **supratentorial.**

★ **T** of the CNS have **unique characteristics** that set them apart from **T** elsewhere in the body, these are:

😐 **(I) Histologic distinction between benign & malignant T** may be **less important** in the CNS than in other organs! **Why**

Because: (I) 😐 **infiltration**, most **T** (even the low-grade CNS **T**, which show low mitotic rate, cellular uniformity & slow growth) are **infiltrative of adjacent brain tissues**, leading to **serious clinical** deficits & poor prognosis.

😐 **(II)** The **anatomic site of the T can have ☠ lethal** consequences, irrespective of histologic classification!
For example, a **benign meningioma, by compressing the medulla, can cause fatal cardiorespiratory arrest**.
In addition, the tumor location may limits the ability to resect it !

يعني ورم حميد لكن موقعه خطير.

😐 **(III)** The **pattern of spread of primary CNS T differs** from that of other body **T**.

قبل فتح الجمجمة.

(I)Before done craniotomy operation, even the most highly malignant gliomas **rarely metastasize** outside the CNS &
(II) the subarachnoid space does provide a pathway for **T** spread, so that seeding along the brain & spinal cord can occur

But once we open the skull, it becomes equal with other tumors.

Gliomas

★ Gliomas are **T** of the glial brain cells. The three major types are: ***astrocytomas, oligodendrogliomas,* & *ependymomas.***

*Tumors of glial cells are much more common than tumors of neuronal cells.

Astrocytoma

★ Several different categories of astrocytic **T** are recognized, the most common being fibrillary & pilocytic astrocytomas.

Diffuse or Fibrillary Astrocytoma

go it is the commonest.

★ Account for **80%** of adult primary brain **T;** • most frequent in the 4th to 6th decades;• usually found in the **cerebral hemispheres;** • most common presenting S&S are, (1) **seizures (epilepsy),** (2)**headaches** & (3) **focal neurologic deficits** related to the anatomical site.

◘ **Histologically,** classified into 3 groups: **well-differentiated**, **anaplastic astrocytoma, & glioblastoma multiforme** which correlates well with clinical course & outcome.

• **Well-differentiated astrocytomas** progress slowly, with a **mean survival of more than 5 years.** Eventually, however, patients usually enter a period of **rapid clinical deterioration** that is generally **correlated** with the appearance of **anaplastic** features & more rapid **T** growth. *well defferentiated cells become poorly deff. cells.

• Many patients present with **glioblastoma multiforme from the start** rather than having their **T** evolve from a lower grade **T**

☠ Glioblastoma prognosis is **very poor**; & current **state-of-the-art treatment**, comprising resection (when feasible) together with radiotherapy & chemotherapy, yields a mean survival of only 6 **months (2007)which increased to 15 months in 2013**.

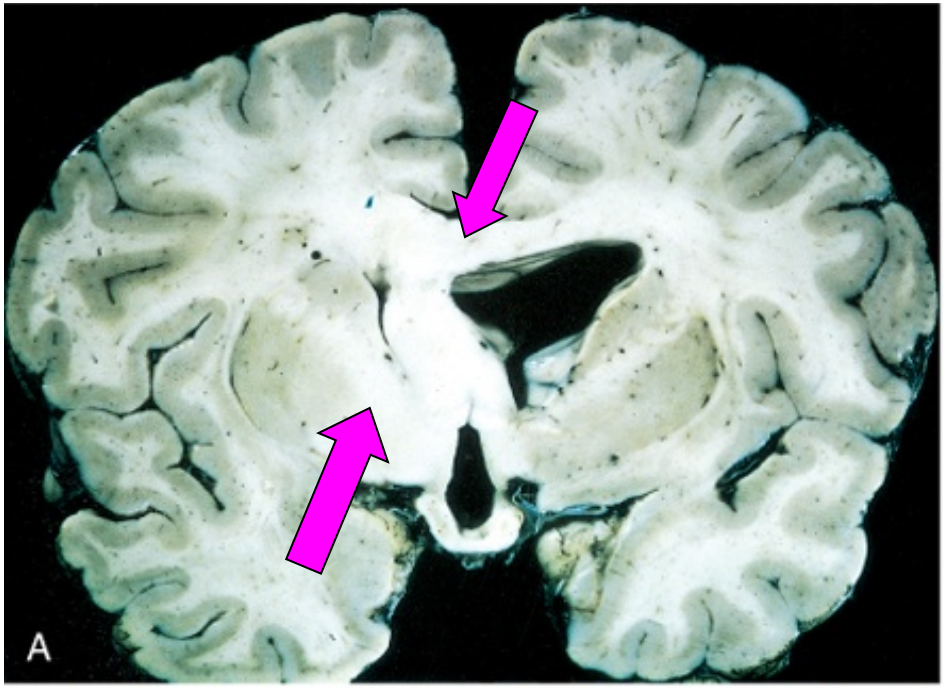
Grossly, fibrillary astrocytoma is a gray, poorly defined, infiltrative **T which *always* infiltrate beyond the grossly evident margins**, expands & distorts the brain, without forming a discrete mass (F23-22A). **T** C/S is either firm or soft & gelatinous with cystic degeneration

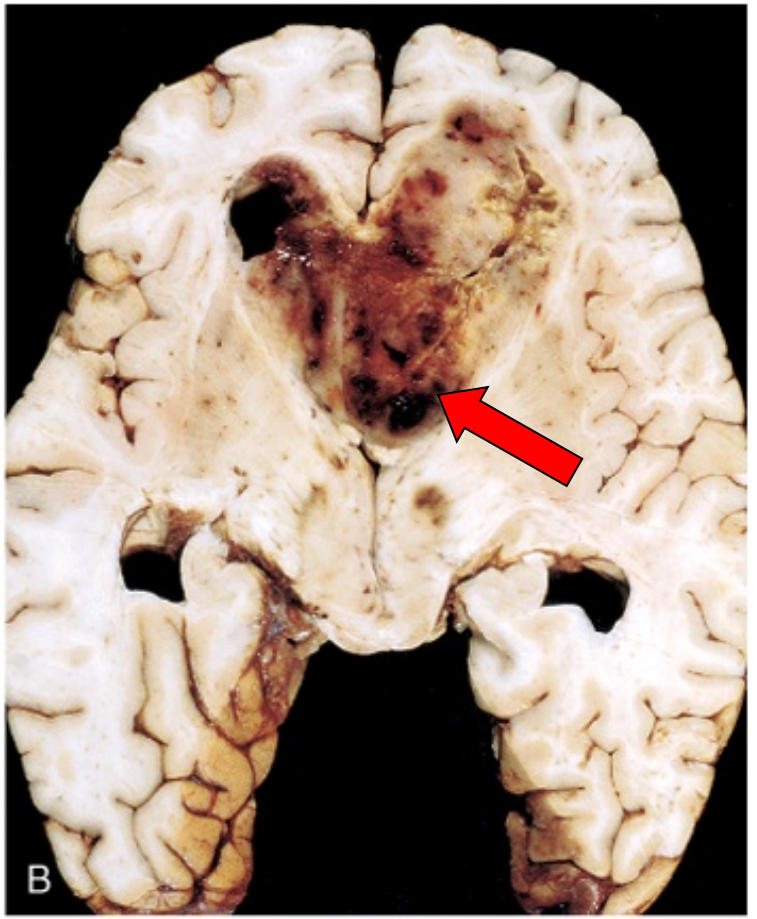
☹ In **glioblastoma multiforme**, **heterogeneity (variation in** the appearance of the **T** from region to region, is characteristic (F23-22B & F 9-67). Some areas are **firm & white**, others are soft & yellow (due to **necrosis**), & others show **cystic degeneration) & hemorrhage.**

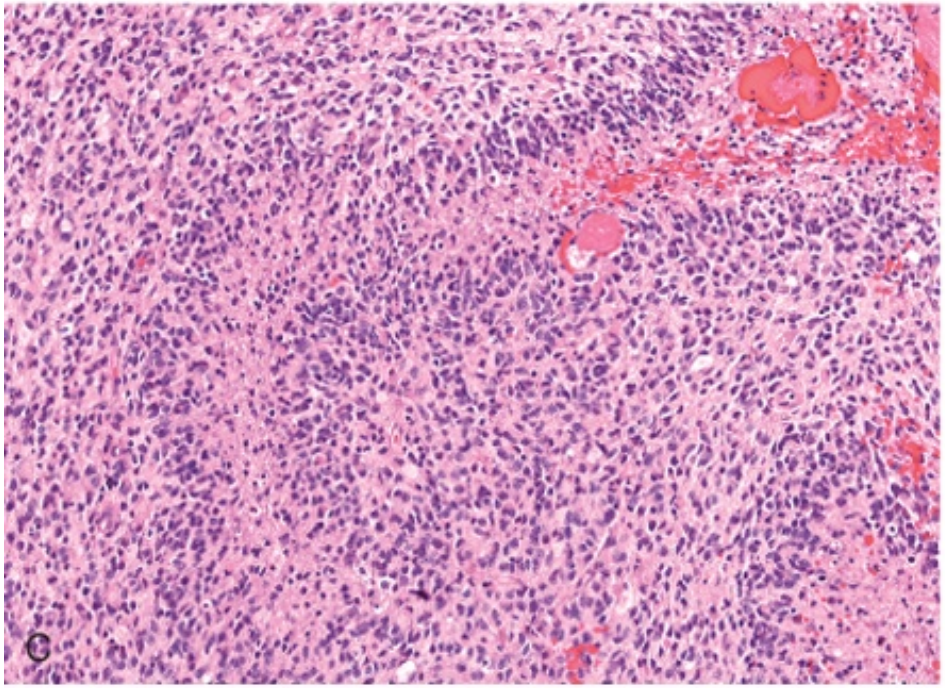
◘ **Well-differentiated fibrillary astrocytomas** (◘ 4.31) are characterized by a mild to moderate ↑ in the number of glial cell nuclei, mild nuclear pleomorphism, & an intervening feltwork of fine, GFAP-positive astrocytic cell processes that give the background a fibrillary appearance.

☹ The **T is infiltrative & transition between neoplastic & normal tissue is indistinct (not clear); & T** cells can be seen infiltrating normal tissue at some distance from the main lesion.

- **Anaplastic astrocytomas** show more dense cellularity, greater nuclear pleomorphism, & ↑ mitoses.





