The Central Nervous System: Tumors
The peripheral nervous system

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CNS tumors

Clinicopathological features:

CNS tumors do not metastasise to other organs

- (only infiltration of adjacent tissues and spreading through
- CSF pathways)

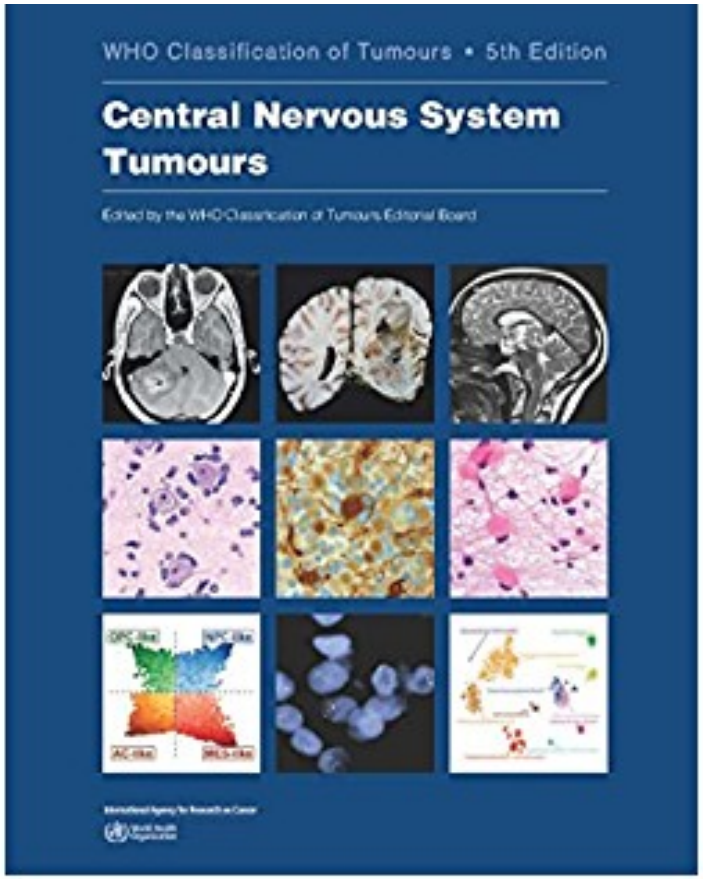
Local effects

- Signs related to the site of the tumor
- e.g. epilepsy with a temporal lobe tumor, paraplegias in spinal cord tumor

Mass effects

- Signs and symptoms of space occupying lesions
- Vasogenic oedema around CNS tumor
- Herniation
- Hydrocephalus in posterior fossa tumor

WHO classification of CNS tumours: 5th edition, 2021



Integrated diagnosis of CNS tumours:

- incorporation of phenotype and genotype

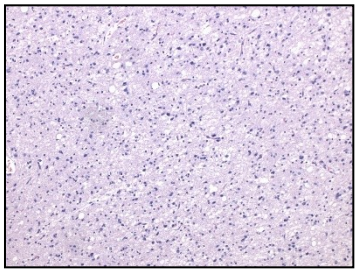
Histopathological diagnosis/typing

Histopathological grading/WHO grade

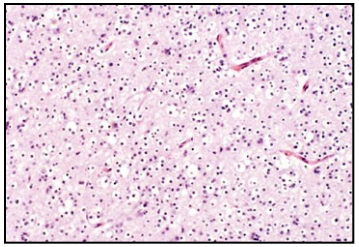
Molecular information

Phenotype of gliomas

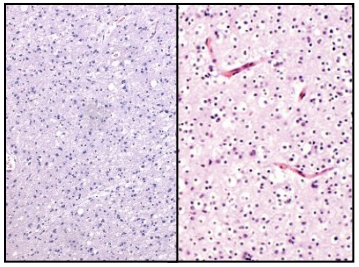
Astrocytic



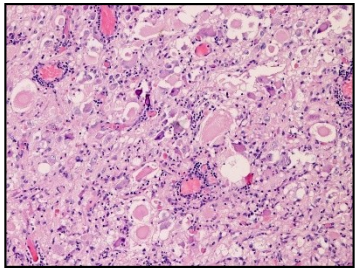
Oligodendrocytic



Oligoastrocytic

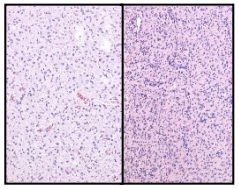


Glioneuronal

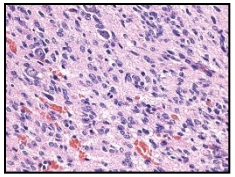


Grading of gliomas

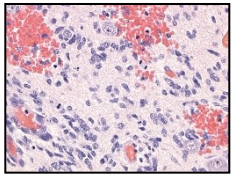
Cellularity



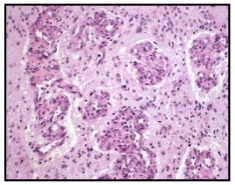
Cytonuclear atypia



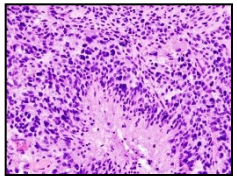
Mitoses



Microvascular proliferates



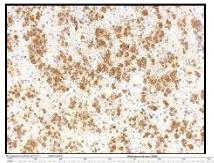
Necroses

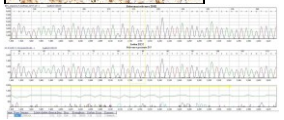


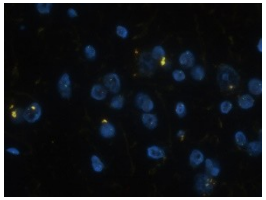
Genotype of gliomas

Mutations IDH1, IDH2

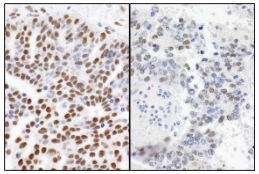
IDH: isocitratedehydrogenasis



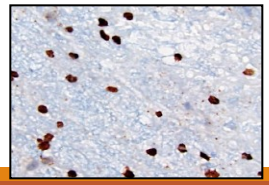




Codeletion 1p/19q



Mutation ATRX



Mutation H3K27M

Tumor of the CNS

Gliomas

Glioneuronal and neuronal tumours

Ependymal tumours

Chorioid plexus tumors (papillomas and carcinomas)

Embryonal tumors

Pineal tumors

Meningiomas

Other primary tumors of CNS

Secondary (metastatic tumors – lung, breast,…)

Gliomas

Adult-type diffuse gliomas

- astrocytoma, IDH mutant (WHO CNS grade 2-4)

- oligodendroglioma, IDH-mutant and 1p/19q-codeleted (WHO CNS grade 2,3)

- glioblastoma, IDH wildtype (WHO CNS grade 4)

(necrosis or microvascular proliferations or TERT promoter mutation or EGFR amplification or +7/-10 CNA)

Paediatric-type diffuse low-grade glioma (WHO CNS grade 1)

- diffuse astrocytoma MYB- or MYBL1-altered, MAPK pathway altered, ……

Paediatric-type diffuse high grade gliomas (WHO CNS grade 4)

- diffuse midline glioma H3 K27 altered

- diffuse hemispheric glioma, H3 G34 mutant

Circumscribed astrocytic gliomas

- pilocytic astrocytoma (G1), pleomorphic xantoastrocytoma (G2,3), subependymal giant cell astrocytoma (G1),…..

Low grade gliomas: grade 1,2
High grade gliomas: grade 3,4

Astrocytoma, IDH mutant, WHO CNS grade 2-4

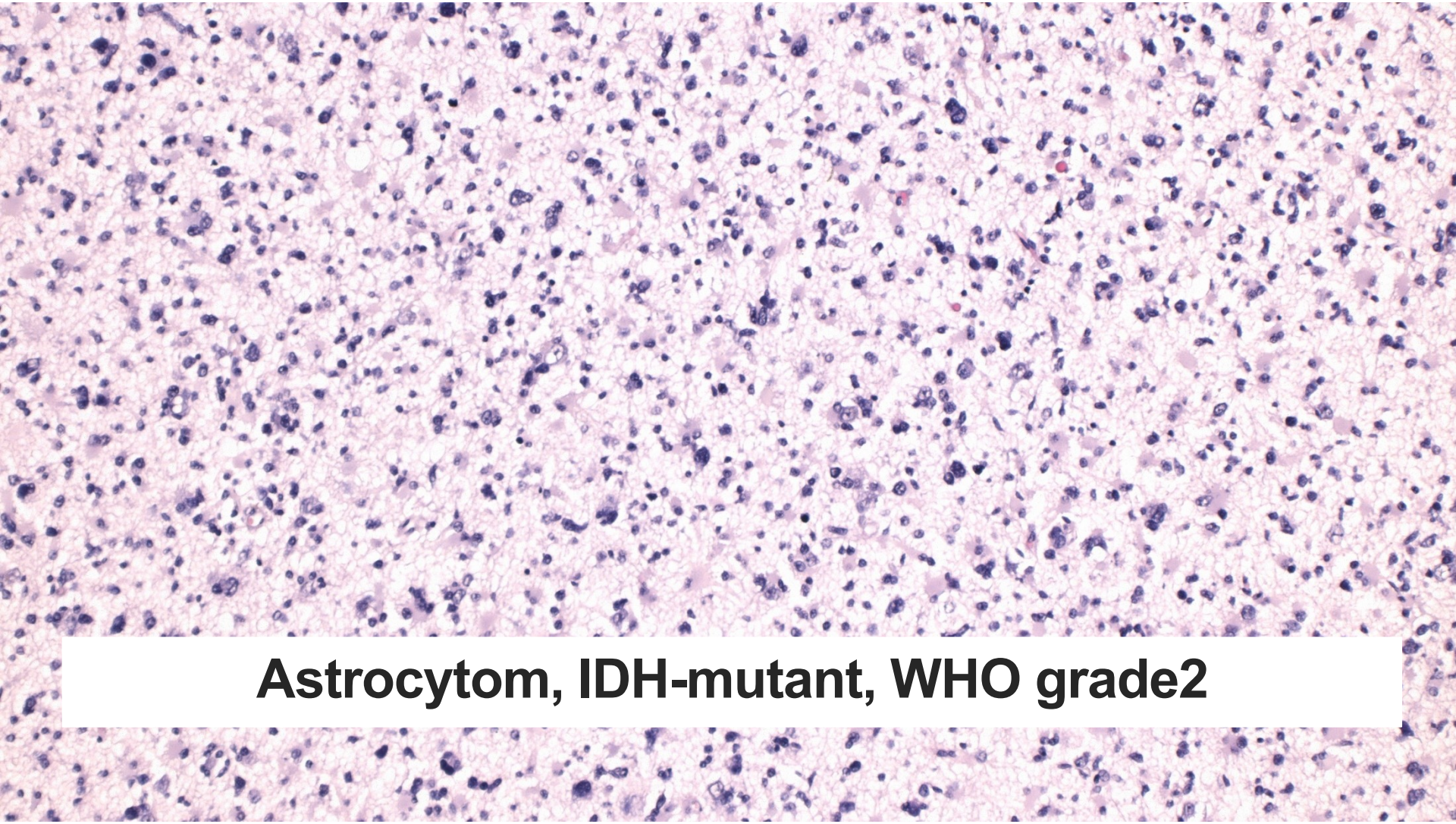
- Astrocytoma, IDH-mutant, is a diffusely infiltrating *IDH1*- or *IDH2*-mutant glioma with frequent *ATRX* and/or *TP53* mutation and absence of 1p/19q codeletion (CNS WHO grade 2, 3, or 4).
- Located in any region of the CNS, including the brainstem and spinal cord, but they most commonly develop in the supratentorial compartment and are usually centred near or within the frontal lobes
- IDH-mutant astrocytomas range from well-differentiated, low-cell-density, and slow-growing tumours (CNS WHO grade 2) to highly anaplastic, hypercellular, and rapidly progressive tumours (CNS WHO grade 4).

