Chapter

2

CNS Lesions

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Case History: A 35-year-old male with temporo-parietal SOL.

Diagnosis: Astrocytoma, IDHm, CNS WHO Grade 2

Imaging

CT shows a poorly defined, homogeneous low-density mass with calcification and cystic change.

Macroscopy

Expansile lesion that blur the grey matter-white matter junction, with cysts and/or calcification.

Microscopy

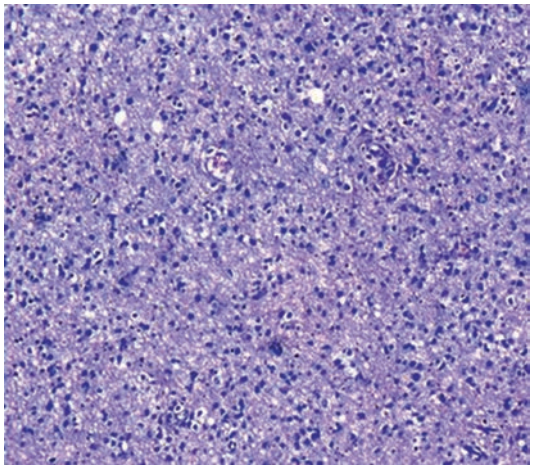


Fig. 2.1: Astrocytoma, IDHm, CNS WHO grade 2

1. Tumors are composed of well-differentiated fibrillary glial cells that diffusely infiltrate the CNS parenchyma. Cellularity is mild to moderate with mild nuclear atypia. Background shows a loosely structured, microcystic matrix. Mitosis is uncommon. A single mitosis in a resected specimen is compatible with CNS WHO grade.
2. Microvascular proliferation and necrosis are absent.

Ancillary Tests

- ***Immunohistochemistry:*** GFAP—positive, IDH1—positive, P53—positive, ATRX—loss of expression (negative), Ki-67 is <4%.
- Molecular—homozygous deletions of CDKN2A and/or CDKN2B are absent.

Differential Diagnosis

1. ***Normal brain:*** Cytoplasm of normal astrocytes, in contrast to astrocytoma cells, is not distinct from the background neurophil. Nuclei are small and regular, having delicate, uniform chromatin.
2. ***Reactive astrocytes:*** Have enlarged nuclei, clearly distinguished cytoplasm. Microcystic change favor neoplasia.
3. ***Oligodendroglioma:*** IDH—positive, P53—positive, ATRX is retained (positive), 1p19q codeleted by FISH.

4. ***Diffuse midline glioma, H3K27—altered:*** Ki-67 is high
5. Diffuse astrocytoma MYB—altered.

Case History: A 40-year-old female with parasagittal SOL.

Diagnosis: Rhabdoid meningioma, CNS WHO grade 3

Imaging

MRI: Highly vascular dural-based contrast enhancing lesion.

Macroscopy

Irregular firm mass on cut section shows yellowish areas of necrosis.

Microscopy

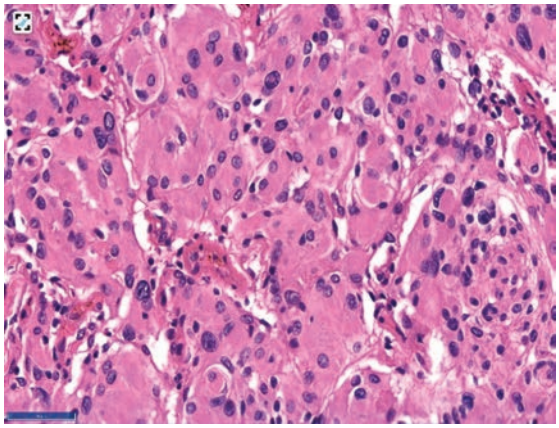


Fig. 2.2: Rhabdoid meningioma, CNS WHO grade 3

- Groups of rhabdoid cells in the setting of anaplastic features.
- Sometimes cells arranged in zellballen pattern and may resemble paraganglioma.
- Nuclei eccentrically placed with deeply eosinophilic cytoplasm.
- Brisk mitotic figures (20 or more MF/10 HPF)
- ***Note:*** "Grading of a meningioma is more important than subtyping".

Ancillary Tests

- ***Immunohistochemistry:*** Vimentin positive, EMA variable positive, Ki-67 is ≥20%.
- Molecular genetics: TERT promoter mutation or homozygous deletion of CDKN2A and/or CDKN2B.