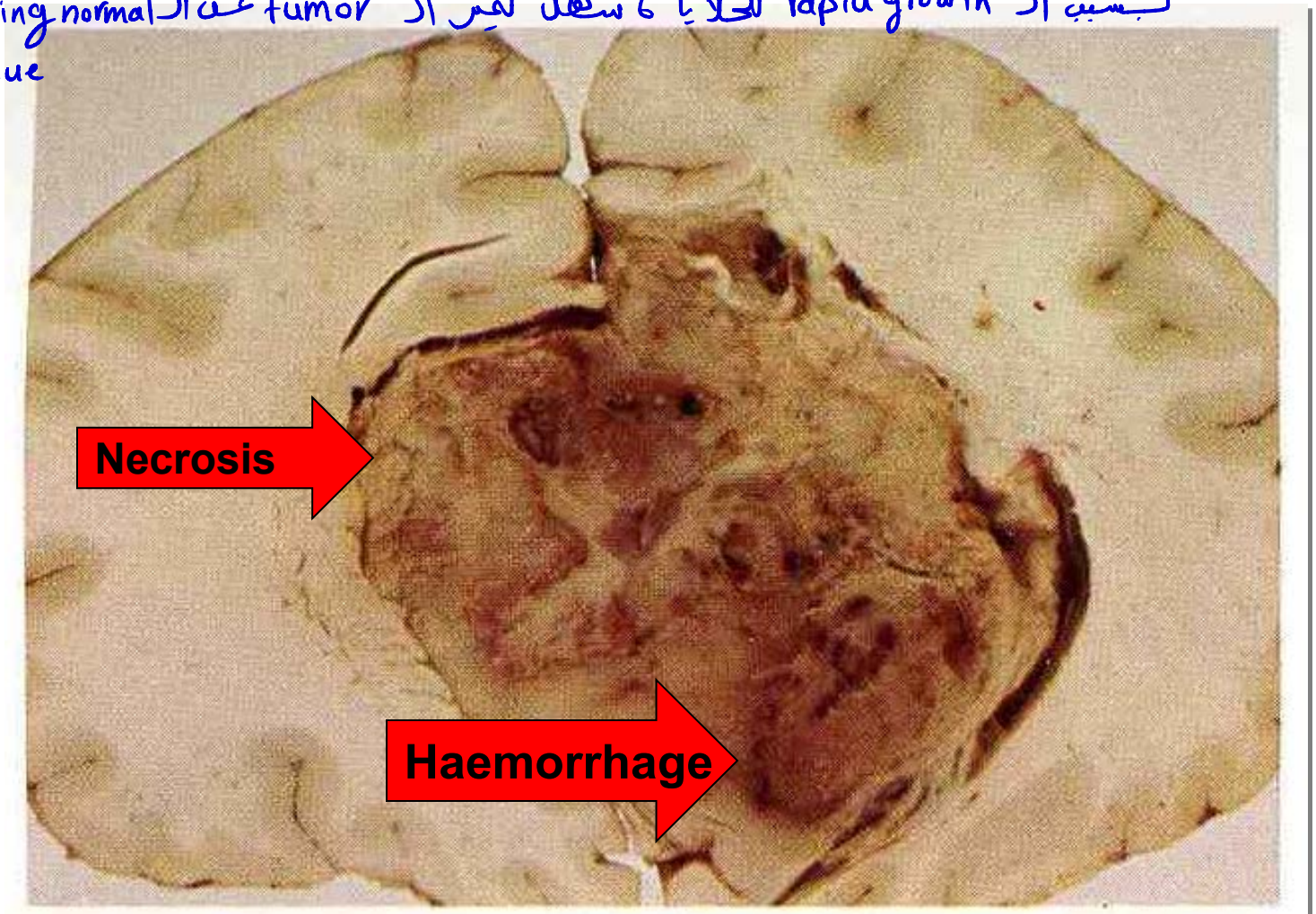


F23-22: **A, Low-grade astrocytoma** is seen as expanded white matter of the left cerebral hemisphere & thickened corpus callosum & fornices.

Glioblastoma: B, Necrotic, hemorrhagic, infiltrating **T;** histologically **C,** show (1) high cellularity + (2) pseudo-palisading of **T** cell nuclei around necrosis. اصطفاف الخلايا حول مناطق الـ necrosis

F 9-67:**Glioblastoma multiforme.** Massive tumor infiltrating the corpus callosum & both cerebral hemispheres; showing yellow-white (necrotic) & reddish-brown (hemorrhagic) areas.

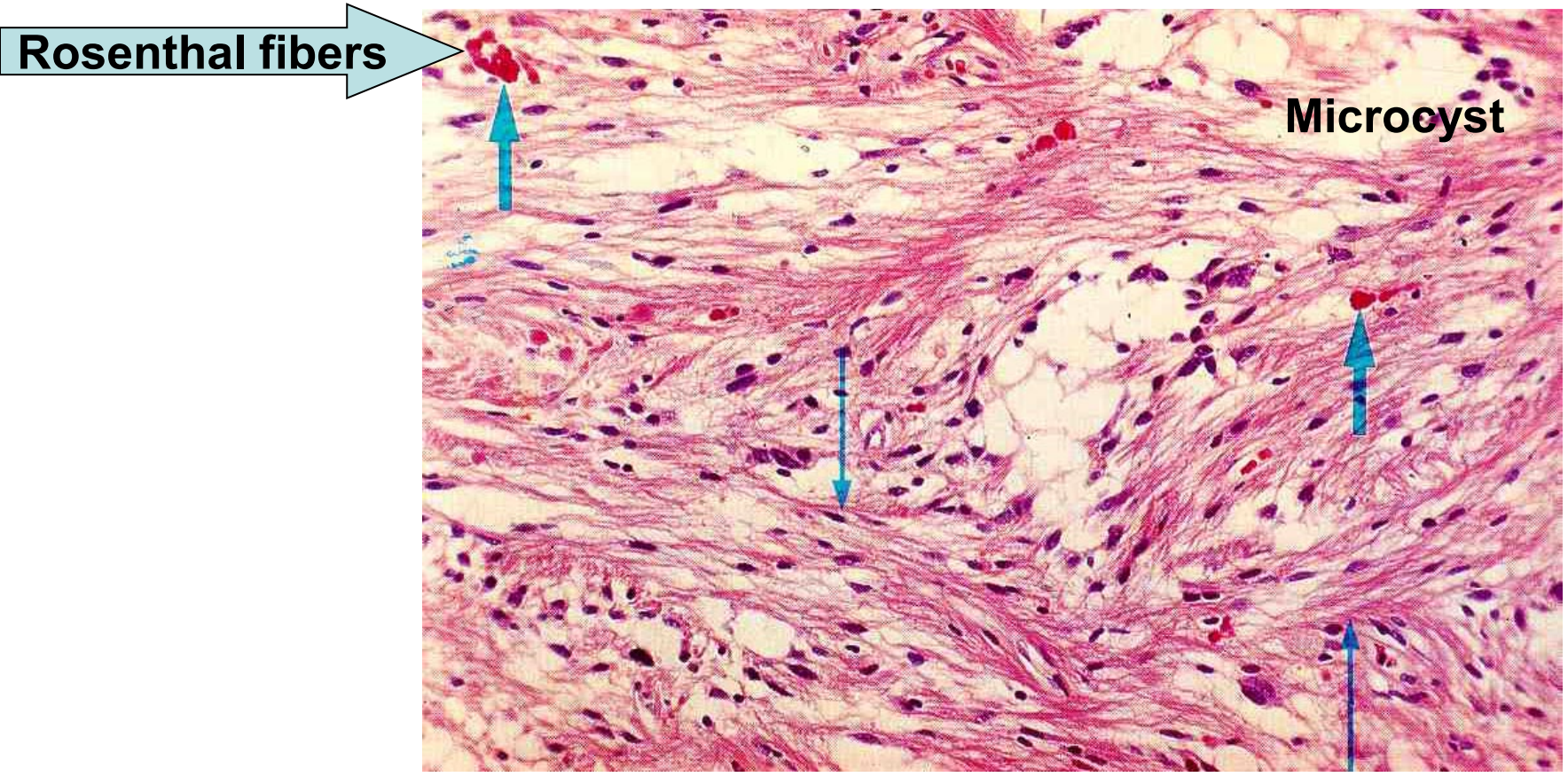
surrounding normal tissue عن الـ tumor يسهل نمو الـ rapid growth بسبب الـ



9.67 Glioblastoma multiforme

◘ 4.31: **Astrocytoma (Fibrillary): brain X 200.**

Consist of mature-looking neoplastic astrocytes with ill-defined cytoplasmic boundaries & pleomorphic ovoid/elongated basophilic nuclei. Their **neurofibrillary processes** are well-developed & abundant & arranged in large eosiniphilic bundles (thin A), within which there are collections of fluid (**microcysts**). The dens red bodies (thick A) are **Rosenthal fibers.**



• The highest grade **T** , known as **glioblastoma**, has a histologic appearance similar to anaplastic astrocytoma with the additional features of (1) **palisading necrosis** (◘ 4.35), **(2) pseudo-palisading nuclei** (F23-22C) & **(3) vascular or endothelial cell proliferation** (◘4.36).

has 3/3 grade.

Pilocytic Astrocytoma (F9-59)

less common.

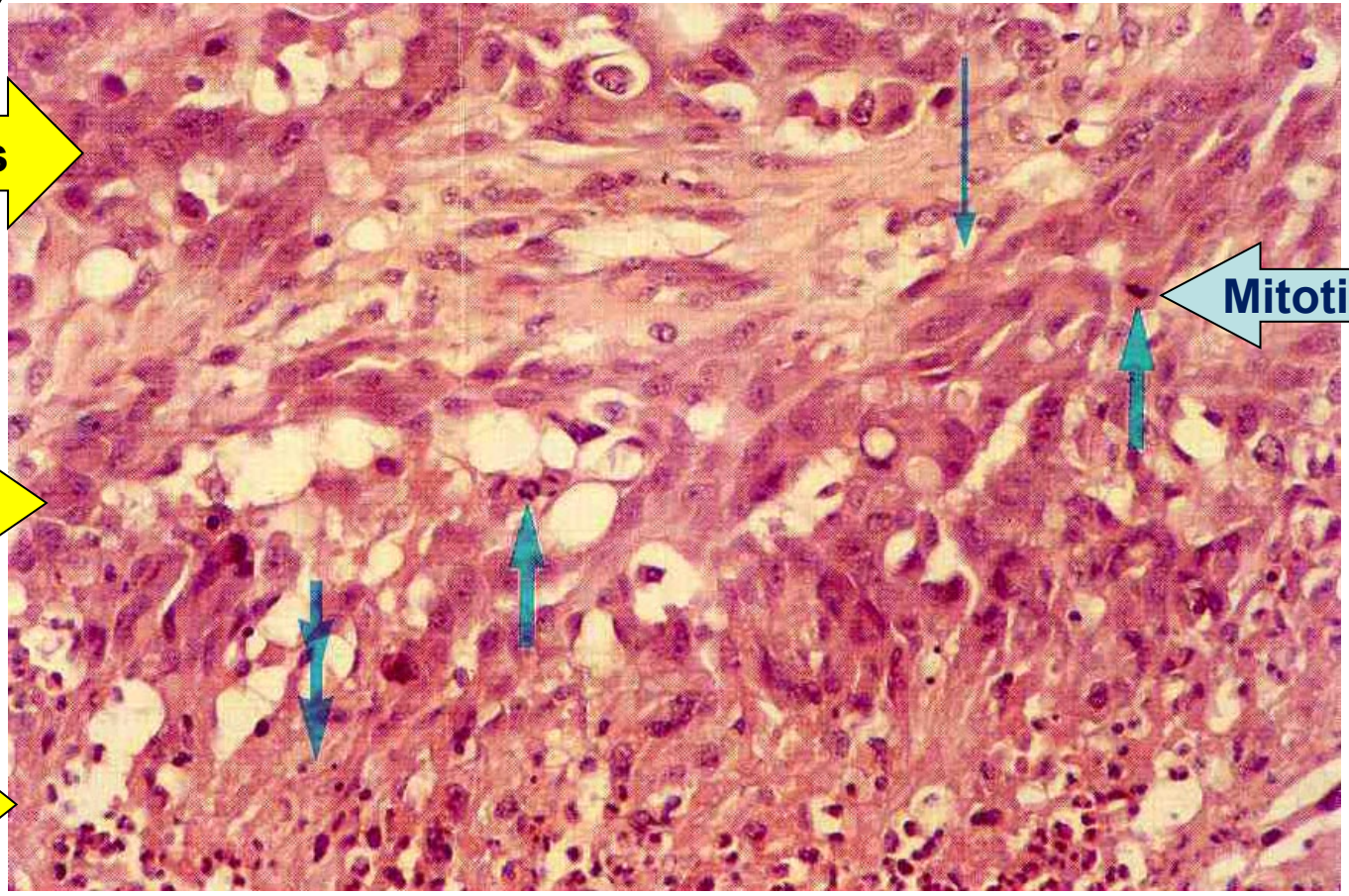
★Pilocytic astrocytomas are **relatively • benign T**, often • **cystic**, that typically occurs in • **children & young adults** & are usually located in the • **cerebellum** but may also appear in the floor & walls of the third ventricle, the optic nerves, & occasionally the cerebral hemispheres.