Previous classification: WHO 2016 versus WHO 2021

most diffuse astrocytoma G2 → astrocytoma, IDH mutant, G2

most anaplastic astrocytoma G3 → astrocytoma, IDH mutant, G3

most secondary glioblastoma G4 → astrocytoma, IDH mutant, G4



Astrocytom, IDH-mutant, WHO grade2

Oligodendroglioma, IDH-mutant and 1p/19q-codeleted

Oligodendroglioma, IDH-mutant and 1p/19q-codeleted, is a diffusely infiltrating glioma with *IDH1* or *IDH2* mutation and codeletion of chromosome arms 1p and 19q (CNS WHO grade 2 or 3).

White matter of cerebral hemispheres (most frequently frontal lobes)

Well circumscribed, gelatinous, gray masses, with cysts, hemorrhage, calcification

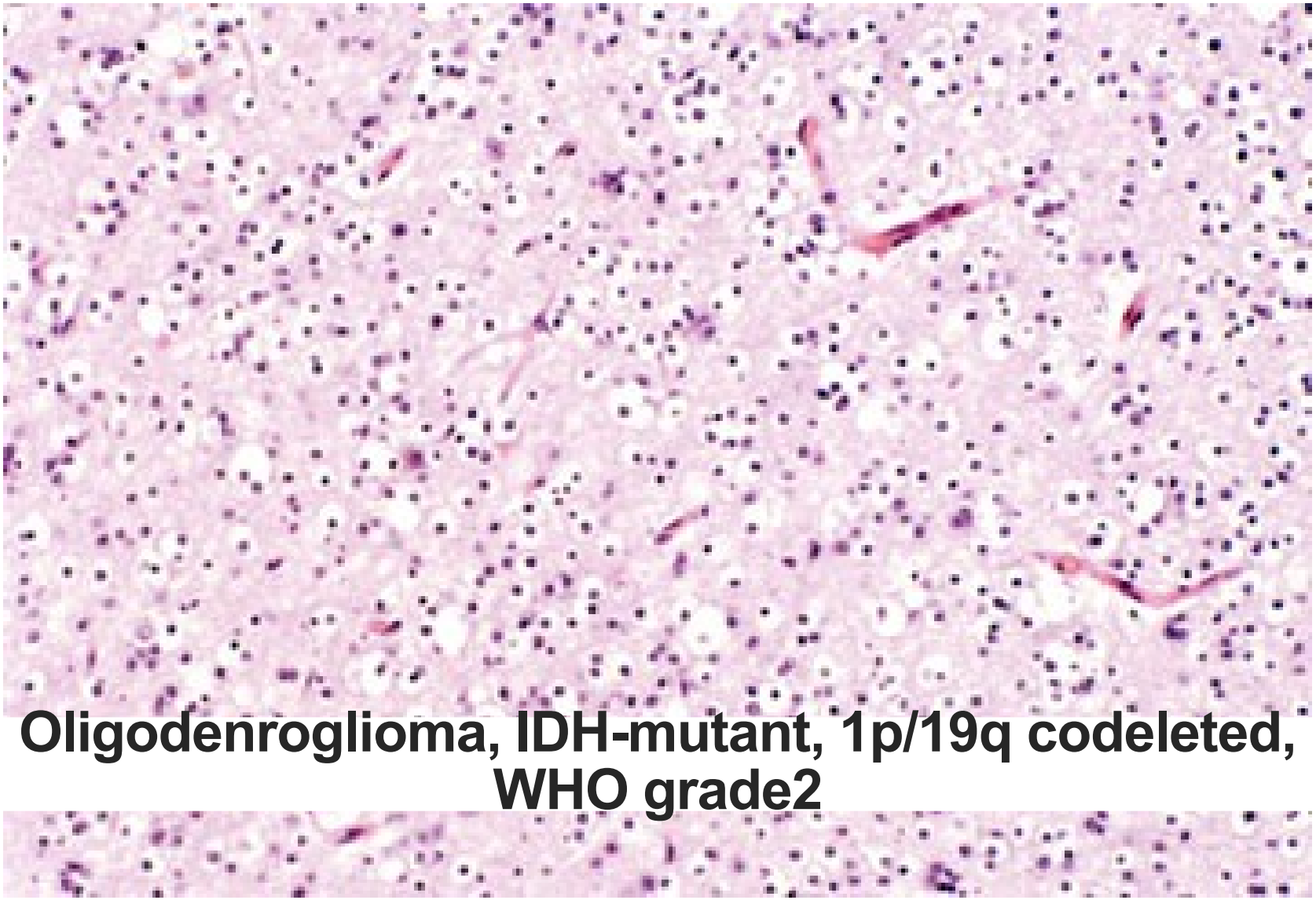
Sheets of regular cells, clear halo of cytoplasm

Delicate network of anastomosing capillaries

Perineuronal satellitosis

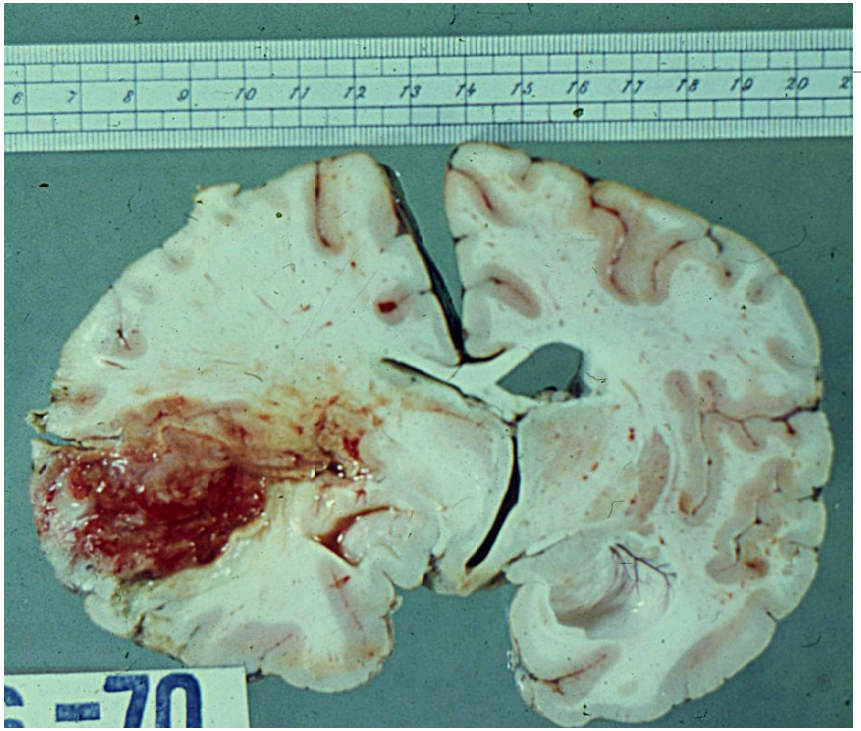
Better prognosis than AC

Grade 3 oligodendroglioma: necrosis, MVP, or substantial mitotic activity

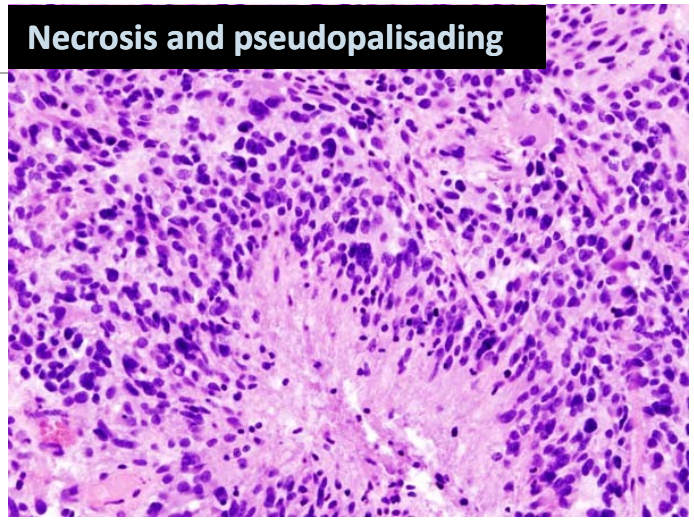


Oligodenroglioma, IDH-mutant, 1p/19q codeleted, WHO grade2

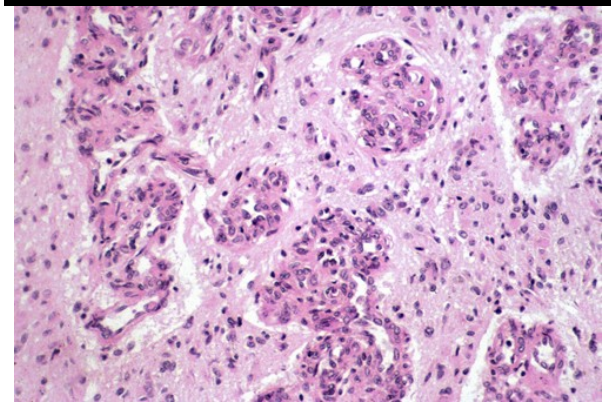
Glioblastoma (GBM), IDH-wildtype, WHO CNS G4