Differential Diagnosis

- ***Metastatic carcinoma:*** Cytokeratin positivity.
- ***Atypical teratoid/rhabdoid tumor:*** Young age, having neuroepithelial, mesenchymal and epithelial differentiation. Biallelic inactivation of SMARCB1 or SMARCA4.
- ***Granular cell astrocytoma/epithelioid glioblastoma:*** Peripherally located, GFAP positive, microvascular proliferation.
- ***Melanoma metastasis:*** HMB45—positive, SOX10—positive.

Case History: A 20-year-old male presented with 4th ventricle SOL.

Diagnosis: Ependymoma, WHO Grade 2

Clinical Features

- ***Bimodal age:*** Infants <1 year of age. Second peak is in the fourth decade (usually spinal cord).
- Occur infratentorially or supratentorially.

Imaging

- Frequently calcified, intraventricular or paraventricular masses.
- Spinal ependymoma on MRI appears as sausage-shaped enhancing mass.

Macroscopy

- Intracranial tumors are well circumscribed.
- Ependymomas of fourth ventricle are typically exophytic.

Microscopy

- Cellular tumor with typically sharply circumscribed borders.
- Cells are monomorphic round to oval with speckled chromatin.
- Perivascular pseudorosettes, true ependymal rosettes, lumina and fibrillar areas.

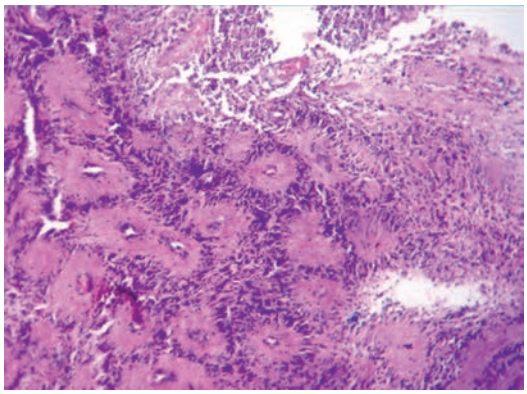


Fig. 2.3: Ependymoma, WHO grade 2

- Can have nonpalisading necrosis, areas of cystic or myxoid degeneration, calcifications, degenerative atypia, neuronal differentiation and rarely metaplastic elements.
- Morphologic subtypes have no clinicopathological significance and include papillary, clear cell and tanycytic.
- Utility of histological grading is debated; the 2021 WHO still recommend assigning either WHO grade 2 or grade 3 to an ependymoma, according to its histopathological features as part of the integrated diagnosis.

Immunohistochemistry

- GFAP, S100 positive
- Perinuclear dot-like pattern of EMA
- L1CAM positive mostly in RELA fusion tumors
- Chromogranin, Olig2 and IDH1 are negative.

Differential Diagnosis

- *Infiltrating glioma:*
  - Infiltrating border, no perivascular pseudorosettes
  - EMA negative, Olig2 positive, IDH1 mutation
- *Astroblastoma:*
  - Astroblastic pseudorosette
  - Exclusively located in the cerebral hemispheres
  - MN1 detectable by FISH
- *Medulloblastoma:*
  - Synaptophysin positive
  - GAB1, YAP1, beta-catenin (nuclear)—positive in subtypes

Case History: A 76-year-old male with contrast enhancing SOL lesion in temporoparietal region.

Diagnosis: Glioblastoma, CNS WHO grade 4, NOS

Imaging

Pattern of ring-like contrast enhancement that reflects their abnormal vascularization and tendency to spontaneous central necrosis.

Macroscopy

- Ill-defined whitish gray mass with areas of hemorrhage and necrosis.
- Can expand gyri and cross the corpus callosum.