☺ Symptomatic recurrence from incompletely resected lesions is often associated with cyst enlargement rather than growth of the solid component.

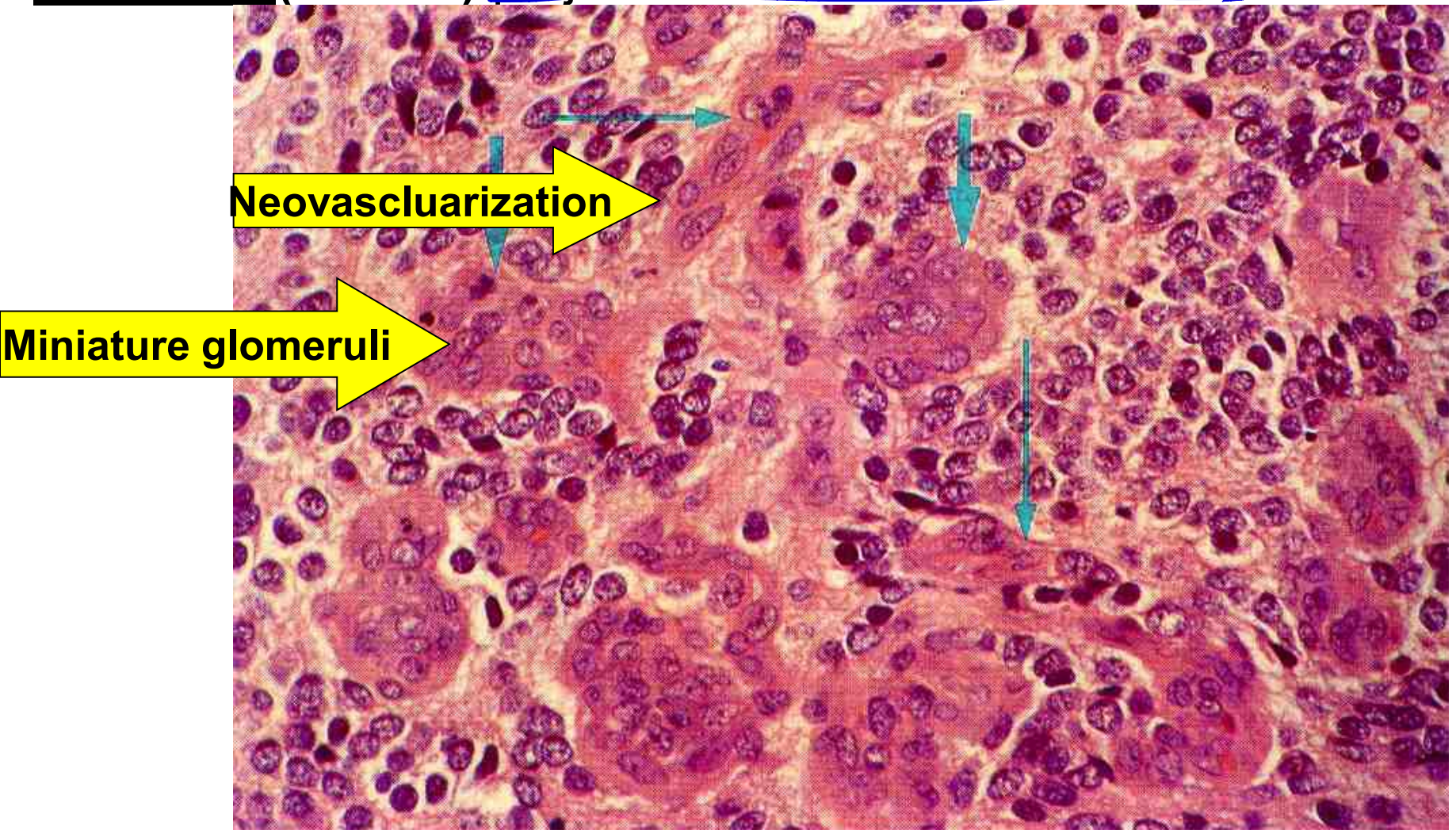
► **Grossly**, pilocytic astrocytoma is often **cystic,** with a **mural nodule in the wall of the cyst**; if **solid**, it is usually well circumscribed.

◘ H, it composed of areas with bipolar cells with long, thin "hairlike" processes that are GFAP positive; Rosenthal fibers, eosinophilic granular bodies, & microcysts are often present. **Necrosis & mitoses are absent**.

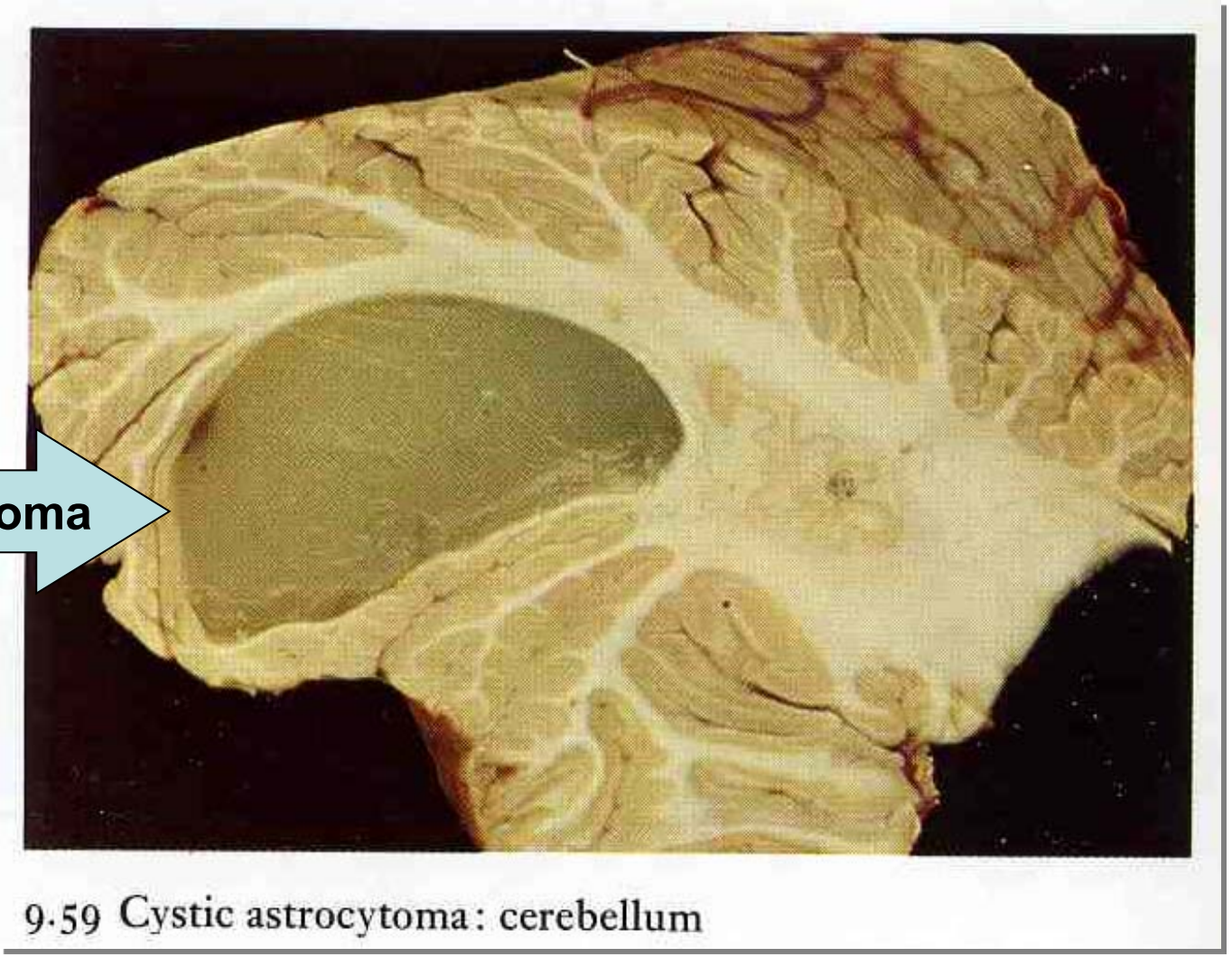
◘ 4.35: **Glioblastoma multiforme: brain.** Grade IV out of IV astrocytoma. Cells are (1) **very pleomorphic,** most are elongated (**thin A**), with long fibrillary processes, elongated nuclei with round blunt ends & many contain prominent **nucleoli** & (2) some are **multinucleated, & many** show (3) **mitotic** figures (**thick A**), some are abnormal; (4) **Necrosis** is marked (**double A**).



◘ 4.36:**Glioblastoma multiforme: Brain X360.** The tumor is very vascular, prominent (1) **neovascluarization (thin A)** lined by large plump EC with abundant cytoplasm. A prominent feature are 'Buds' of proliferating EC, resembling (2) **miniature glomeruli (thick A)** project from the surface of the BV.



F 9-59: **Pilocytic (cystic) astrocytoma: cerebellum.** Crescentic **cyst** cavity, filled with gelatinous pale green fluid occupying the lateral lobe of the **cerebellar** hemisphere. The tumor is slowly-growing & affects mainly **children & young adults**.



9·59 Cystic astrocytoma: cerebellum

Oligodendroglioma

★ Constitute 5% to 15% of all gliomas. • Most common in the 4th & 5th decades. •Found mostly in the cerebral hemispheres.

•The most common genetic findings are loss of heterozygosity for chromosomes 1p 7 19q. • Patients may have had neurologic complaints, including **seizures**.

▶**Grossly**, **infiltrative** gelatinous, gray **T** & may show cysts, focal hemorrhage, while **calcification is present in 90% of T.**

in most cases.