Necrosis and pseudopalisading



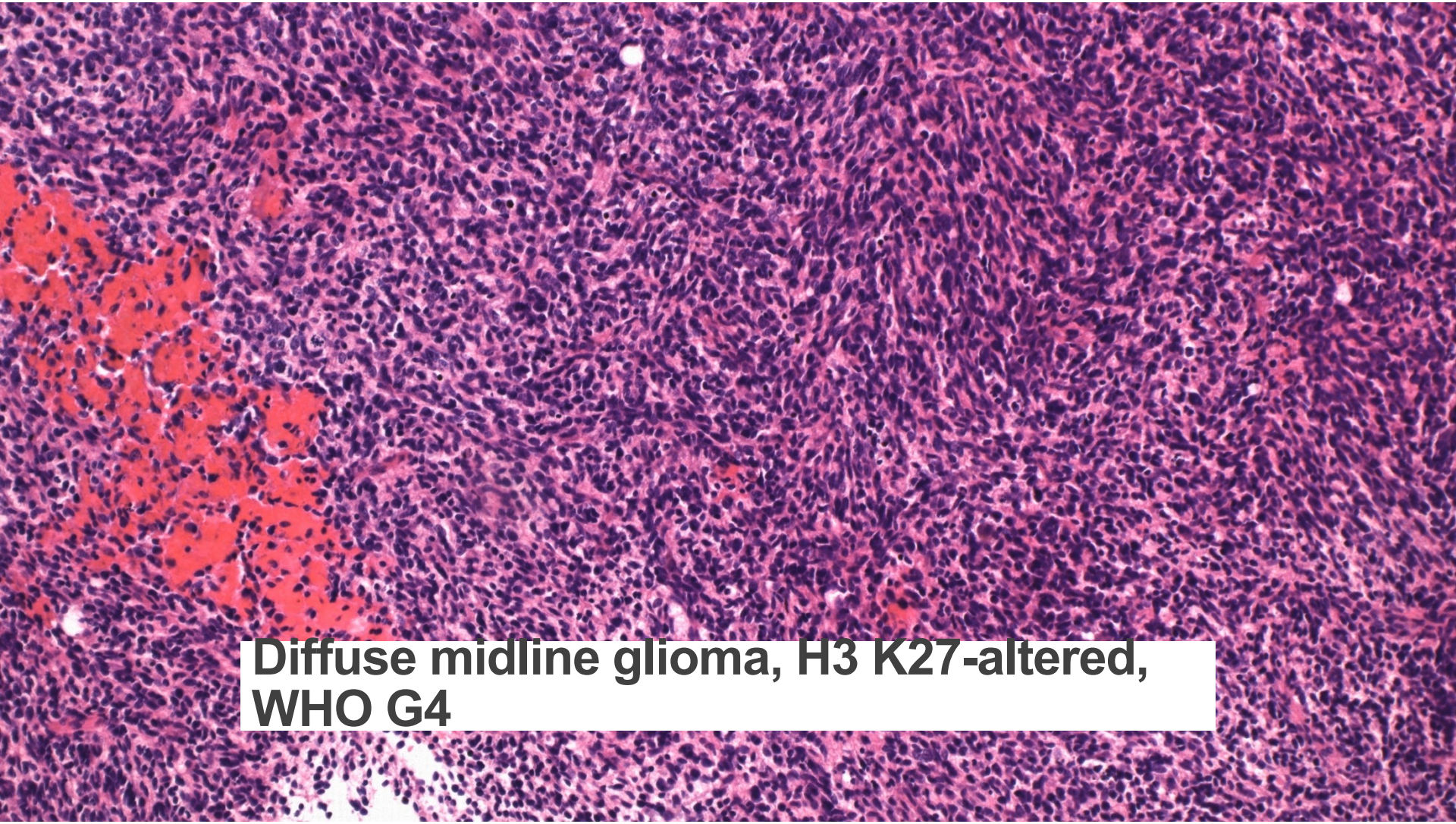
Microvascular endothelial proliferation



Diagnostic features:

- IDH wildtype diffuse glioma, non-midline
- necrosis or microvascular proliferation
- or molecular features of GBM

  EGFR amplification or TERTp mut or +7/-10 CNA


Diffuse midline glioma, H3 K27-altered, WHO G4

Circumscribed astrocytic gliomas

Pilocytic astrocytoma (WHO grade 1)

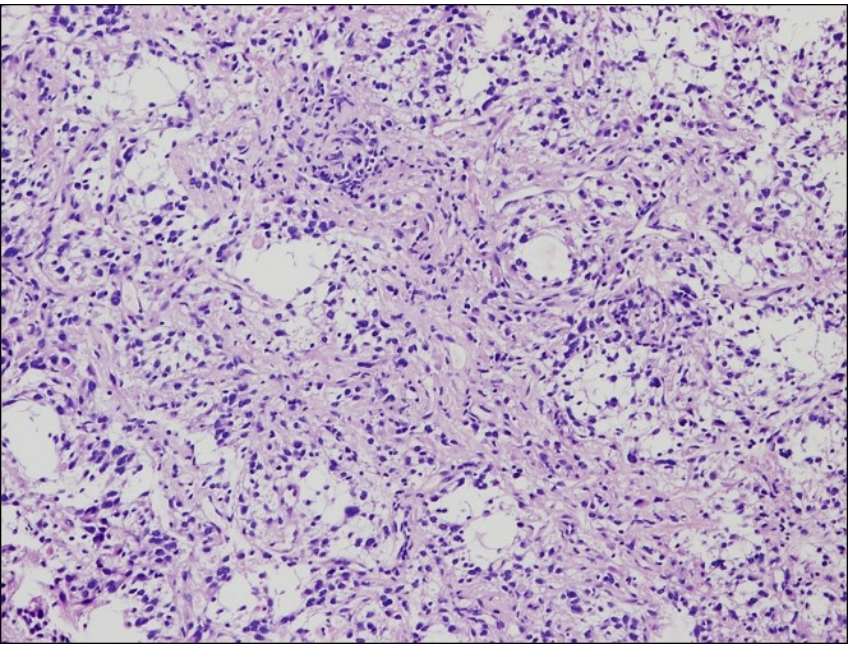
- Often cystic, also solid
- Usually circumscribed, arising from optic nerve to conus medullaris
- Bipolar cells („hair cells“) + Rosenthal fibers and eosinophilic granular bodies
- Often biphasic (fibrillary areas + loose microcystic pattern)
- Usually first two decades

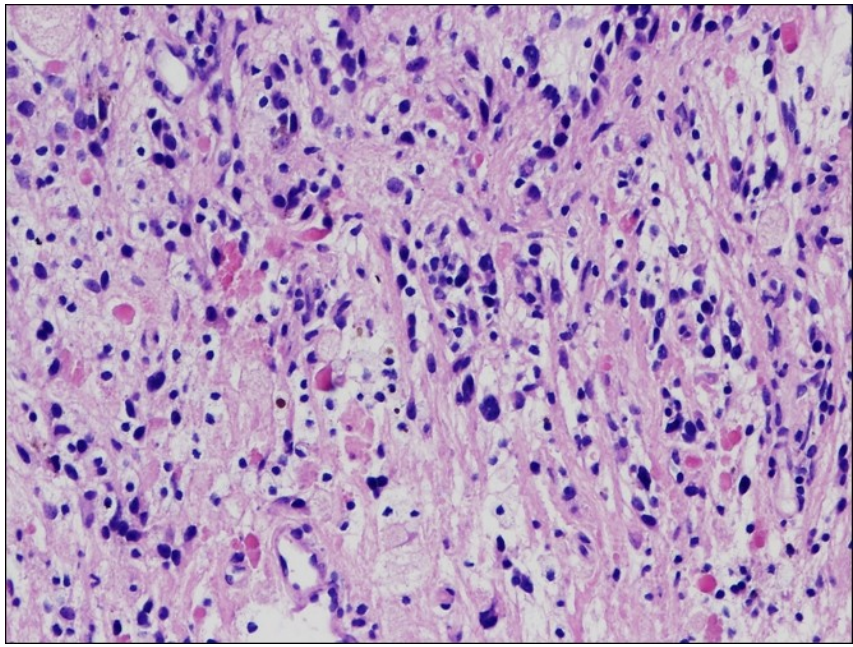
Pleomorphic xantoastrocytoma (WHO grade 2 or 3 (anaplastic)

- Temporal lobe of children and young adults
- Neoplastic occasionally bizarre astrocytes, also lipidized
- Necrosis and mitotic activity indicate higher grade

Subependymal giant cell astrocytoma (WHO grade 1)

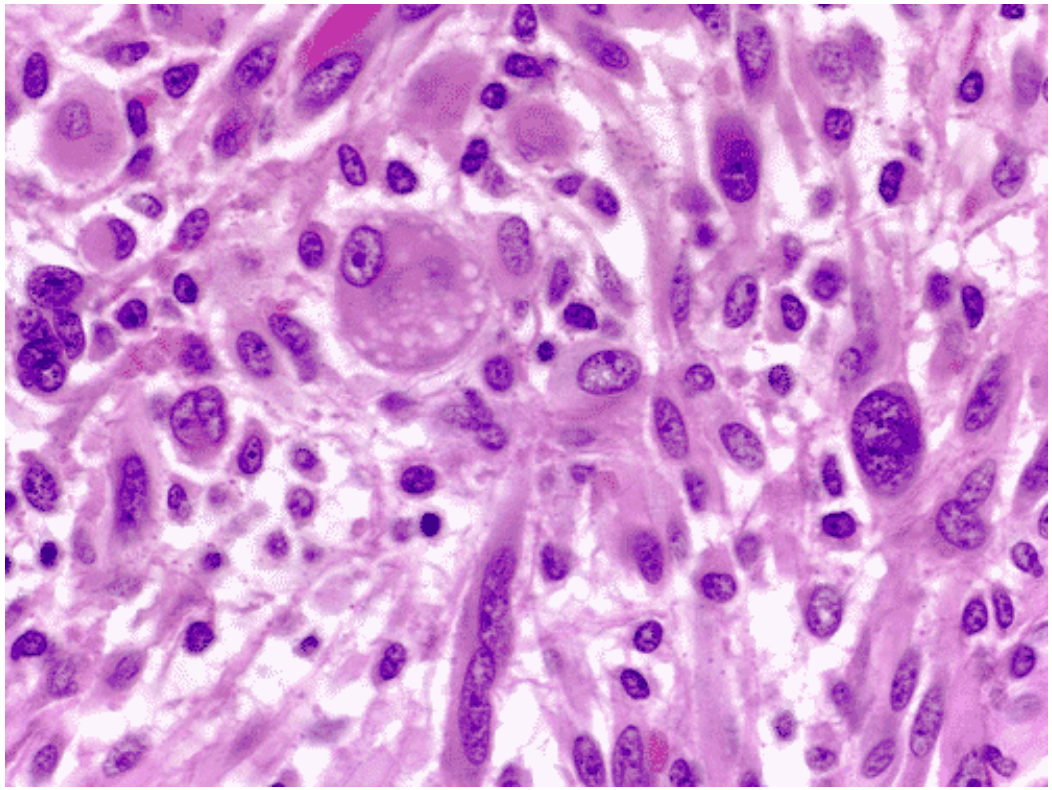
Pilocytic astrocytoma





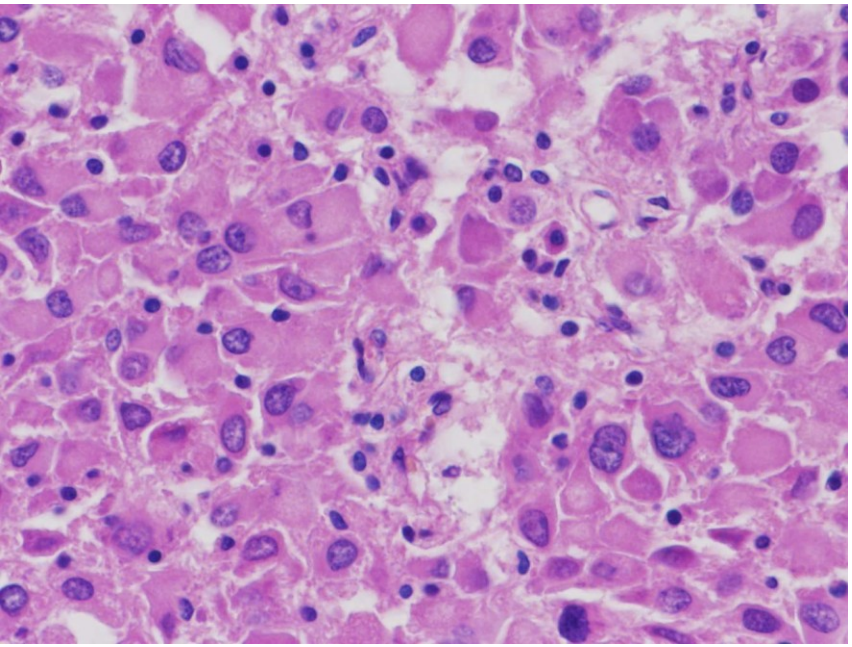
- WHO GI, relatively circumscribed, slowly growing, often cystic
- histologically biphasic pattern (compacted bipolar cells and loose-textured multipolar cells + Rosenthal fibers and eosinophilic granular bodies)