Microscopy

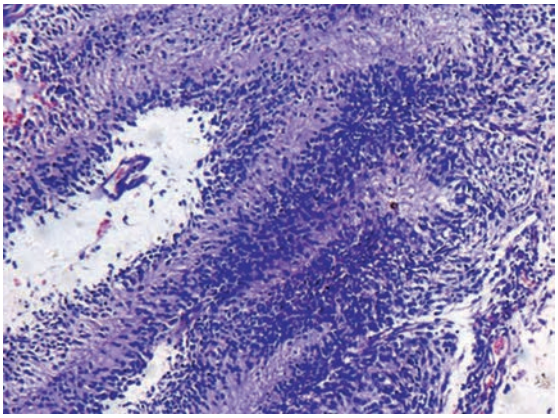


Fig. 2.4: Glioblastoma, CNS WHO grade 4, NOS

- Infiltrating, hypercellular astrocytic neoplasm often with hyperchromatic, elongated nuclei and irregular nuclear membranes. Bizarre giant cells, rhabdoid cells or small anaplastic forms may be seen.
- Typically, mitotically active, though not required, if molecular criteria are met.
- Microvascular proliferation or necrosis is required for a histologic diagnosis of glioblastoma.

Ancillary Tests

- ***Immunohistochemistry:*** MIB-1 and GFAP-immunoreactive.
- ***Molecular genetics:*** p53 mutation, loss of heterozygosity on chromosome 17p and EGFR amplification.

Differential Diagnosis

- ***Metastatic tumor:*** Displaces rather than infiltrating the glial parenchyma, no fibrillary background, GFAP is negative.
- ***Lymphoma:*** Angiocentric and angioinvasive, CD45 positive.
- ***Meningioma, CNS WHO grade 3:*** EMA positive
- ***Other gliomas:*** Mitosis, necrosis, endothelial proliferation.

Case History: A 15-year-old boy with suprasellar SOL.

Diagnosis: Craniopharyngioma-adamantinomatous, CNS WHO Grade 1

Clinical Features

- ***Peak age incidence:*** 5–10 years
- Symptoms and signs due to increased intracranial pressure, compression of the optic pathways.

Macroscopy

- Admixture of cystic and solid components are characteristics.
- Cysts may contain a thick liquid resembling machine oil.
- Papillary variant is more circumscribed and does not contain calcification or oil-like cyst fluid.

Microscopy

- Cords, lobules, nodular whorls and trabeculae of well-differentiated squamous epithelium bordered by palisading columnar epithelium.
- Peripheral cells surround looser plumper cells called stellate reticulum.

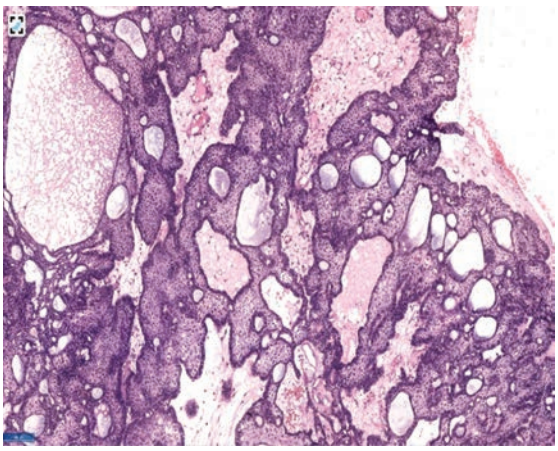


Fig 2.5: Craniopharyngioma-Adamantinomatous, CNS WHO grade 1

- Nodules of plump, anucleate squamous cells (ghost cells) and wet keratin seen.
- Microscopic brain invasion common with tongues.
- Degenerative changes with cystic degeneration, calcifications and xanthogranulomatous reactions.

Differential Diagnosis

- ***Epidermoid cyst:*** Keratohyaline granules seen.
- ***Dermoid cyst:*** Adnexal structures seen.
- ***Pilocytic astrocytoma:*** Microcystic degeneration and loose sheets of astrocytes seen.
- ***Rathke cleft cyst with squamous metaplasia:*** Mostly epithelium will have cilia or goblet cells.
- ***Papillary craniopharyngioma:*** No palisading, no wet keratin, no calcifications, no "motor oil" cystic fluid, no xanthogranulomatous reaction. Harbors a BRAF V600E mutation and is negative for beta catenin.

Case History: A 25-year-old female with headache and seizures.

Diagnosis: Meningothelial meningioma, CNS WHO grade 1

Clinical Features

- Symptoms by compression of adjacent structures.
- Specific deficits depend upon the location of the tumor.
- Headache and seizures often herald the presence of a meningioma.

Macroscopy

- Most meningiomas are rubbery or firm, well-demarcated, sometimes lobulated, rounded masses that feature broad dural attachment.
- Invasion of underlying dura or of dural sinuses is quite common.