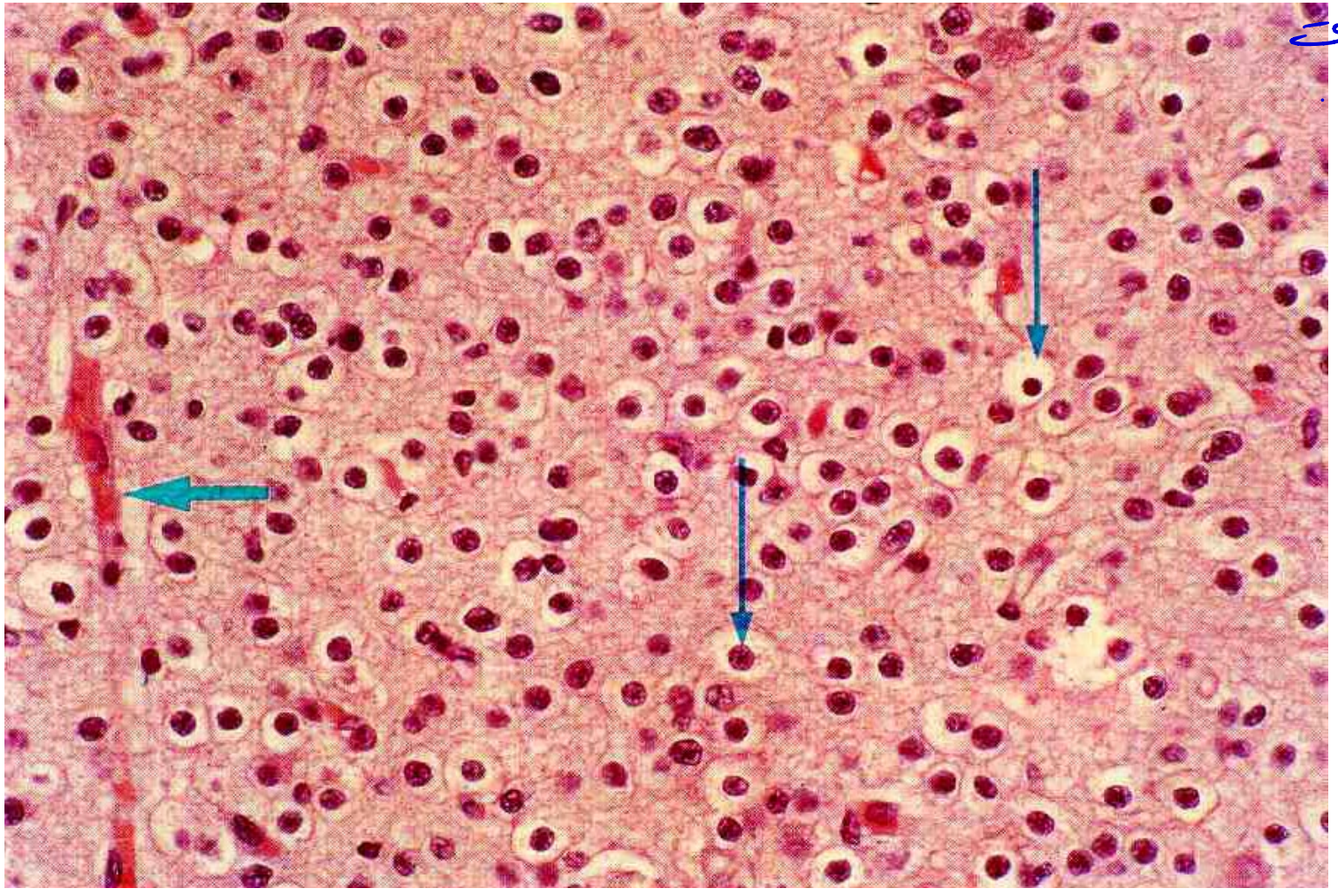
◘ **T** cells are regular (similar to normal oligodendrocytes), with spherical nuclei, containing finely granular chromatin surrounded by a clear halo of cytoplasm (F23-23A & ◘ 4.31), with delicate network of anastomosing capillaries & very rare mitotic figures, **Calcification** present in 90% of **T**.

☹ Anaplastic oligodendroglioma shows ↑ cell density & mitotic activity, nuclear anaplasia, & necrosis.

• **Prognosis** is better than that of astrocytomas. Combine surgery, chemotherapy, & radiotherapy yields an average survival of 5 to 10 years.

☹ Anaplastic oligodendroglioma have worse prognosis. than the usual type oligodendroglioma.

◘ 4.31:**Oligodendroglioma: brain X360.** Highly cellular **T**, each cell has (I) a moderate amount of eosinophilic cytoplasm, bounded by a well-defined membrane & (II) a small rounded darkly basophilic nucleus, surrounded by a perinuclear, large clear halo (thin A), appearance called '**boxing' of the nucleus**.

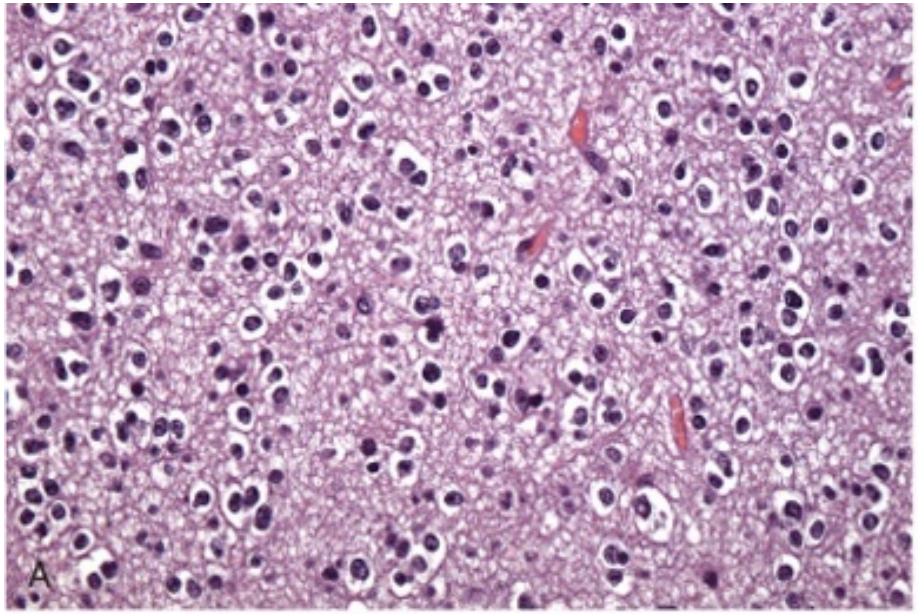


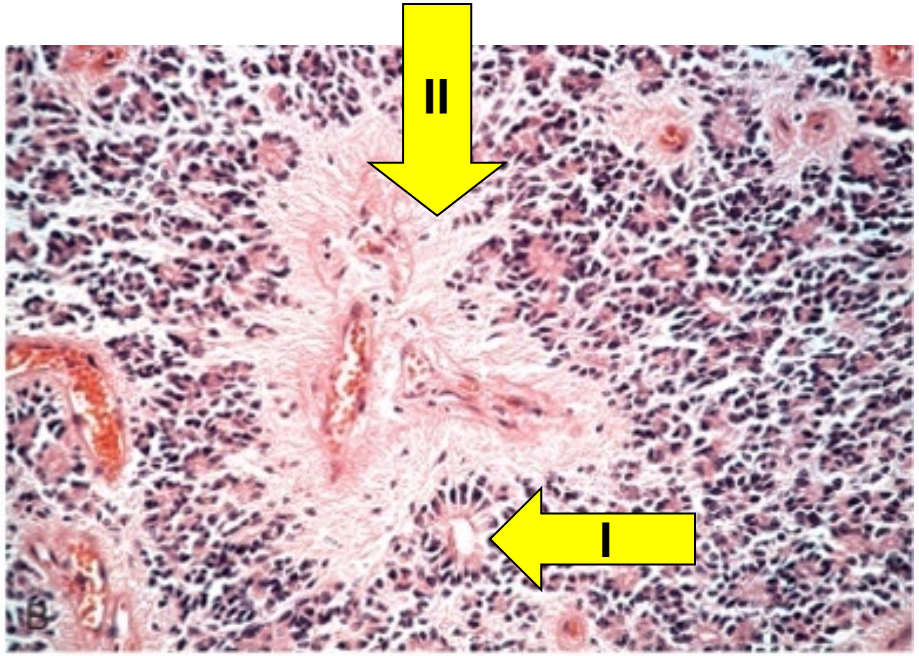
F23-23: **A, Oligodendroglioma.** Regular cells having round nuclei, with a cytoplasmic halo.

B, Ependymoma: (I) tumor cells form round or elongated structures (**rosettes**, canals) resemble the embryologic ependymal canal, with long, delicate processes extending into a lumen & **(II) perivascular pseudo-rosettes,** with tumor cells arranged around vessels with an intervening zone consisting of thin ependymal processes directed toward the wall of the BV.

قناة وحولها خلايا.

على شكل أزهار حول الـ vessels.





Ependymoma

★Mostly arise next to the ependyma-lined ventricular system, including the central canal of the spinal cord.

- In the **first two decades** of life, they constitute 5% to 10% of the primary brain **T** & they typically occur near the **4th ventricle**
- In **adults**, the spinal cord is their most common location; & in which they are particularly frequent in neurofibromatosis type 2.
- **Because ependymomas usually grow within the ventricles, CSF dissemination is a common occurrence.**

►**Grossly**, in the 4th ventricle, **T** are typically solid or papillary masses extending from the floor of the ventricle.

◘ H, **T** cells, with regular round to oval nuclei & abundant granular chromatin. Between the nuclei there is a variably dense fibrillary background. **T** cells may form:

(I) rosettes or canals (round or elongated structures that resemble the embryologic ependymal canal, with long, delicate processes extending into a lumen {F 23- 23B (I) }.

◘ (II) **perivascular pseudo-rosettes** are more frequently seen, in which **T** cells are arranged around vessels, with an intervening zone consisting of thin ependymal processes directed toward the wall of the vessel {F23- 23B (II) & ◘ 4.38).

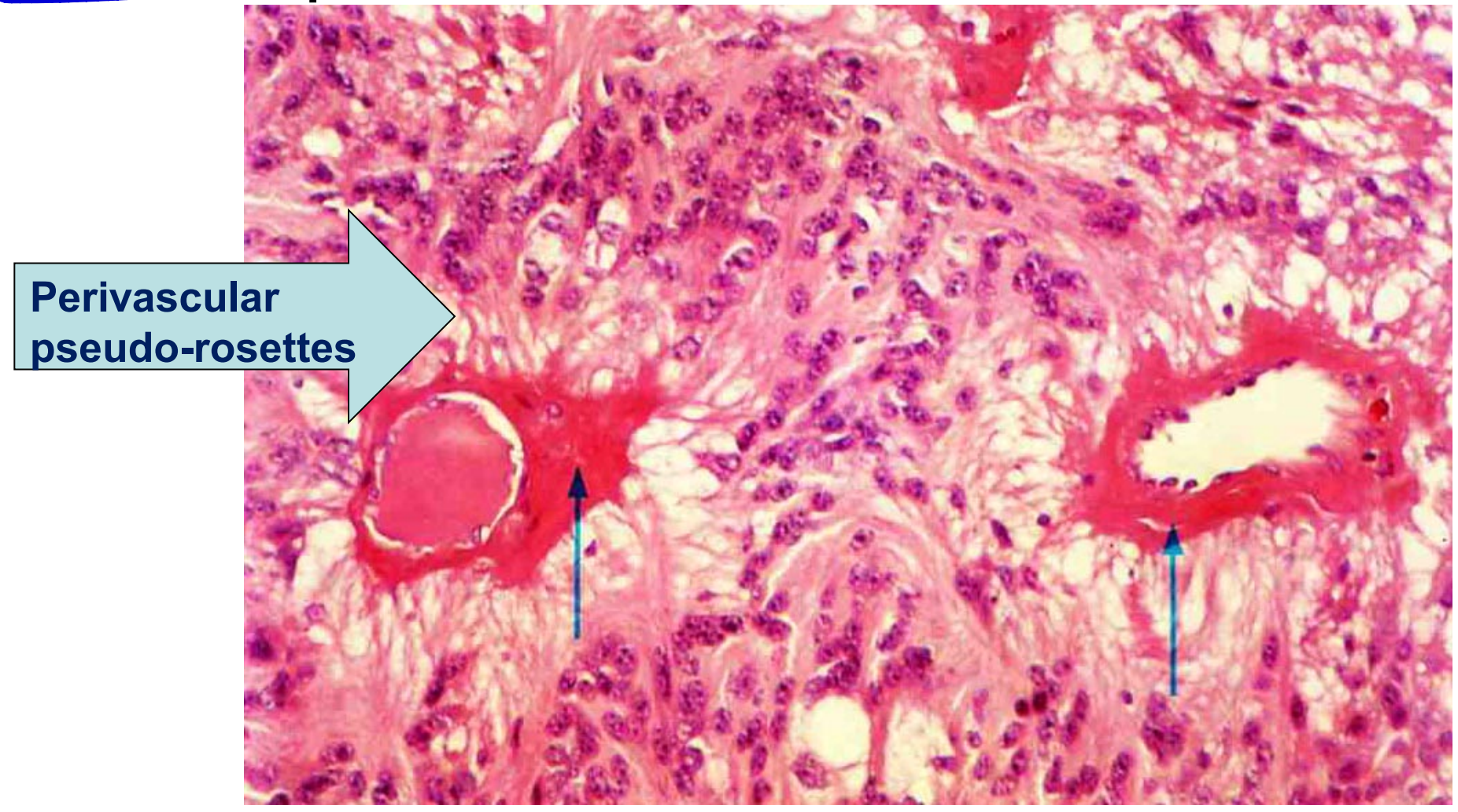
• **Anaplastic ependymomas** show ↑ cell density & mitotic rates, necrosis, & less evident ependymal differentiation.