Pleomorphic xantoastrocytoma

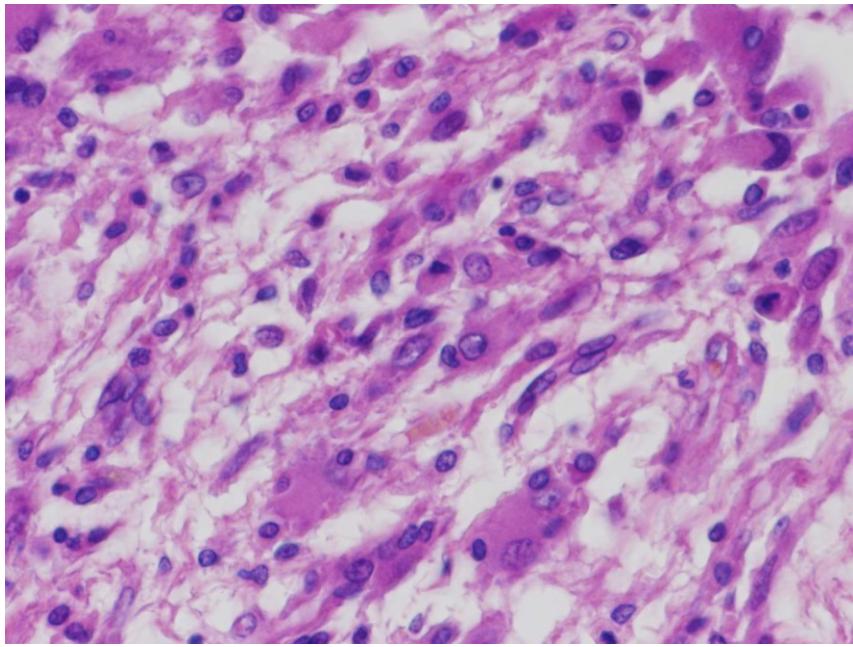


- superficial localisations in cerebral hemispheres + involvement of meninges
- pleomorphic lipidized cells

Subependymal giant cell xanthoastrocytoma



Pleomorphic eosinophilic tumour cells



Elongated tumour cells forming streams

- WHO G1; tuberous sclerosis complex
- benign, slowly growing, arising in the wall of the lateral ventricles, composed of the large ganglioid astrocytes

Neuronal and mixed (glio)neuronal tumors

Gangliogliomas (G1, rare G2, 3)

Dysembryoblastic neuroepithelial tumor (DNET), G1

- In temporal lobe
- Associated with epilepsy
- Usually grade I; gangliogliomas may be gr. II/III

Dysplastic gangliocytoma of the cerebellum (G1)

Central neurocytoma (G2)

- LG neuronal neoplasms
- Within vetricular system

Spectrum of long-term epilepsy associated tumors

Usually low grade, well differentiated, with low proliferating activity and low malignant potential, superficially localized (cortical or subcortical; frontal and temporal localization)**, mixed neuronal-glial tumors, expression of stem cell marker CD34**

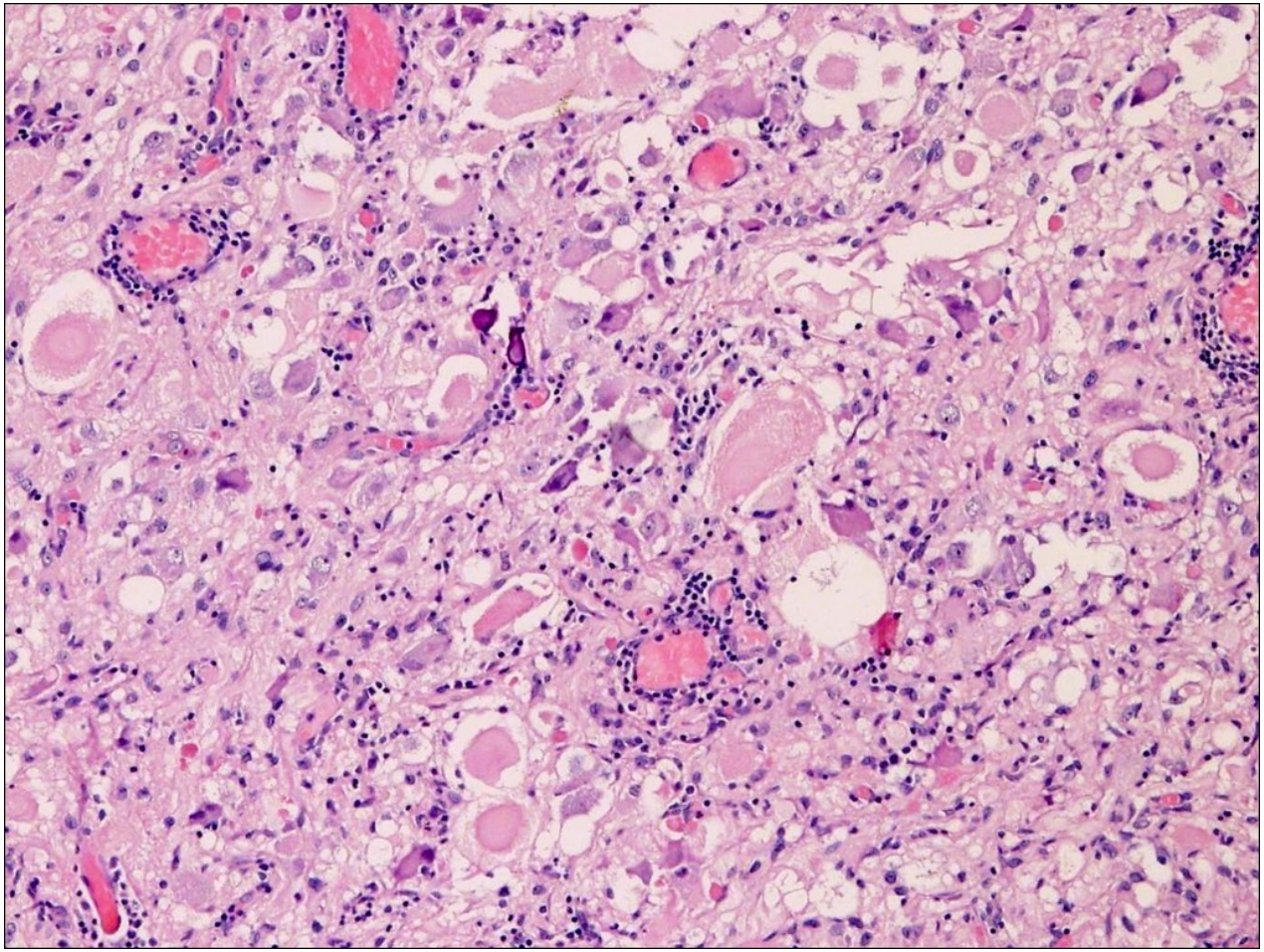
Mixed neuronal-glial tumors :

- Ganglioglioma
- Dysembryoplastic neuroepithelial tumor (DNET)

Others:

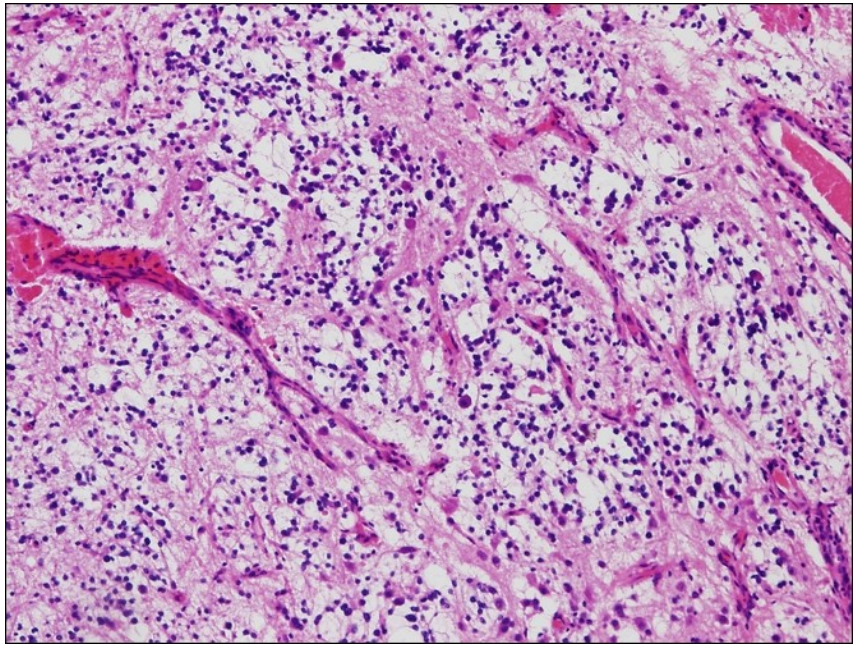
- Pilocytic astrocytoma
- Astrocytoma
- Oligodendroglioma
- Pleomorphic xanthoastrocytoma
- Subependymal giant cell astrocytoma
- Angiocentric glioma

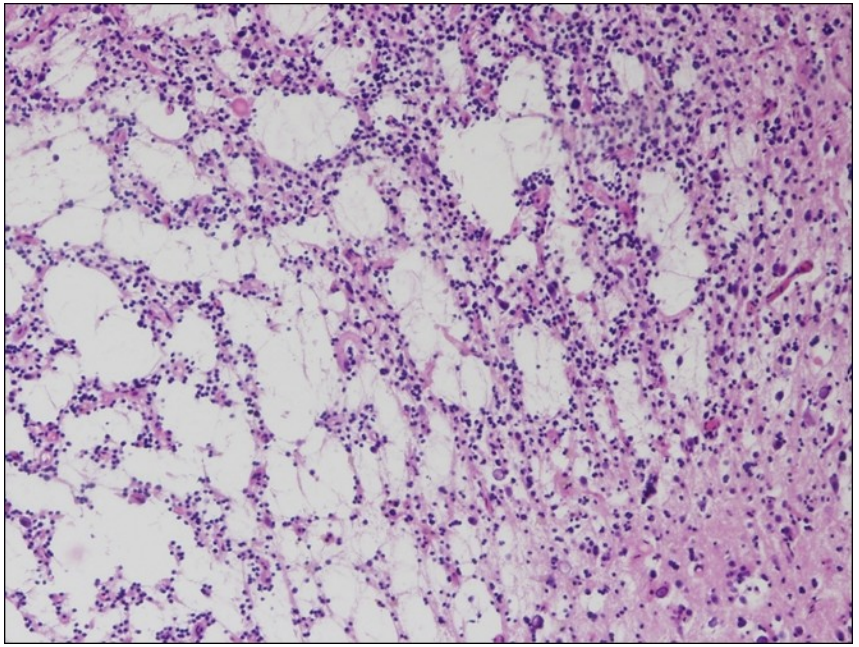
Gangliоglioma



- well differentiated, slowly growing neuroepithelial tumor
- neoplastic ganglion cells + neoplastic glial cells
- WHO GI; higher grades very rare; >70 % in temporal lobe