Microscopy

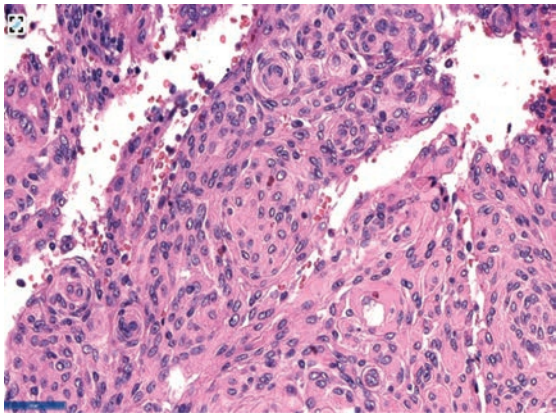


Fig. 2.6: Meningothelial meningioma, CNS WHO grade 1

- Tumor cells form lobules, often with whorls and arranged in syncytial arrangement.
- Like normal arachnoidal cap cells, the tumor cells are largely uniform, with oval nuclei with delicate chromatin that on occasion show central clearing, or the formulation of cytoplasmic nuclear inclusions. May contain psammoma bodies.

Ancillary Tests

- ***Immunohistochemistry:*** Somatostatin receptor 2a (SSTR2a) is a specific meningioma marker in CNS tumors.
- ***EMA is usually patchy positive. Progesterone receptor:*** Diffuse strong nuclear in low-grade meningiomas and diminished in high-grade meningiomas.

Molecular Genetics

- Fibrous, transitional and psammomatous—NF2 mutation.
- Atypical meningiomas have loss of NF2, or loss of SMARCB1.
- Clear cell meningioma SMARCE1 mutation.

Differential Diagnosis

- ***Metastatic carcinoma:*** Clear cell meningioma (PAX8 negative) from metastatic clear cell renal cell carcinoma (PAX8 +)
- ***Hemangiopericytoma:*** Spindle cells with staghorn vessels, storiform pattern, CD34 positive.
- ***Solitary fibrous tumor (SFT):*** STAT6 positive, whereas fibrous meningioma is STAT6 negative.

Case History: A 7-year-old girl presented with posterior fossa cystic SOL.

Diagnosis: Pilocytic astrocytoma, CNS WHO grade 1

Clinical Features

- Most common gliomas in children.
- In the visual system, it can arise in the optic nerve proper and causes loss of vision.

Imaging

- Well circumscribed and contrast enhancing.
- Cysts may be solitary and massive with the tumor presenting as a mural nodule.
- Bright enhancement on T1-weighted image reflects the proteinaceous content in the tumor and aids in distinction from other forms of astrocytoma.

Macroscopy

- Relatively well circumscribed.
- Often has heterogenous consistency with firm and mucoid areas.
- Focal calcification may be present.

Microscopy

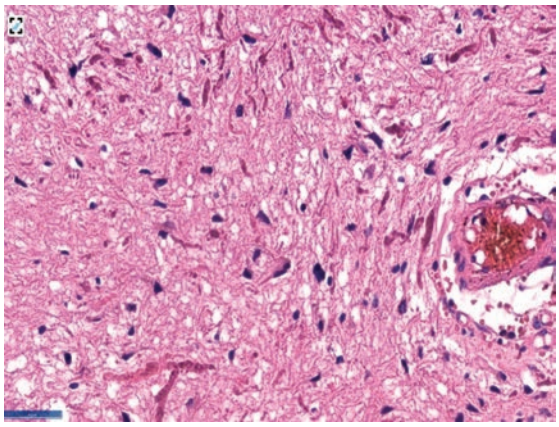


Fig. 2.7: Pilocytic astrocytoma, CNS WHO grade 1

- Typically have a biphasic appearance.
- Compact fascicles of elongated cells with piloid/stellate cells with branching cytoplasmic processes may enclose a fine mesh work of microcysts.
- Nuclear pleomorphism and hyperchromasia may be present.
- Rosenthal fibers and eosinophilic granular bodies are classic features.

Ancillary Tests

- ***IHC:*** GFAP is positive, IDH1 is negative
- ***Molecular genetics:*** In patients with NF-1, about 15% develop pilocytic astrocytoma.