Neuronal Tumors → less common tumors.

★ ***Central neurocytoma*** is a low-grade neuronal **T** found within & adjacent to the ventricular system (most commonly the lateral or 3rd ventricles), characterized by evenly spaced, round, uniform nuclei & often islands of neuropil.

★ ***Ganglio-gliomas*** are **T** with a mixture of glial elements (looking like a low-grade astrocytoma) & mature-appearing neurons (ganglion like). Most of these **T** are **slow growing**, but the glial component occasionally becomes frankly anaplastic, & the disease then progresses rapidly. These lesions often **present with seizures**.

◘ 4.38: **Ependymoma: brain X 360.** Two dilated BV, with thick hyalinized deeply eosinophilic walls (arrows); surrounded by tumor cells arranged around & attach to the walls of BV by their elongated filamentous (& very vacuolated) bases, so-called **Perivascular pseudo-rosettes**.



★*Dysembryoplastic neuroepithelial tumor*

★A distinctive, low-grade **T** of childhood, showing slow growth & a relatively good prognosis after resection; it often **present with seizures**.

★These lesions are typically located in the superficial temporal lobe.

◘ **consist of small round cells with features of neurons** arranged in columns & around central cores of processes. These typically form multiple discrete **intracortical nodules** that have a myxoid background. منفصلين عن بعض

There are well-differentiated "floating neurons" that sit in the pools of mucopolysaccharide-rich fluid of the myxoid background.

Medulloblastoma →

★Occurs mainly in • **children** (accounting for 20% of pediatric brain **T**) & exclusively **(ONLY)** in the • **cerebellum.** It is largely **undifferentiated T,** although it is of **neuroectodermal origin** & may express neuronal & glial markers.
It is • **highly malignant with poor prognosis** for untreated patients, however, it is very • **radiosensitive** With total excision & radiation, the 5-year survival rate may be 75%.
• **T** of similar histology & poor degree of differentiation can be found elsewhere in the CNS (called CNS primitive neuroectodermal tumor or CNS PNET).

►**Grossly**, in children, medulloblastomas are located in the **midline of the cerebellum**; lateral **T** occur more often in adults. **T** is well **circumscribed, gray, & friable**, & may be seen extending to the surface of the cerebellar folia (F 9-72) & **involving the leptomeninges** (F23-24A).

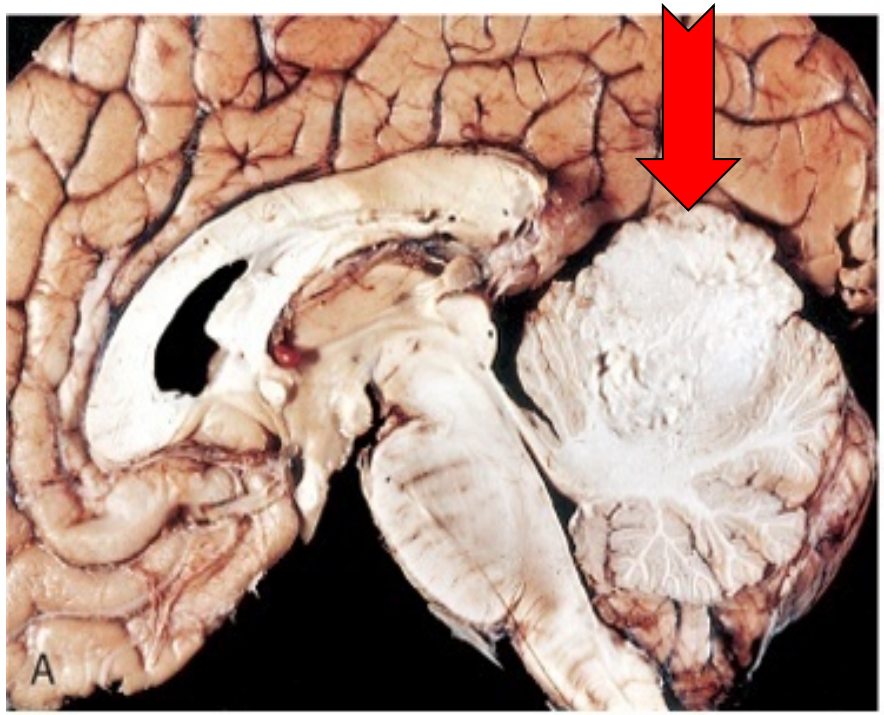
◘ **T** are extremely cellular, with sheets of anaplastic **("small blue") cells.** The Individual **T** cells are small, with little cytoplasm & hyperchromatic nuclei; mitoses are abundant (F23-24B). **T** cells spread by the CSF.

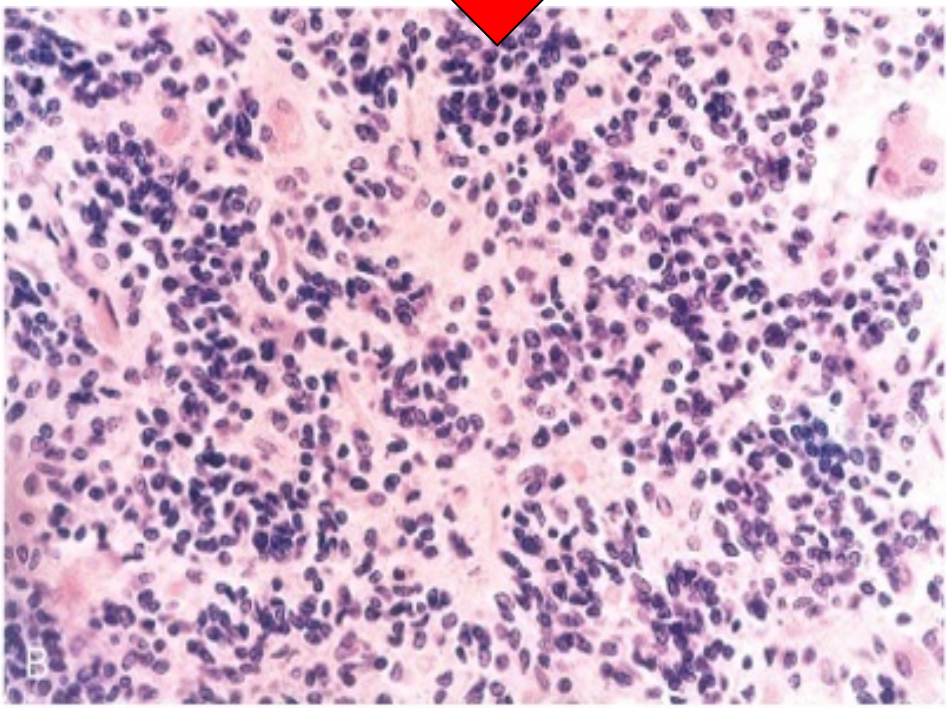
*most common tumors that spread by CSF:-
1- Ependymoma 2- Medulloblastoma.

F23-24: **Medulloblastoma: Brain**

A, Sagittal section of brain showing medulloblastoma destroying the superior midline cerebellum.

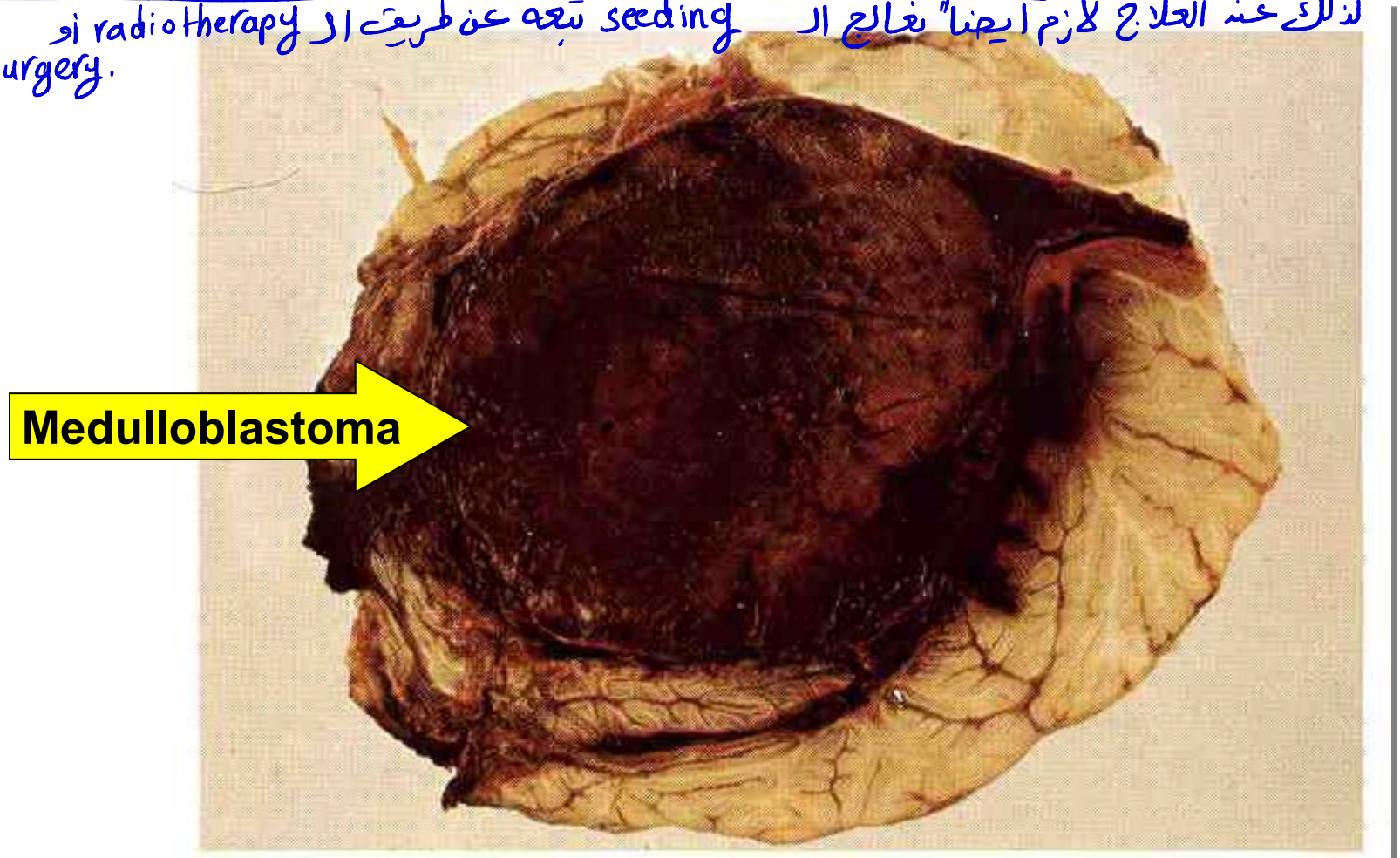
B, ◘ H, An extremely cellular tumor, with sheets of anaplastic **("small blue ells").** The individual tumor cells are small, with little cytoplasm & hyperchromatic nuclei; mitoses are abundant.