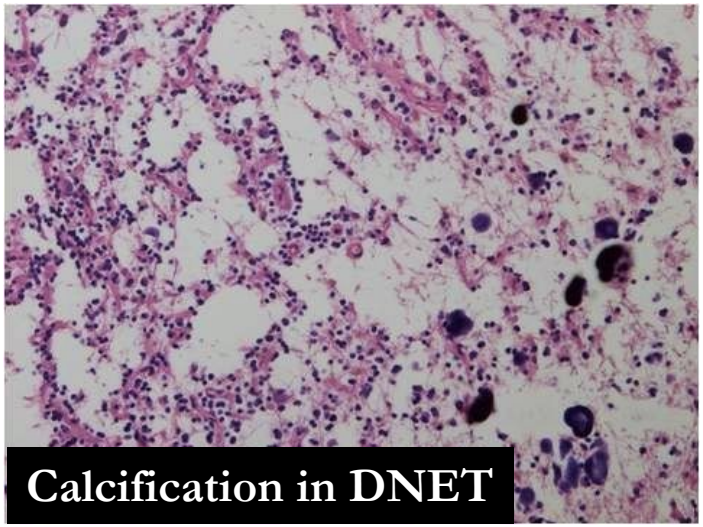
Dysembryoplastic neuroepithelial tumor (DNET)



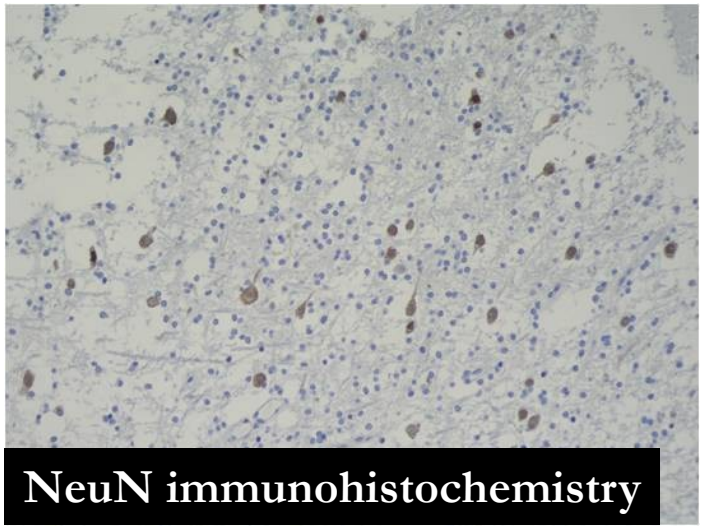


- WHO GI, benign, usually supratentorial glial-neuronal neoplasms
- in children and young adults
- cortical location
- complex columnar and multinodular architecture, „specific glioneuronal elements“ (bundles of axons lined by oligodendroglia-like cells+floating neurons)

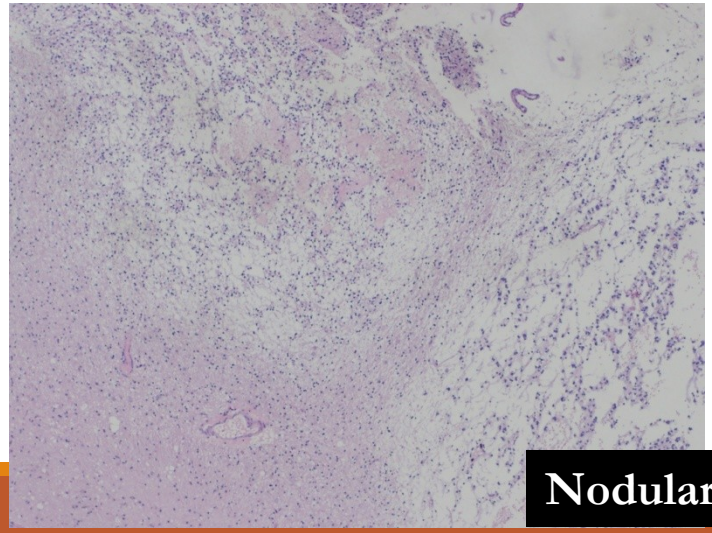
DNET



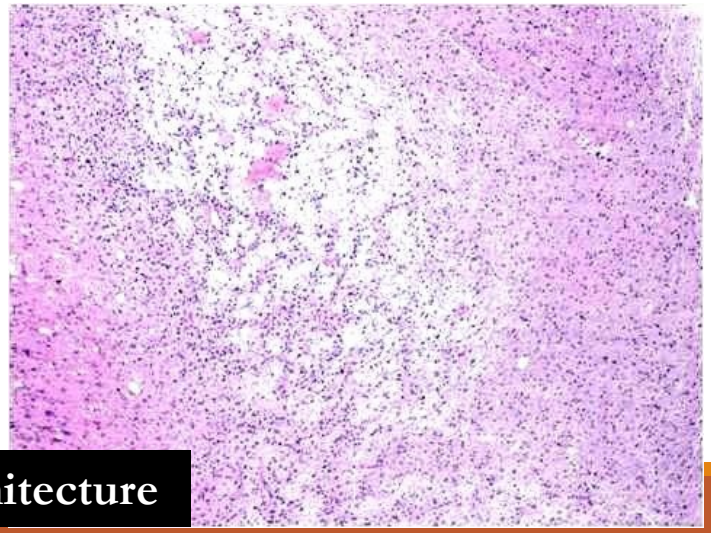
Calcification in DNET



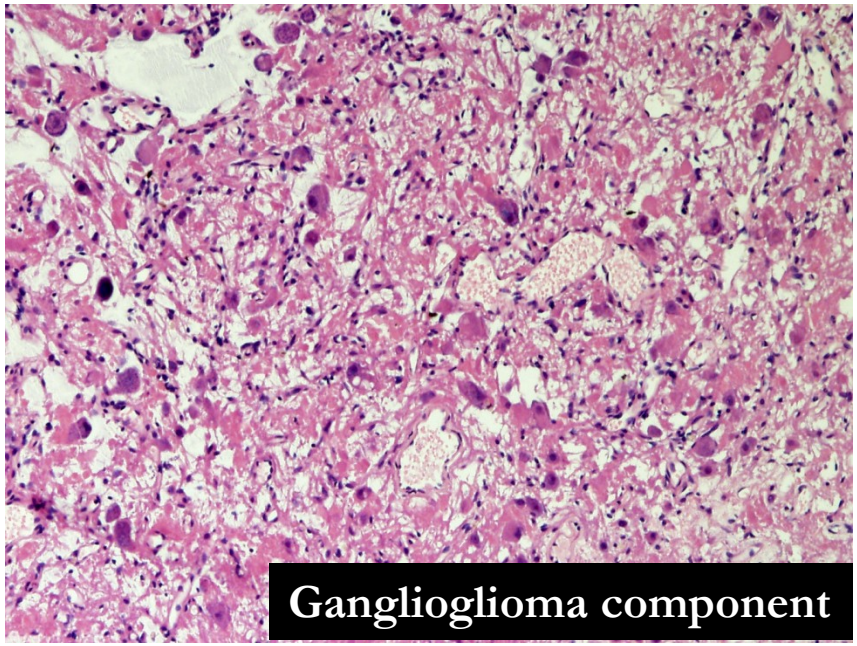
NeuN immunohistochemistry

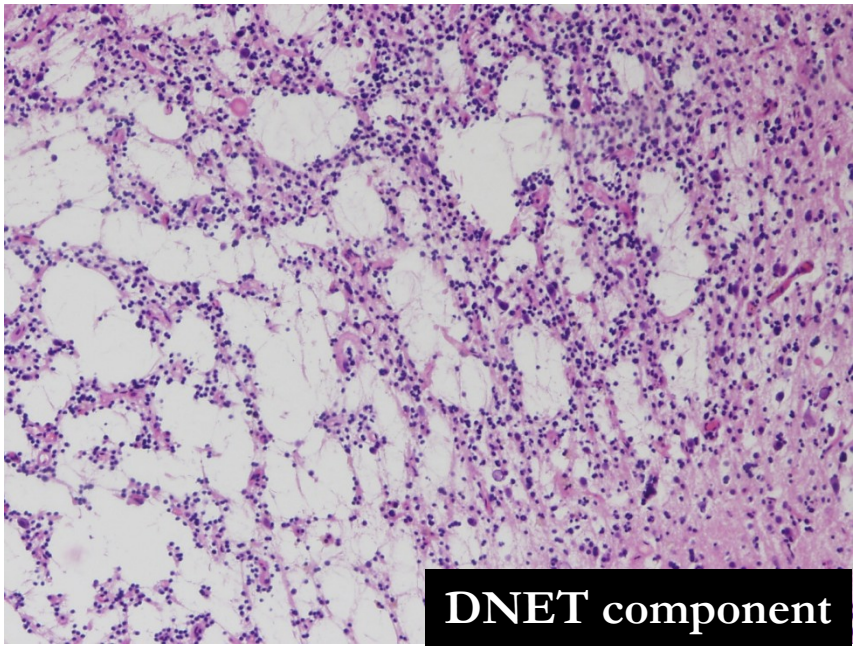


Nodular architecture

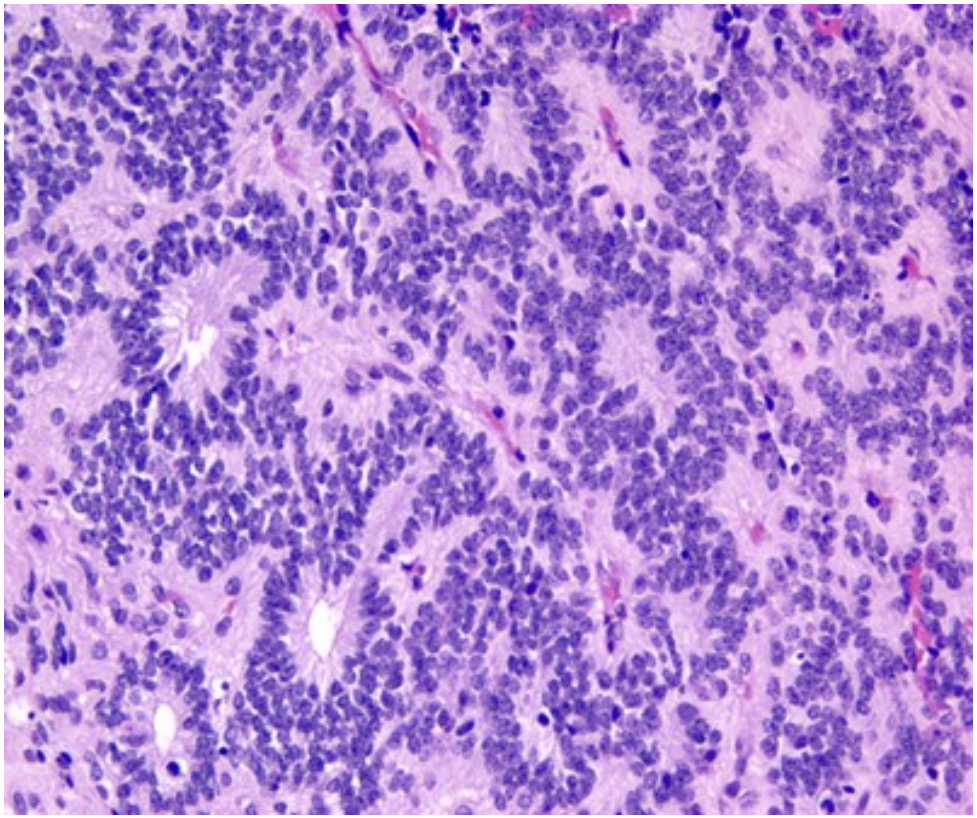


Composite glioneuronal tumour:
DNET and ganglioglioma component





Ependymoma



- classified according to a combination of histopathological and molecular features and anatomical site