Differential Diagnosis

- Extensive astrocytic gliosis with rosenthal fiber formation: May mimic a PA, either as part of reactive conditions or around neoplasms.
- ***Diffuse astrocytomas:*** Distinct on neuroimaging. Diffuse astrocytoma do not have the circumscribed nature and biphasic architecture and are IDH1 positive.
- ***Glial component of ganglioma:*** PA rarely infiltrates the adjacent brain sufficiently to entrap neurons. Neoplastic population of ganglion cells are absent in PA.
- ***Glial component of dysembryoplastic neuroepithelial tumor (DNT):*** DNT is cortical in location with a nodular architecture. Specific glioneuronal element helps to exclude a diagnosis of PA.

Case History: A 30-year-old female L1–L3 intramedullary SOL.

Diagnosis: Myxopapillary ependymoma, CNS WHO grade 2

Important Points

Seen in spinal region. Frequently related to conus or filum terminale. Usually present in patients aged 20–40 years. Associated with type 2 neurofibromatosis. Perivascular and intercellular mucin deposition is a feature.

Microscopy

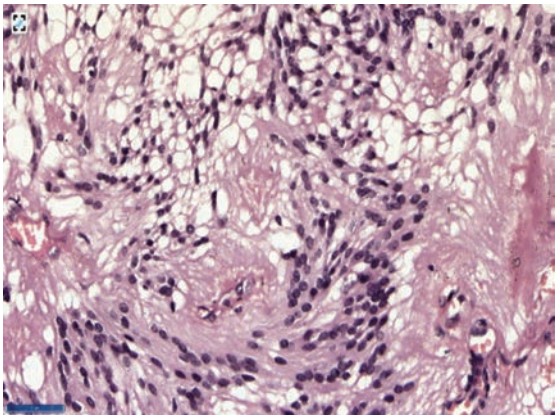


Fig. 2.8: Myxopapillary ependymoma, CNS WHO grade 2

Well-differentiated cuboidal to elongated tumor cells radially oriented around vascularized myxoid cores with a myxopapillary appearance. No atypia, low mitotic count.

Ancillary Tests

- ***Immunohistochemistry:*** Characterized by immunoreactivity for GFAP, vimentin.
- Molecular genetics: Gains in chromosomes 5, 7, 9, 16, 18.

Differential Diagnosis

- ***Chordoma:*** Presence of physaliphorous cells, keratin positive
- ***Myxoid chondrosarcoma:*** Lack of GFAP

- ***Schwannoma and paraganglioma:*** Common intradural tumors in this region.

Case History: A 35-year-old male with temporoparietal SOL

Diagnosis: Oligodendroglioma, IDH-mutant, CNS WHO grade 2

Clinical Features

Predominantly adult male, usually presenting with seizures.

Imaging

On CT, it appears as hypo-/isodense well demarcated and shows little perilesional edema.

Macroscopy

Frontal lobe is involved frequently. It appears well-defined, grayish pink, soft with calcifications.

Microscopy

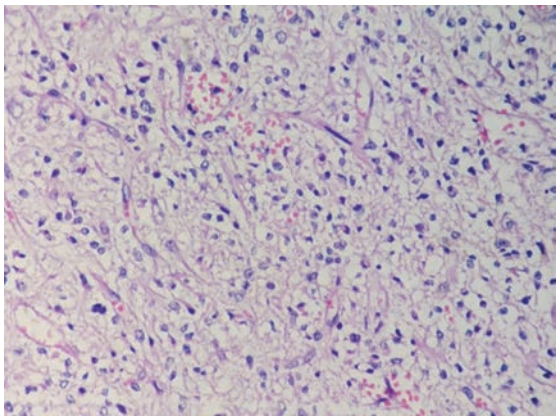


Fig. 2.9: Oligodendroglioma, IDH-mutant, CNS WHO grade 2

- Monomorphous, moderately cellular, diffusely infiltrating gliomas
- Uniform round to oval nuclei with perinuclear halos giving a honeycomb or, fried egg appearance (It is a formalin fixation artifact and it will not be seen on frozen sections or smear preparations.)
- Occasional mitotic figures
- Tumor cells are separated by branching chicken wire-like capillary network.
- Calcospherites (microcalcifications) noted.