F 9-72: **Medulloblastoma.** Large, rounded, friable, necrotic & hemorrhagic well-demarcated, tumor expanding cerebellar hemisphere; occuring predominantly in children (5 to 8 yr) tumor tend to spread through CSF allover the brain & spinal cord.

لذلك عند العلاج لازم ايضا" نعالج ال seeding تبعه عن طريق ال radiotherapy او surgery.



9.72 Medulloblastoma

Other Parenchymal Tumors

Primary Central Nervous System Lymphoma

- accounts for 2% of extranodal lymphomas & 1% of intracranial tumors. * most common site of lymphomas → in GIT (stomach).
- The **most common CNS neoplasm in immunosuppressed** individuals (including transplant recipients & AIDS patients); in which lymphomas are nearly **all driven by Epstein-Barr virus.**
- In nonimmunosuppressed populations the incidence ↑ after 60 years of age; most of these **T** are **diffuse large B-cell lymphomas**.
- **All primary brain lymphomas are aggressive with relatively poor response** to chemotherapy as compared with peripheral lymphomas.

► **Grossly**, **T** often infiltrate all of the white, gray matter & cortex. Periventricular spread is common.
The **T** are **relatively well defined** as compared with glial neoplasms but are not as discrete as metastases.

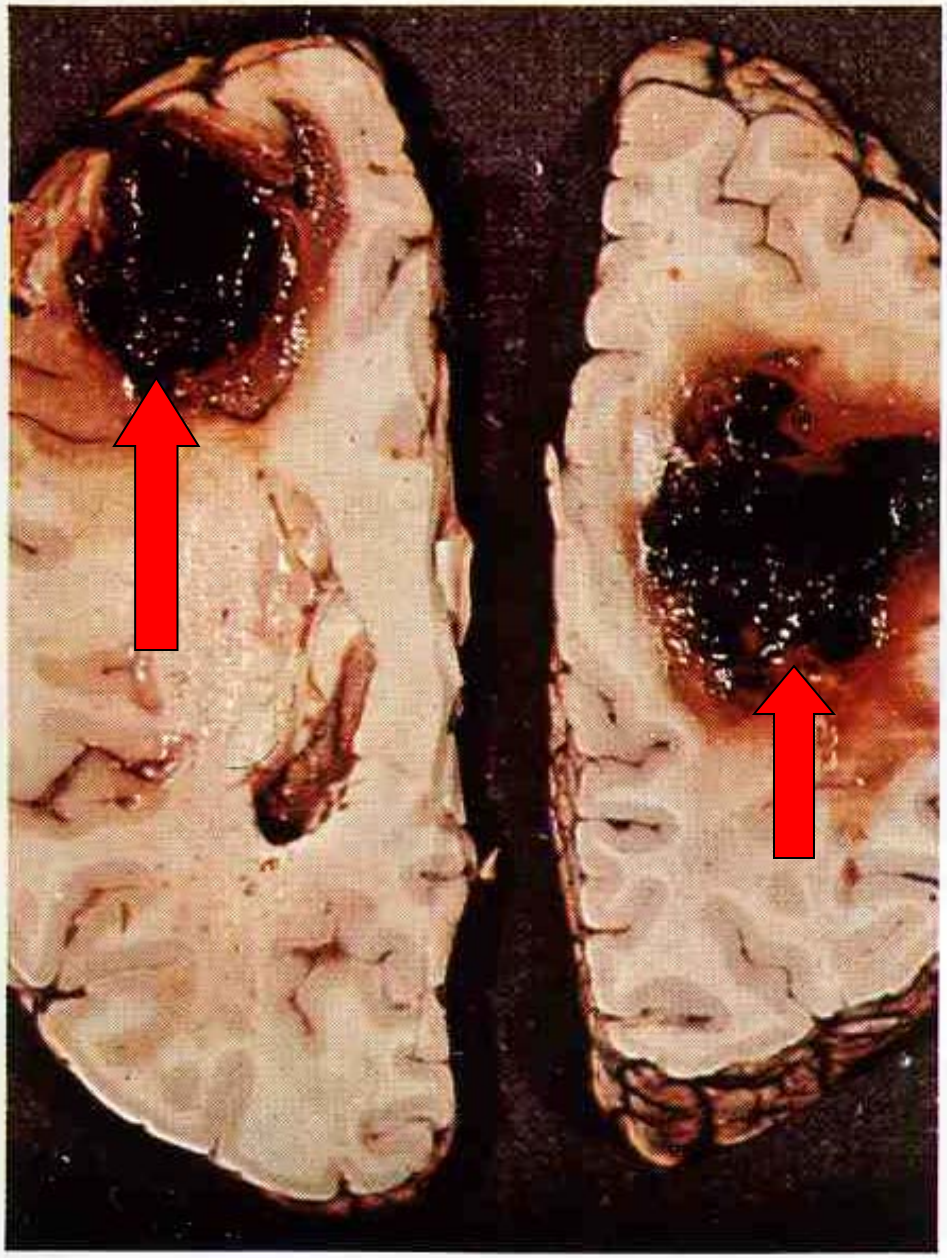
◘ H, most commonly, they are large-cell lymphomas, showing extensive areas of **central necrosis;** infiltrating the parenchyma of the brain & accumulate around BV.

* الـ metastasis بكون مفيز حدا عن الـ tissue المحيط 6 في هذه الحالة بكون بالوسط يعني مش كتير مميز

Germ-Cell Tumors → testis or ovaries. بالعادة

★ **Primary** brain germ-cell **T** occur **along the midline**, most **commonly in the pineal & the suprasellar regions.**

- They account up to 1% of brain **T** in people of European descent but as many as **10% of brain tumors in Japanese.**
- (**90% occurs during the first two decades**) Germ-cell **T** in the pineal region show a strong male predominance.
- Germ-cell **T** in the brain share many of the features of their counterparts in the gonads. CNS **T** that is the counterpart to the **testicular seminoma** is called a **germinoma.** → in CNS of males or females. ↳ if in female ovaries → dysgerminoma
- CNS involvement by a gonadal germ-cell **T** **secondareies** is not uncommon (F9-79).



9·79 Secondary choriocarcinoma: brain

F 9-79: **Secondary choriocarcinoma: Brain**.

☠ Two large hemorrhagic lesions are present (which resemble intracranial hemorrhages).
Histology reveals secondary choriocarcinoma in the brain

The patient was a 36 years old man with testicular choriocarcinoma.

Meningiomas (F23-25A & F 9-51)

★A predominantly • **benign T of adults**, **attached to the dura,** & • arising from the **meningothelial cell of the arachnoid.**

• May be found along any of the external surfaces of the brain as well as **within the ventricular** system, where they **arise from the stromal arachnoid cells of the choroid plexus.**

★They usually present with• **vague** nonlocalizing symptoms, or with • **focal findings** due to compression of underlying brain.

•When **multiple meningiomas** are present, especially in association with 8th nerve schwannomas or glial **T**, a possible diagnosis of **neurofibromatosis type 2** should be considered.

•50% of meningiomas, not associated with NF2, still have mutations in the NF2 gene on the long arm of chromosome 22.

▶**Grossly**, meningiomas grow as • **well-defined dural-based masses** that • **compress underlying brain** but are **easily separated from it** (F23-25A & F 9-51). Extension into the overlying bone may be present.

tendency الورم له
to infiltrate the adjacent tissue.

F23-25: **Meningioma.**

A, Parasagittal multilobular meningioma *attached* to the *dura* with *compression* of the underlying brain; but it is easily separated from it

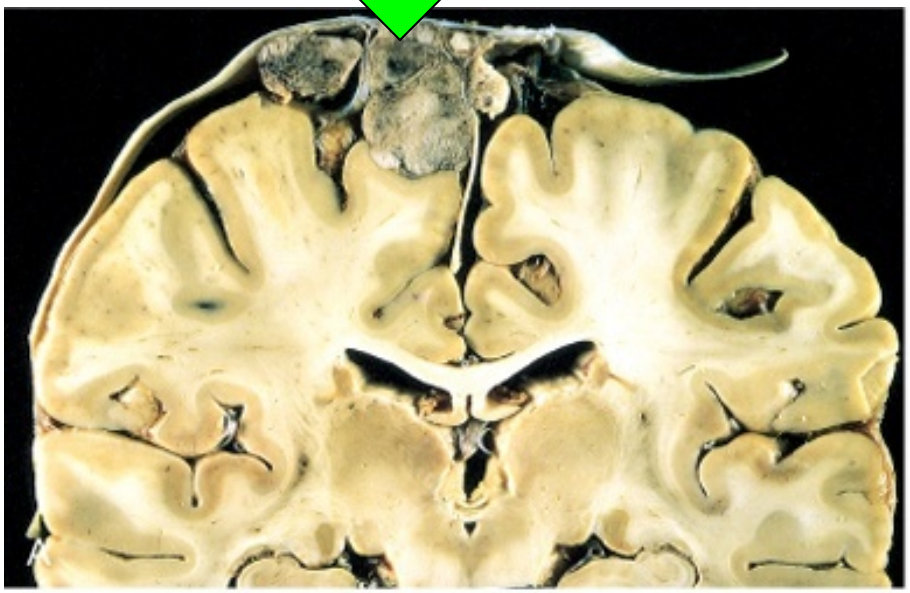
. brain tissue وبتركك حفرة في ال

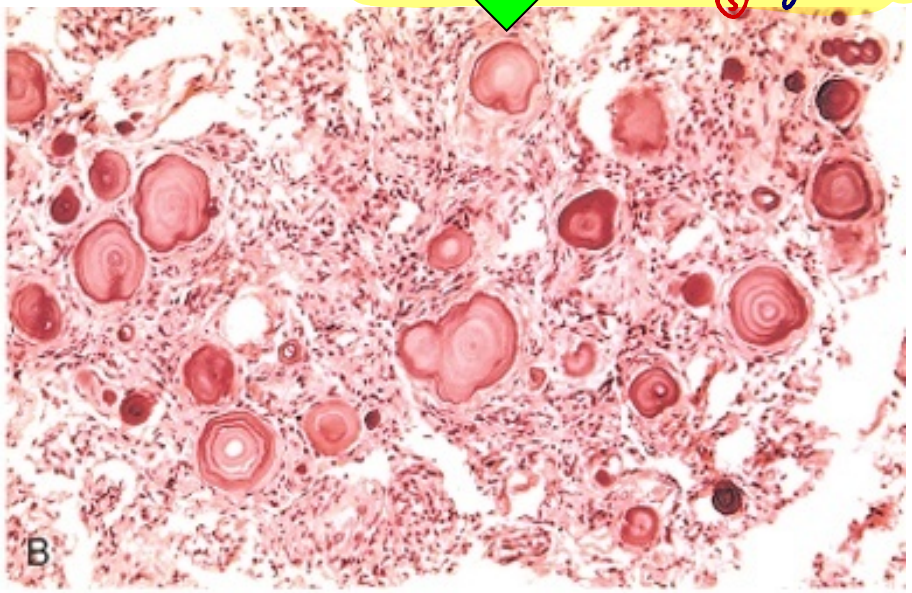
B, ◘ H, Whorled pattern of cell growth & psammoma bodies

على شكل دوائر.