- supratentorial ependymoma
- two molecularly defined types of posterior fossa ependymoma
- spinal tumour

WHO G2, 3

Separate entities:

- Myxopapillary ependymoma (G2)
- Subependymoma (G1)

Medulloblastoma (G 4)

Embryonal tumor

20 % of brain tumors in children

In the midline of cerebellum; 4th ventricle, hydrocephalus

Well circumscribed, grey

hypercellular, „small blue cells“, neuroblastic rosettes (Homer Wright rosettes)

High proliferation, mitoses

Expression of neuronal markers (synaptophysin, NF; GFAP+ cells, vimentin)

Dissemination through the CSF

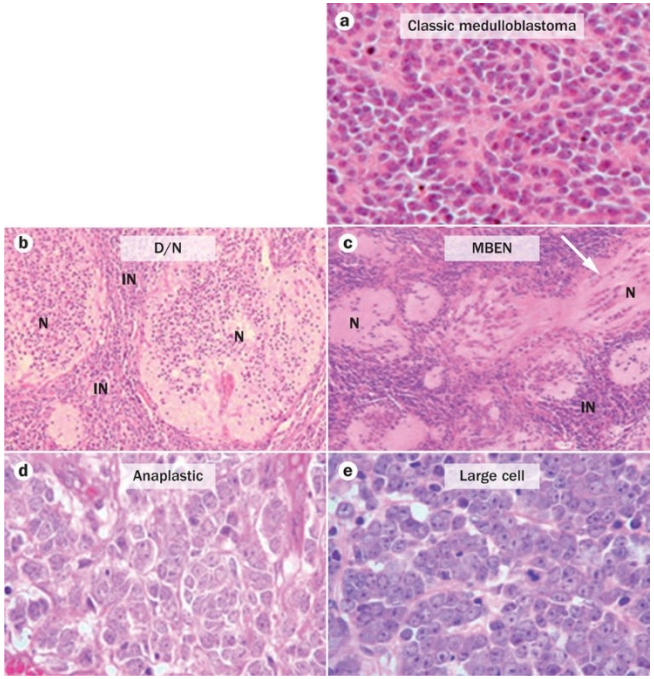
4 histological subtypes; 4 molecular subtypes

Prognosis in untreated dismal; with total excision and irradiation: 5-year survival rate as high as 75 %

Integrated diagnosis of medulloblastomas:

- histopathological diagnosis/typing
- genetic profiling – 4 molecular subtypes

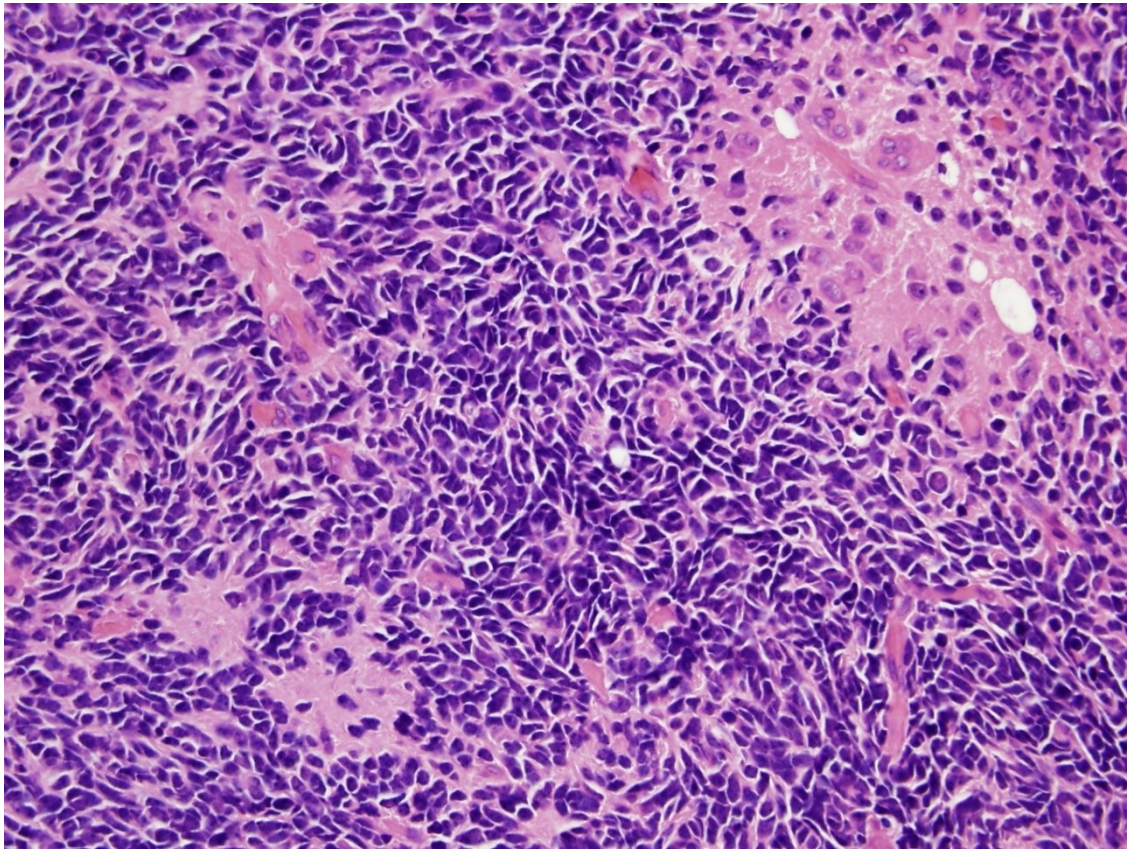
Genetic profile	Histology	Prognosis
Medulloblastoma, WNT-activated	Classic	Low-risk tumour; classic morphology found in almost all WNT-activated tumours
	Large cell / anaplastic (very rare)	Tumour of uncertain clinicopathological significance
Medulloblastoma, SHH-activated, *TP53*-mutant	Classic	Uncommon high-risk tumour
	Large cell / anaplastic	High-risk tumour; prevalent in children aged 7–17 years
	Desmoplastic / nodular (very rare)	Tumour of uncertain clinicopathological significance
Medulloblastoma, SHH-activated, *TP53*-wildtype	Classic	Standard-risk tumour
	Large cell / anaplastic	Tumour of uncertain clinicopathological significance
	Desmoplastic / nodular	Low-risk tumour in infants; prevalent in infants and adults
	Extensive nodularity	Low-risk tumour of infancy
Medulloblastoma, non-WNT/non-SHH, group 3	Classic	Standard-risk tumour
	Large cell / anaplastic	High-risk tumour
Medulloblastoma, non-WNT/non-SHH, group 4	Classic	Standard-risk tumour; classic morphology found in almost all group 4 tumours
	Large cell / anaplastic (rare)	Tumour of uncertain clinicopathological significance



Histological subtypes of medulloblastomas

- Classic medulloblastoma
- Desmoplastic/nodular medulloblastoma
- Medulloblastoma with extensive nodularity
- Large cell / anaplastic medulloblastoma

Medulloblastoma



Other embryonal tumors/ WHO G 4

Atypical teratoid/rhabdoid tumour

Cribriform neuroepithelial tumour

Embryonal tumour with multilayered rosettes

CNS neuroblastoma, FOXR2-activated

CNS tumour with BCOR internal tandem duplication

CNS embryonal tumour NEC/NOS

Other tumors of CNS

Primary CNS lymphomas (DLBCL)

Germ cell tumors

- Midline structures, pineal region, suprasellar region
- Teratomas; germinomas (similar to seminomas),…

Pineal parenchymal tumors

- Pinealoblastomas (high grade tumors)
- Pineocytomas (well differentiated)
- Gliomas in pineal region

Tumors of the meninges

Meningioma (meningothelial)

- nonmeningothelial

Meningeal hemangiopericytoma (so-called)

Solitary fibrous tumors

Meningioma (G1-3)

Usually well defined rounded masses, adjacent to dura; encapsulated, extension into bone (reactive hyperostotic changes); less common „en plaque“ growth

Grade 1 meningiomas:

- meningothelial
- fibroblastic
- transitional
- psammomatous
- microcystic, secretory, angiomatous,….

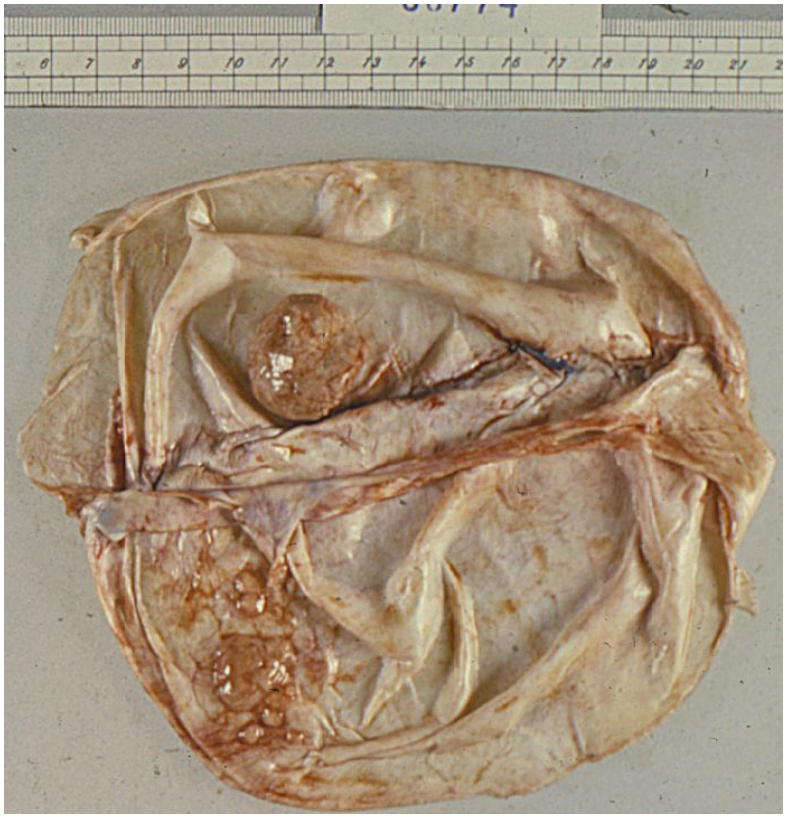
Grade 2 meningiomas:

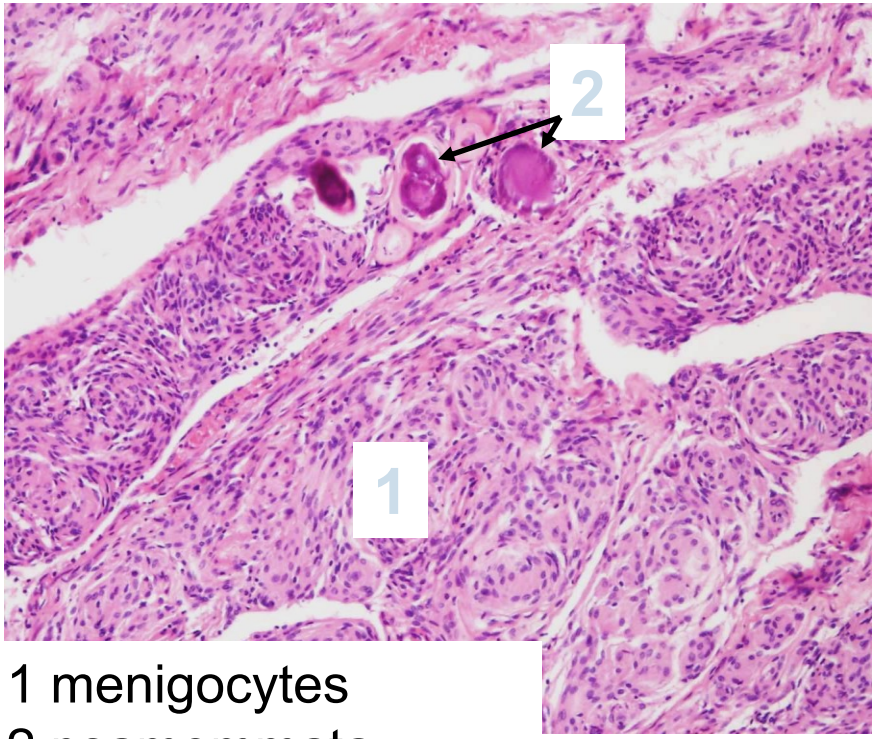
- atypical, clear cell, chordoid

Grade 3 meningiomas:

- anaplastic (malignant), rhabdoid, papillary

Meningioma





1 menigocytes
2 psamommata

Craniopharyngeoma:

- Arise from squamous cell rests (derived from Rathke pouch) in sellar region
- Benign (G 1), partly cystic epithelial tumor

Hemangioblastoma:

- Sporadic or ass. with VHL sy (in younger)
- Cerebellum (medulla, spinal cord,…., supratentorial, retinal in VHL)
- Well circumscribed, cystic, with mural nodule(s)
- Capillary-size and larger thin-walled vessels with intervening neoplastic „stromal cells“ (large polygonal, vacuolated, lipid-rich, PAS+)

Familial tumor syndromes with involvement of tumor suppressor gene (AD)

Cowden syndrome

- *PTEN* mutation
- Dysplastic gangliocytoma of the cerebellum

Li Fraumeni syndrome

- Inactivation of p53
- Medulloblastoma

Turcot syndrome

- Mutations in *APC* or mismatch repair gene
- Medulloblastoma or glioblastoma

Gorlin syndrome

- *PTCH* mutations, upregulation of SHH
- medulloblastoma

Neurofibromatosis type I

- AD; neurofibromas (plexiform and solitary)+gliomas of optic nerve+pigmented nodules of iris-cutaneous hyperpigmented macules *(café au lait spots)*
- Malignant transformation of neurofibromas
- *NF1* gene (17q11.2); neurofibromin

Neurofibromatosis type II

- AD; 8th nerve schwannomas and multiple meningiomas + gliomas, ependymomas of spinal cord + non-neoplastic lesions of Schwann cells, meningeal cells, hamartia
- *NF2* gene (22q12); merlin

Tuberous sclerosis complex

- AD; hamartomas and benign tumors of the brain and other tissues: cortical tubers (epileptogenic), subependymal nodules, subependymal giant cell astrocytomas,…, + renal angiomyolipomas, retinal glial hamartomas, pulmonary lympangioleiomyomatosis, cardiac rhabdomyoma + cysts – cutaneous lesions (angiofibromas, subungual fibromas, hypopigmented lesions)
- tuberin or hamartin genes mutated

Von Hippel Lindau Disease

- AD; hemangioblastomas + cysts (pancreas, liver, kidney) + renal carcinomas, pheochromocytomas tumor suppressor gene – pVHL – 3p25-p26

Peripheral nerve sheath tumors

Schwannoma

- benign, from neural crest-derived Schwann cell, component of NF2
- well circumscribed, encapsulated, attached to nerve; 2 patterns: Antoni A and Antoni B
- often vestibular branch of 8th nerve; sensory nerves preferentially involved (trigeminus, dorsal roots,..); extradurally – large nerve trunks

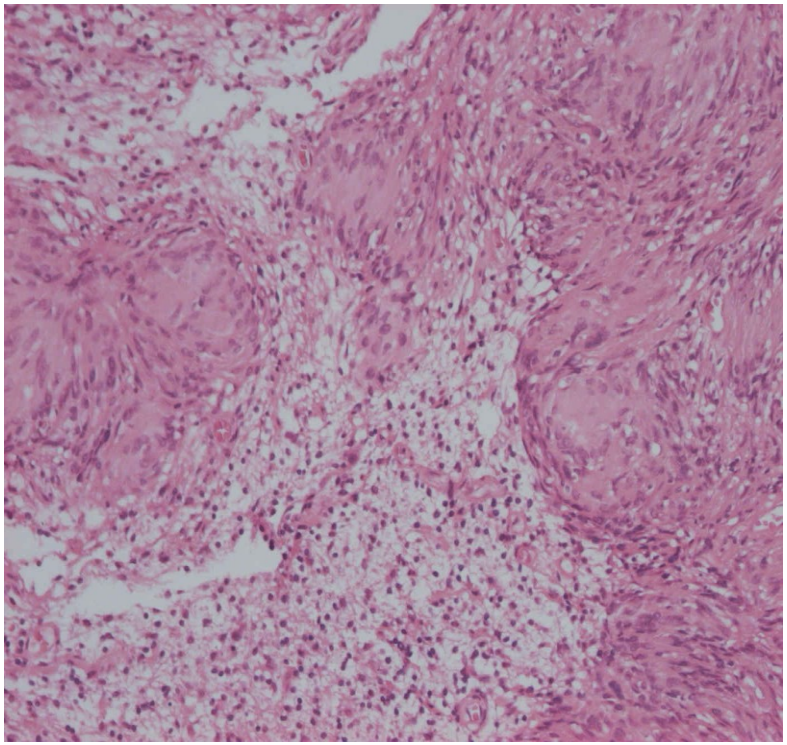
Malignant peripheral nerve sheath tumor

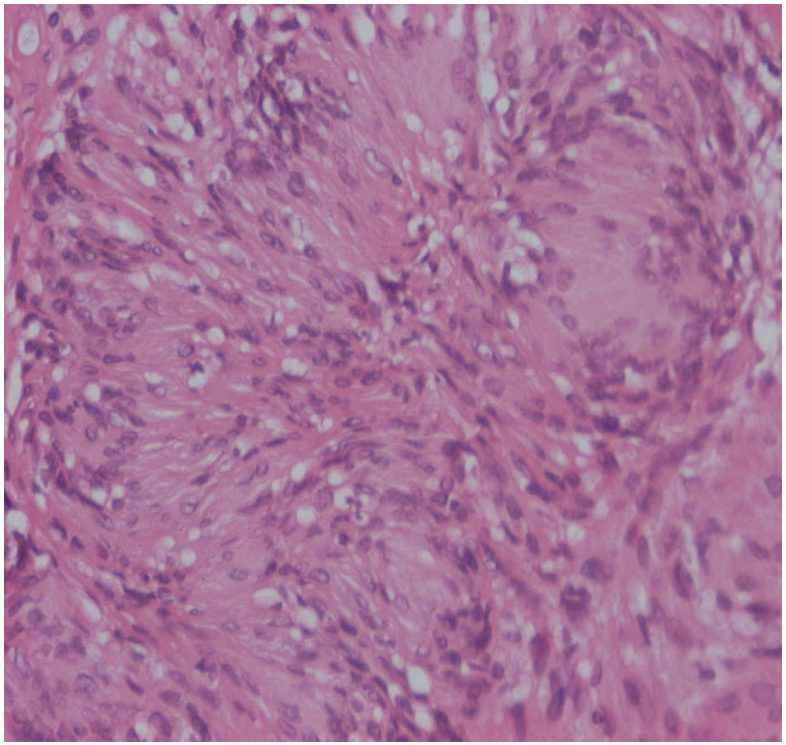
- highly malignant, medium and large nerves affected; in NF1

Neurofibroma:

- Cutaneous: localized, in dermis or subcucateously
- Plexiform: infiltrating lesion growing within and expanding a peripheral nerve; NF1; potential for malignant transofrmation; significant neurologic deficits

Schwannoma





Diseases of peripheral nerves

Inflammatory neuropathies

Infectious polyneuropathies

Hereditary neuropathies

Acquired metabolic and toxic neuropathies

Traumatic neuropathies

Inflammatory neuropathies

Immune mediated neuropathies: Guillain-Barré syndrome – GBS (acute inflammatory demyelinating polyradiculoneuropathy)

- Weakness in distal limbs, ascending paralysis, hospital intensive care before recovering normal function (up to 20 % long term disability); in some patients followed by a subacute or chronic course
- Inflammation and demyelination of spinal nerve roots and peripheral nerves (radiculoneuropathy)
- Infections or prior vaccination ass. with GBS
- T-cell mediated immune response

Infectious polyneuropathies

Leprosy (Hansen disease)

- Lepromatous leprosy: Mycobacterium leprae invading Schwann cells
- Segmental demyelination, remyelination, loss of axons; endoneurial fibrosis and multilayered thickening of perineurial sheats
- Symmetric polyneuropthy; pain fibers (loss of sensation)
- Tuberculoid leprosy: cell-mediated immune response to M. leprae – granulomatous inflammation in dermis, cutaneous nerves affected

Diphteria (diphteria exotoxin; selective demyelination of axons)

Varicella zoster virus (varicella zoster virus; following chickenpox virus persists in neurons and sesory ganglia with potential ractivation)

Hereditary neuropathies

Hereditary motor and sensory neuropathies (HSMN I-III,….)