Ancillary Tests

- IDH1 (R132H) is positive. Negative staining is not incompatible with oligodendroglioma, if 1p/19q codeletion is present.
- ATRX (retained expression)
- p53 (negative or weak staining in rare cells)
- A combination of IDH1 (R132H), ATRX and p53 is useful to distinguish oligodendroglioma from IDH mutant astrocytoma.
- GFAP—focally in the gliofibrillary oligodendrocytes and mini-gemistocytes
- Ki-67 below 5%
- 1p19q codeletion is the hallmark alteration demonstrated by FISH.

Differential Diagnosis

- ***Diffuse astrocytoma:*** Lack honeycomb pattern, perinuclear halo, diffuse GFAP staining, lack of 1p19q codeletion
- ***Pilocytic astrocytoma:*** Pediatric, location in cerebellum, brainstem, lack IDH mutations and lack of 1p19q codeletion
- ***Clear cell ependymoma:*** Perivascular psuedorosettes, dot-like EMA positivity
- ***Central neurocytoma:*** Positive neural markers, intraventricular location, lack of 1p19q codeletion.
- ***Polymorphous low grade neuroepithelial tumor of the young (PLNTY):*** Oligodendroglioma-like components. CD34 is positive, absence of 1P/19Q codeletion and BRAF V600E mutant.

Case History: A 40-year-old male with parietal SOL.

Diagnosis: Oligodendroglioma, IDH-mutant, CNS WHO grade 3

Clinical Features

Majority arise in adults and in males. Seizures are the most common presenting symptom. They develop *de novo* or secondarily from a low-grade oligodendroglioma.

Imaging

It appears heterogeneous due to necrosis, hemorrhage, cystic degeneration, calcification. Ring enhancement is uncommon.

Macroscopy

Heterogeneous due to hemorrhage, cyst formations and necrosis.

Microscopy

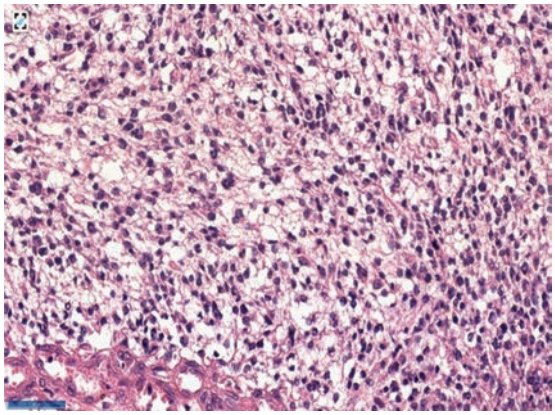


Fig. 2.10: Oligodendroglioma, IDHmutant, CNS WHO grade 3

- High cellularity, nuclear pleomorphism, moderate-to-high mitosis (>6 mitoses/10 HPF)
- Microvascular proliferation and necrosis (with or without palisading)
- Infiltration with perineuronal satellitosis

Ancillary Tests

Immunohistochemistry: IDH positive, ATRX retained expression, Ki67 labeling index >10% of tumor nuclei, P53 negative. CDKN2B homozygous deletion (not seen in grade 2 oligodendrogliomas)

Differential Diagnosis

- ***Metastatic clear cell carcinomas:*** Solid and sharply demarcated, keratin and EMA positive, IDH negative
- ***Macrophage-rich lesion*** (e.g. demyelinating diseases): IDH negative
- ***Glioblastoma, small cell type:*** 1p19q codeletions absent, presence of EGFR amplification
- ***Neurocytoma:*** IDH negative
- ***Dysembryoplastic neuroepithelial tumor:*** IDH negative
- ***Ependymomas containing clear cells:*** Perivascular pseudorosettes, IDH negative, dot-like/ring-shaped EMA positive

Case History: An 8-year-old male with 4th ventricle SOL

Diagnosis: Medulloblastoma, CNS WHO grade 4

Clinical Features

They present with raised intracranial pressure. Most common location in children is the cerebellar vermis.

Imaging

- Radiologically, they invade the adjacent brain and generally show patchy enhancement with contrast on CT.
- On MRI, they appear as solid, contrast enhancing masses.

Macroscopy

- Located in the midline appearing as pink or gray masses that arise in the region of the vermis to occupy the fourth ventricle.
- Desmoplastic medulloblastoma tends to be more firm and circumscribed.