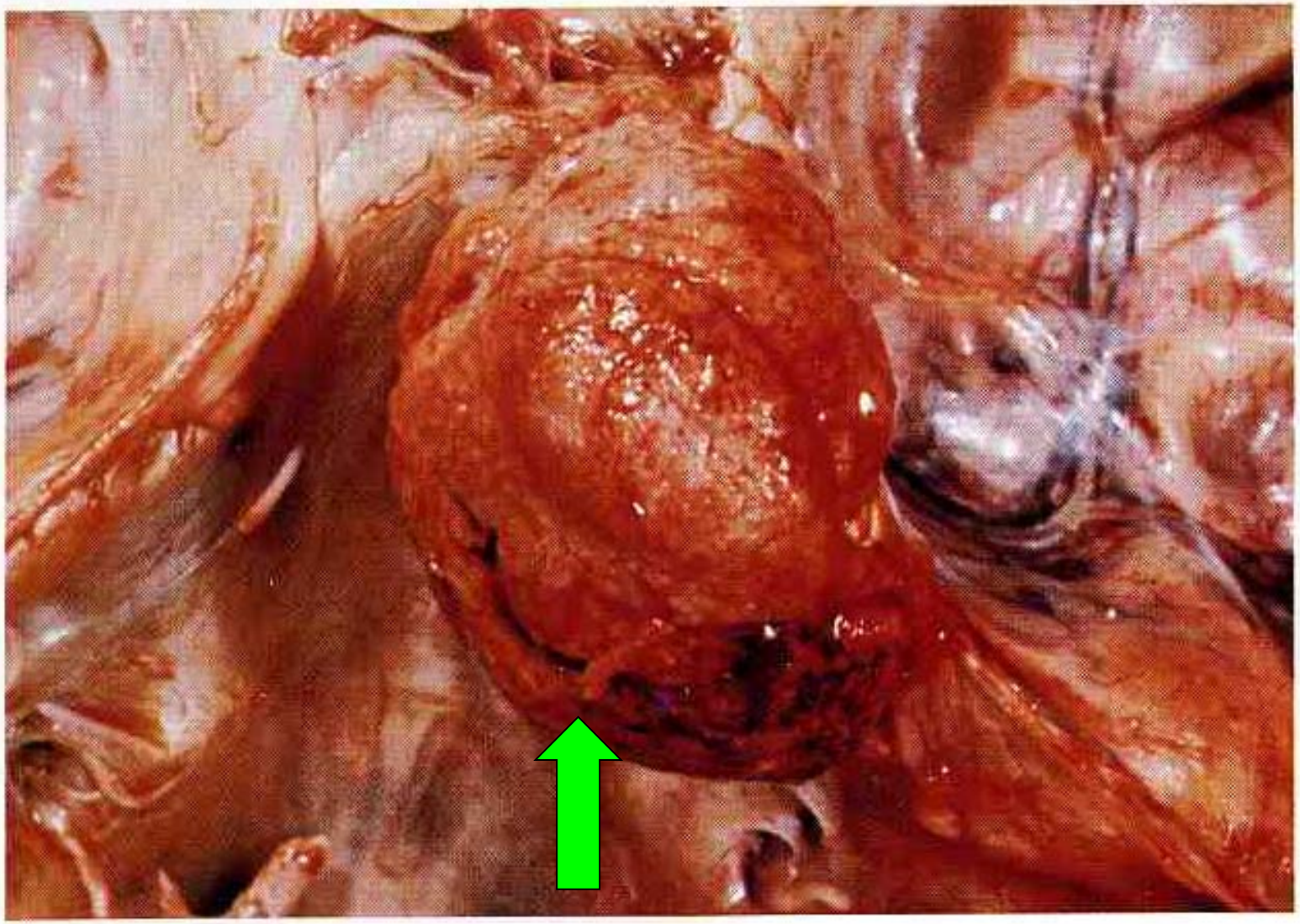
مع هذا "

in papillary carcinoma of thyroid, papillary carcinoma of the ovaries and Meningioma.





F 9-51: **Meningioma.** A large smooth, lobulated, pink-red tumor situated posterior to the dorsum sellae (skull base).



9.51 Meningioma

◘ H, patterns: • **Syncytial**, with whorled clusters of cells that sit in tight groups without visible cell membranes; • **Fibroblastic,** with elongated cells & abundant collagen deposition between them; • **Transitional** (◘ 4.30), which shares features of the syncytial & fibroblastic types; • **Secretory**, with PAS-positive intracytoplasmic droplets; • **Microcystic**, with a loose, spongy appearance, & • **psammomatous**, with numerous psammoma bodies (F23-25B).

Atypical meningiomas

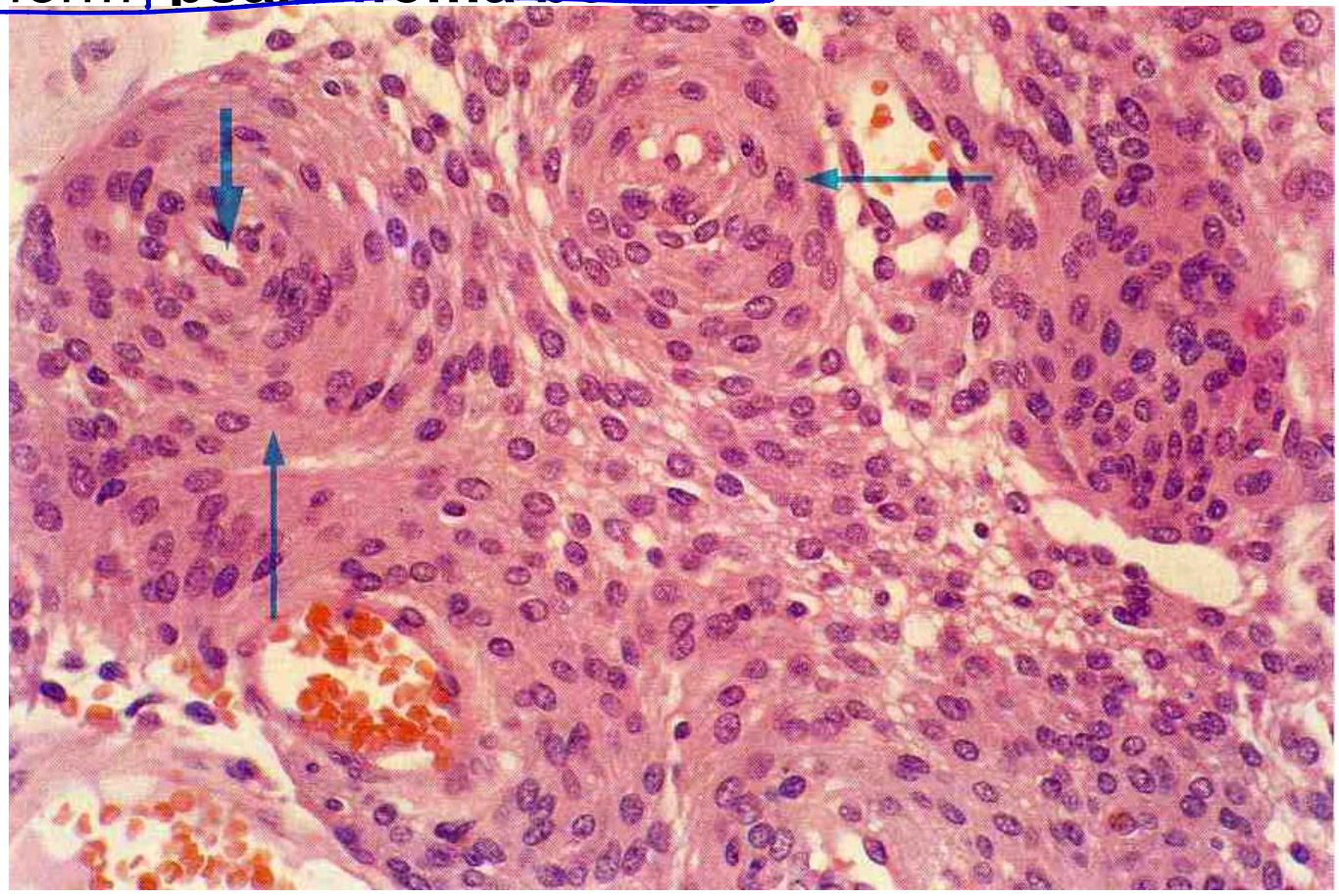
• **Are T** recognized by a ⇨higher mitotic rate, showing ⇨ more aggressive local growth, ⇨ higher rate of recurrence.
• **Anaplastic (malignant) meningiomas** are highly aggressive **T**, resemble high-grade **sarcoma,**

★ Most meningiomas are easily separable from underlying brain, but **some infiltrate the brain.** Brain invasion is associated with ↑ risk of meningioma **recurrence.**

• Prognosis of meningiomas is influenced by the *size* & *location* of the lesion, *surgical accessibility*, & *histologic grade*.

◘ 4.30: **Meningioma, Transitional type. X360.** 5 Compact **whorls** of uniform tumor cells (thin arrows), having abundant eosinophilic cytoplasm, & ill-defined boundaries. The nuclei are uniform ovoid & vesicular & their chromatin is pale & finely granular. A small cavity at the center of the whorls (thick A) is seen, & the central cells eventually become hyalinized & may calcify to form **'psammoma bodies'.**

calcification of the center.



Metastatic Tumors in the CNS

They are more common than the primaries.

★ 50% of intracranial (Brain & meninges) **Tumors** are metastatic & mostly are carcinomas.

★ The commonest 5 primary cancer sites, which account for about 80% of all metastases are: **lung** (■ 4.48), **breast** (F9-76 & ■ 4.47), **skin melanoma** (F23-26), **kidney**, & **GIT**.

► **GROSSLY**, In the brain, metastases may be single but often are **multiple**, form **sharply demarcated masses**, usually surrounded by a zone of **edema** (F23-26) & microscopically the **boundary** between **T** & brain parenchyma is well defined.

★ ***Paraneoplastic syndromes*** may involve the peripheral & CNS, sometimes, **even before** the clinical recognition of the malignant **T**. These syndromes are most **commonly** associated with **small-cell ca of the lung**.