Hereditary sensory and autonomic neuropathies (HSANs)

Familial amyloid polyneuropathies

Peripheral neuropathy accompanying inherited metabolic disorders

HSMN

HSMN - Charcot-Marie-Tooth (peripheral myelin protein 22, myelin, connexin,…

- Demyelinating neuropathy; usually AD
- Repetitive de- and remyelinations (onion bulbs – Schwann cell hyperplasia)
- Slowly progressive, progressive muscular atrophy (legs), muscle weakness, pes cavus

HSMN II (kinesin family member KIF1B)

- Axonal form – loss of myelinated axons

HSMN III – Dejerine-Sottas neuropathy

- AR, genetically heterogeneous (the same genes as in HSMN I)
- Enlarged peripheral nerves, trunk and limb muscles affected

Acquired metabolic and toxic neuropathies

Peripheral neuropathy in adult onset diabetes mellitus (polyol pathway and nonenzymatic glycation of proteins involved)

- Distal symmetric sensory or sensorimotor neuropathy
- Autonomic neuropathy
- Focal or multifocal asymmetric neuropathy
- Loss of small myelinated fibers, also unmyelinated fibers
- Thickening of endoneurial arterioles

Metabolic and nutritional neuropathies

- Uremic neuropathy
- Chronic liver disease, respiratory insuf., thyroid dysfunction
- Thiamine deficiency (neuropathic beriberi)
- Avitaminosis B_{12}, B_6, and E

Neuropathies associated with malignancy

- Brachial plexopathy (apex of a lung), obturator palsy (pelvic tumors), cranial verve palsies (intracranial tumors,….)
- Paraneoplastic effect (small cell ca of lungs, plasmocytoma)

Toxic neuropathies

- Heavy metals, lead, arsenic

Tumors of autonomic nervous system

Extraadrenal paragangliomas (carotid body paragangliomas, vagal and other paragangliomas)

- non-chromaffin paragangliomas, usually related to parasympathetic nervous system
- Alveolar pattern, cell nests; chief cells and sustentakular cells
- Also malignant forms

Extraadrenal paragangliomas of sympathoadreal neuroendocrine system (anywhere from the pelvic floor to the neck)

Pheochromocytomas (adrenal paraganglioma) (production of katecholamins, hypertension, usually benign)

Gangliocytic paraganglioma (benign, in duodenum)

Tumors of autonomic nervous system

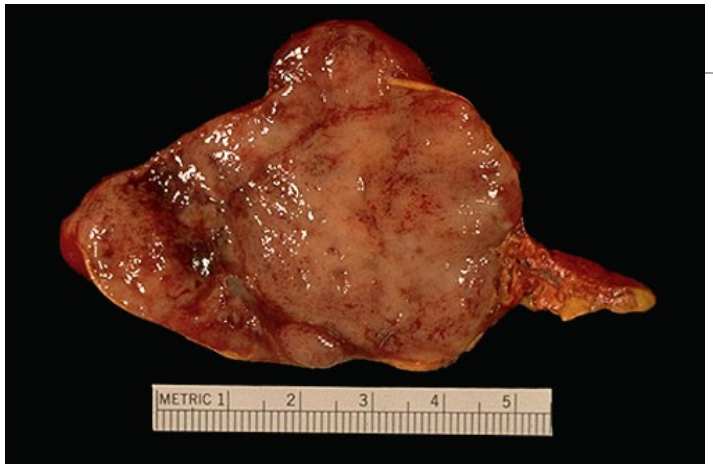
Neuroblastoma and ganglioneuroblastoma

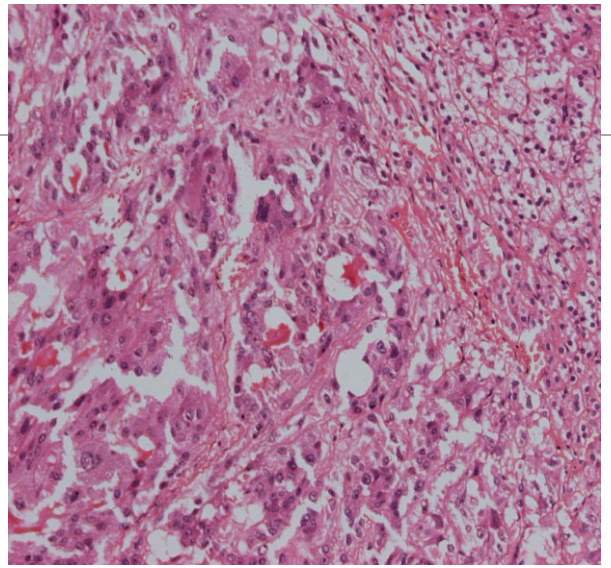
- In children under 4 ys (85 %)
- In adrenal gland or intra-abdominal sympathetic chain (70 %) and in thorax (at least 20 %)
- „Small blue cell“ tumor, bulky, multinodular, hemorrhages and necrosis often, calcification, also pseudocystic, lobular or nesting pattern, fibrillary material between cells (neuritic cell processes) – neurofibrillary matrix, rosettes, chromatin: „salt-and- pepper“ appearance
- Ganglioneuroblastoma – some cytodifferentiation or maturation with recognizable ganglion cells

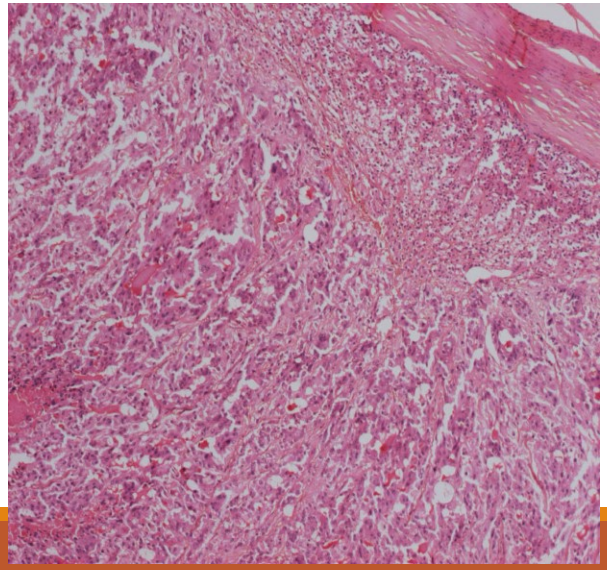
Ganglioneuroma

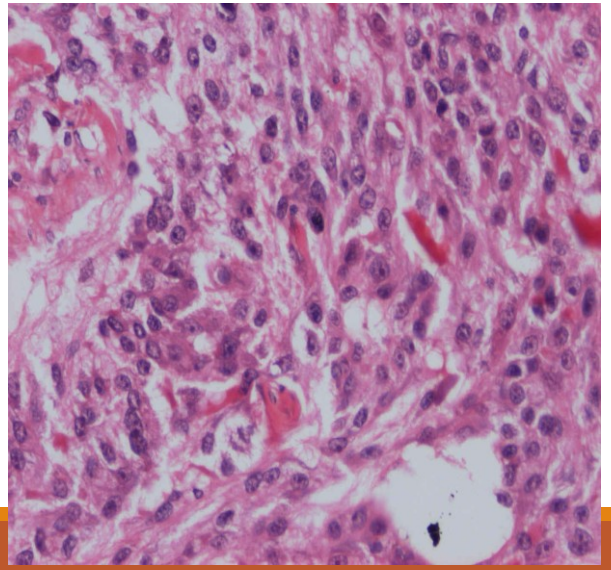
- In posterior mediastinum or retroperitoneum; some arising in adrenal gland
- Patient over 10 ys
- Well, circumscribed, with no necrosis or hemorrhages, on cut surface whorled or trabecular pattern
- Spindle cell matrix and mature ganglion cells

Pheochromocytoma

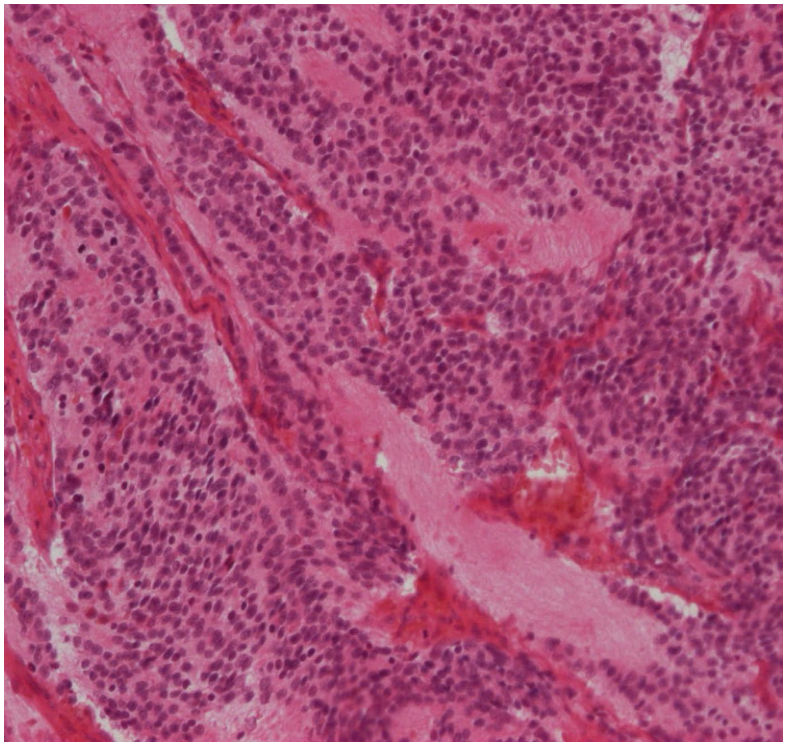


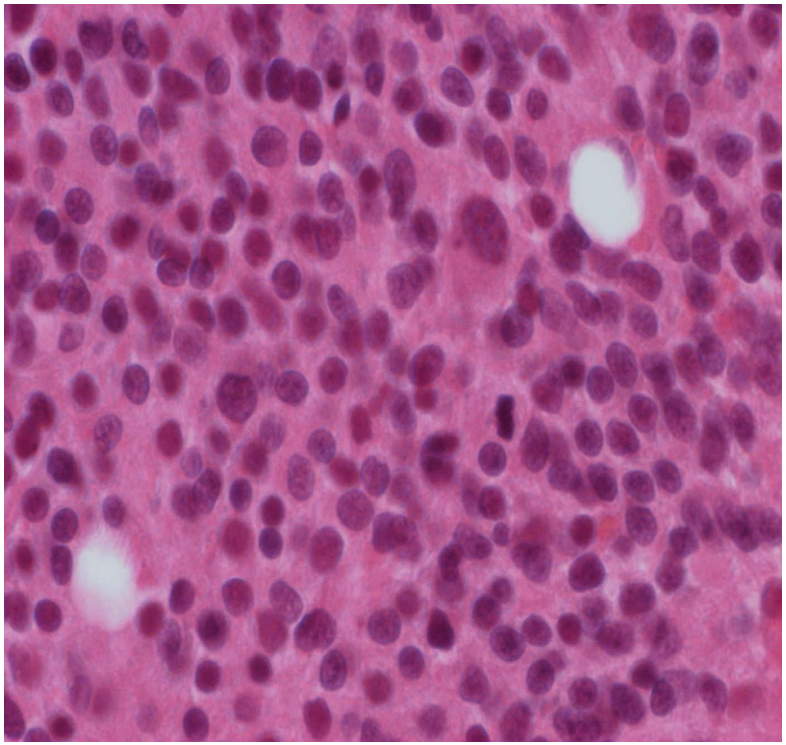






Neuroblastoma





Thank you for your attention …