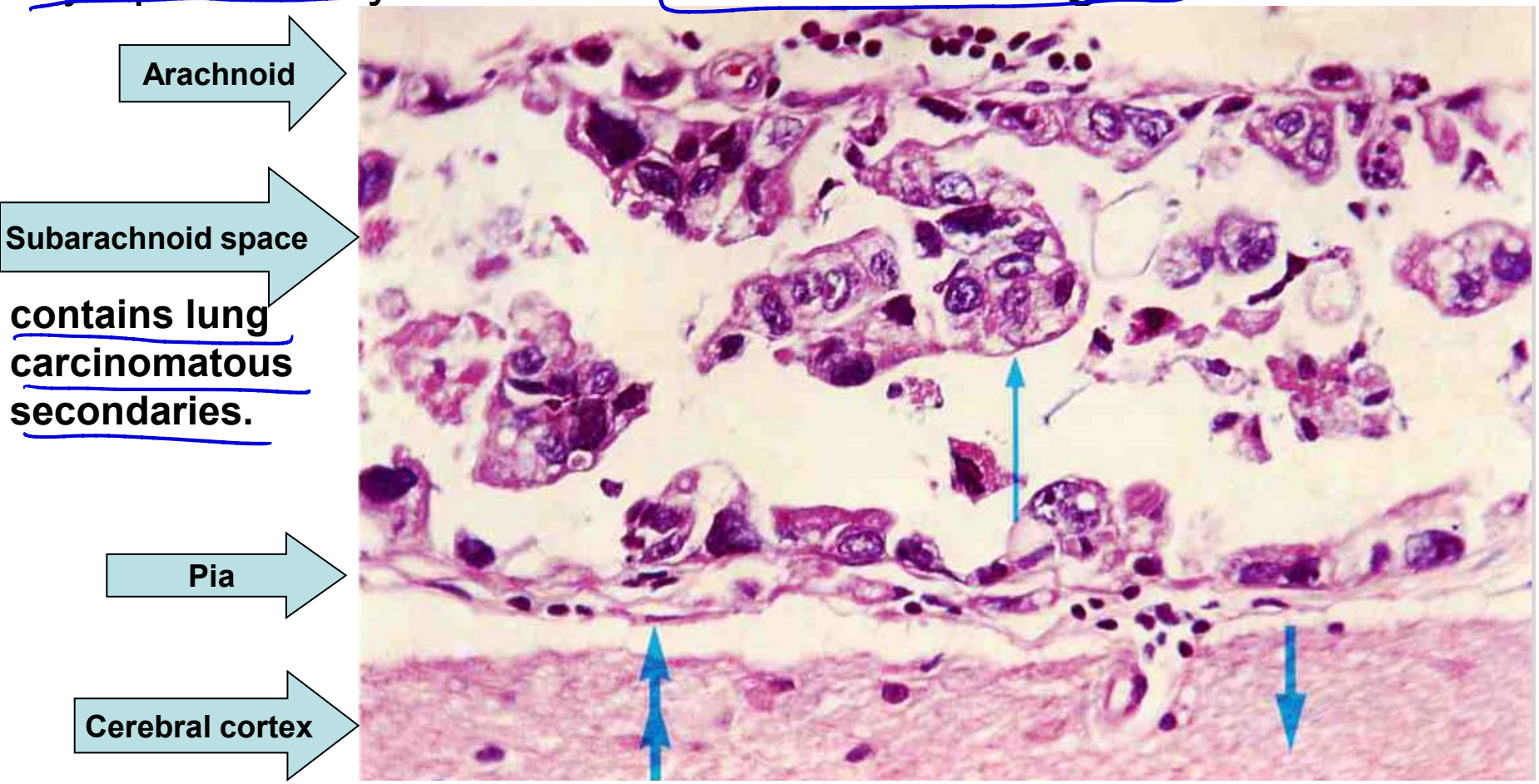
most common cause of it is small cell carcinoma of the lung

★ Characteristic paraneoplastic syndromes patterns include:

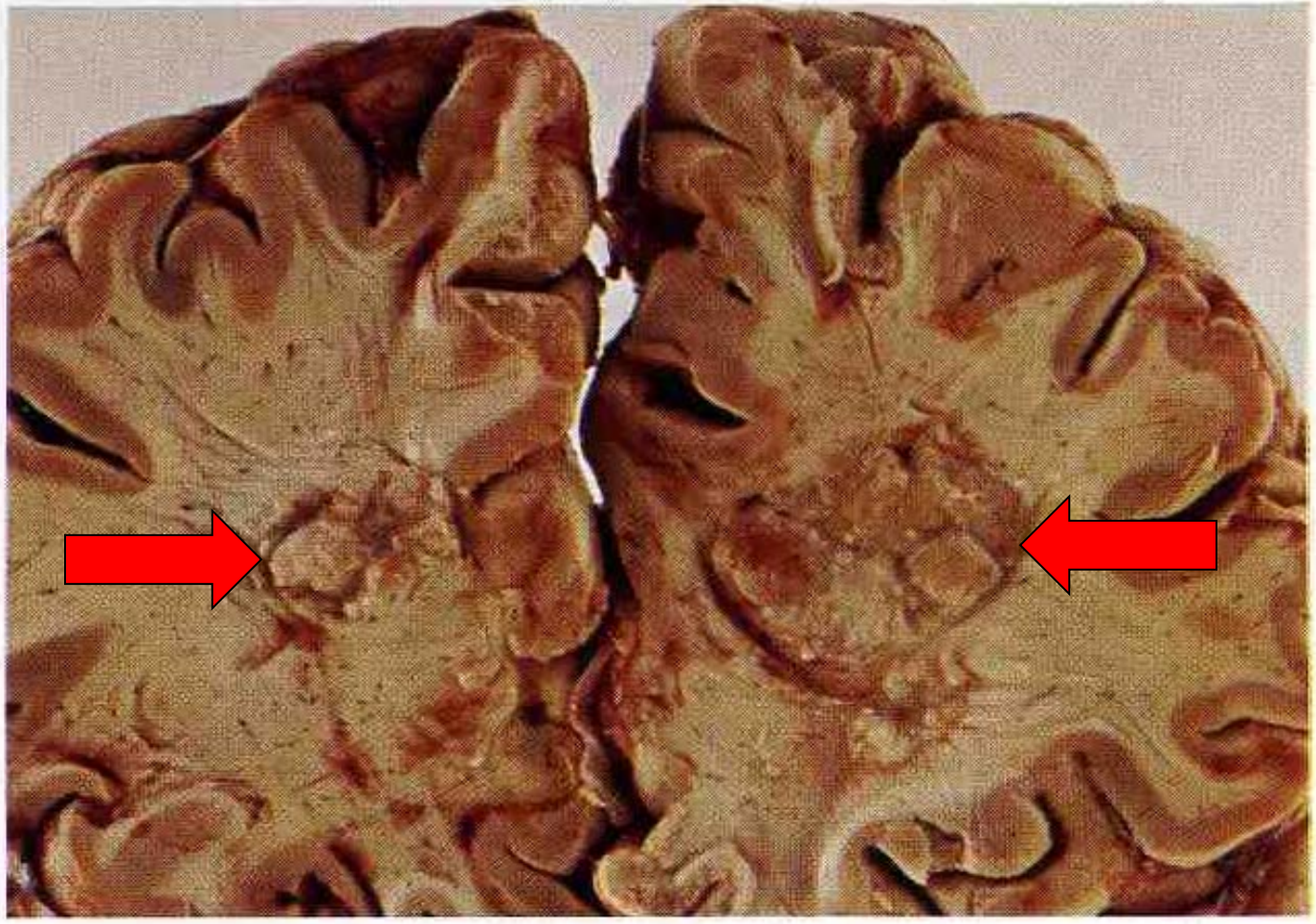
- ***Limbic encephalitis*** causing a subacute dementia,
- ***Subacute cerebellar degeneration*** resulting in ataxia, with destruction of Purkinje cells,
- ***Subacute sensory neuropathy*** leading to altered pain sensation with loss of sensory neurons from dorsal root ganglia.

◘ 4.48: **Secondary carcinoma: brain X160.**

The **subarachnoid space** contains malignant • **carcinomatous cells secondaries** (thin A) from the **lung** with very pleomorphic, large pale vesicular nuclei & prominent nucleoli & vacuolated cytoplasm. Such lesion may give rise to clinical signs & symptoms very similar to • **bacterial meningitis.**

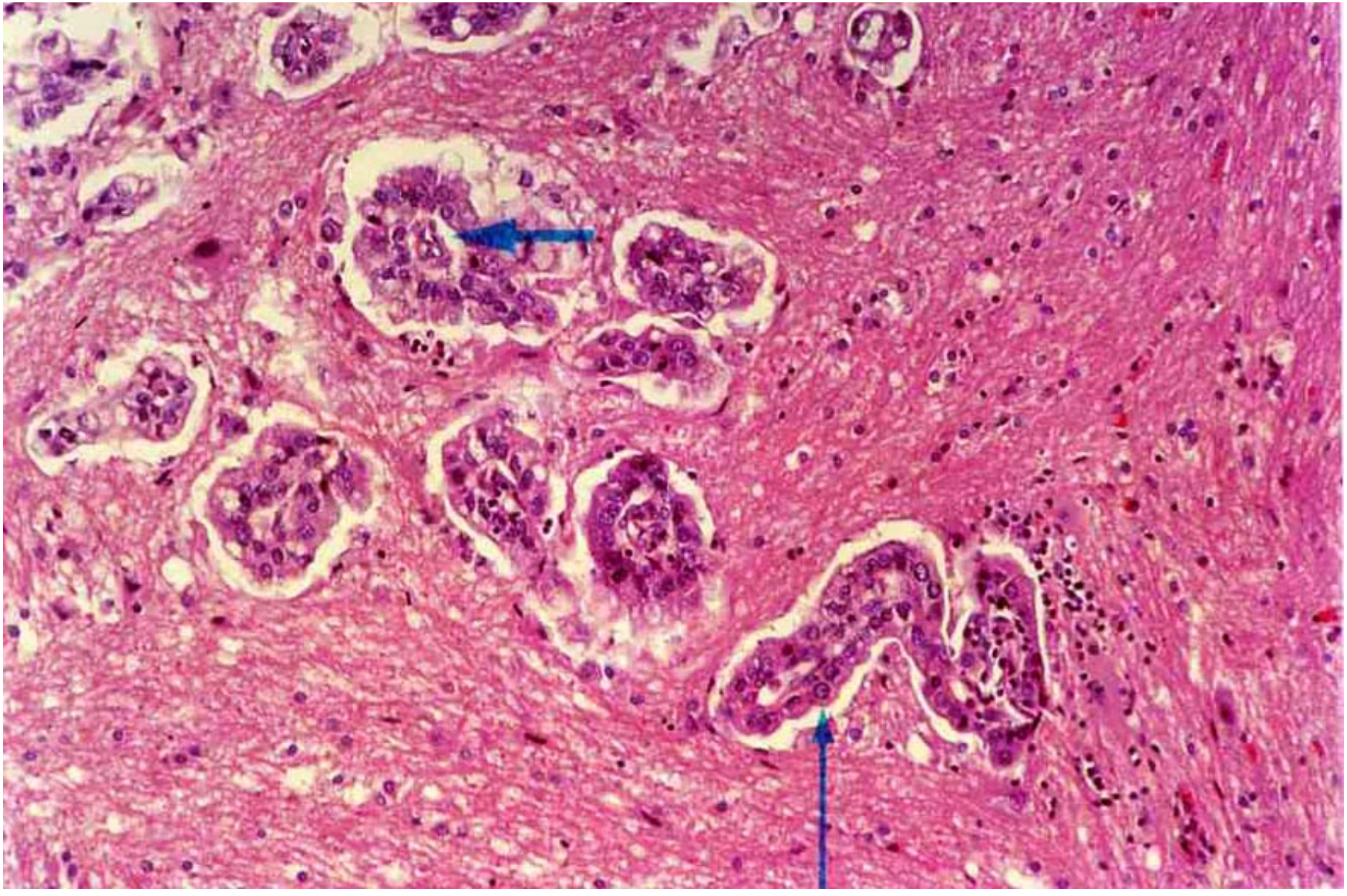


F 9-76: **Secondary carcinoma: brain.**
The patient had carcinoma of the **breast**. Frontal region section shows two large necrotic secondary deposits in the central white matter of both cerebral hemispheres.



9.76 Secondary carcinoma: brain

◘ 4.47: **Breast carcinomatous secondaries in the brain.**
Well-differentiated , papillary adenocarcinomatous (thin arrow) tumor secondaries infiltrate the brain white matter.



F23-26: **Metastatic melanoma.** Metastatic tumors secondaries are **distinguished** grossly from most primary CNS tumors by their (1) ***multicentric*** **& their (2)** ***well-demarcated margins.***
☠The dark pigment in the **15** tumor secondaries in this brain section is characteristic of malignant melanoma. by the route of blood