Microscopy

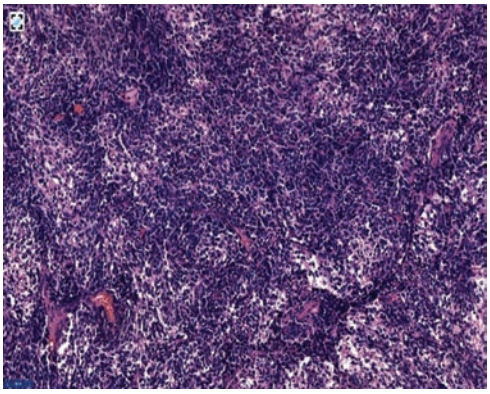


Fig. 2.11: Medulloblastoma, CNS WHO grade 4

- ***Classic medulloblastoma:*** It is the most common variant and consists of primitive appearing cells with round to oval hyperchromatic nuclei surrounded by scant cytoplasm. Homer Wright rosettes may be observed. Mitosis and necrosis may also be observed.
- ***Large cell/anaplastic medulloblastoma:*** Contains cells at least twice the size of those in classic medulloblastoma. Cells are discohesive with uniform round vesicular nuclei, cellular cannibalism and prominent nucleolus. They have higher mitotic counts.
- ***Desmoplastic medulloblastoma:*** Round to oval islands of low cellularity, reticulin free islands surrounded by highly cellular reticulin forming tumor cells.
- ***Medulloblastoma:*** Clinicopathological correlates of SHH, WNT and non-SHH/WNT molecular subgroups.

Immunohistochemistry

- Synaptophysin positive, GAB1 and YAP1 immunopositivity indicate SHH activated tumors and immunonegativity suggests non-WNT/non-SHH tumors.
- Ki-67 >30%

Differential Diagnosis

- ***Metastatic neuroblastoma, retinoblastoma, lymphoma:*** Appropriate IHC
- ***High-grade gliomas:*** Fibrillary matrix with GFAP positivity
- ***Germ-cell tumor:*** Positive for germ-cell markers
- ***Atypical teratoid rhabdoid tumor (ATRT):*** Loss of INI1, vesicular nuclei with prominent nucleoli

Case History: A 22-year-old male with lateral ventricle SOL.

Diagnosis: Central neurocytoma, CNS WHO grade 2

Incidence and Localization

- Occurs in young- to middle-aged adults.
- Intraventricular in location.

Imaging

- Large, globular, intraventricular mass.
- Many are calcified.
- May be cystic and solid.

Macroscopy

Well circumscribed, gray and gritty.

Microscopy

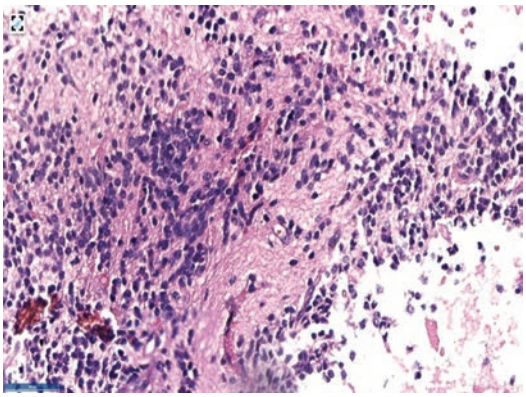


Fig. 2.12: Central neurocytoma, CNS WHO grade 2

- Monotonous round to oval cells which have fibrillary cytoplasm and round nuclei with finely granular chromatin.
- Streaming of cells in fine fibrillary background.
- Artifactual perinuclear halo seen.
- Rosettes may be seen.

Ancillary Tests

Immunohistochemistry: Fibrillar zones immunoreactive for both synaptophysin and NeuN. TTF1 may also be positive. Ki-67 index is low.

Differential Diagnosis

- ***Oligodendroglioma:*** Chicken wire vasculature with perinuclear halos, molecular studies
- ***Cellular ependymoma:*** Especially clear cell ependymoma may involve paraventricular region. GFAP will be positive in ependymoma.
- ***Cerebral neuroblastoma:*** Brisk mitosis will be there.

Case History: A 5-year-old male with history of headache and vomiting.

Diagnosis: Choroid plexus papilloma, CNS WHO grade 1

Clinical Features

Signs and symptoms of increased intracranial pressure. Located supratentorially in the lateral ventricles.

Imaging

Hyperdense contrast enhancing masses within the ventricles.

Macroscopy

- Circumscribed cauliflower-like masses that may adhere to ventricular wall.
- Cysts and hemorrhage may occur.

Microscopy

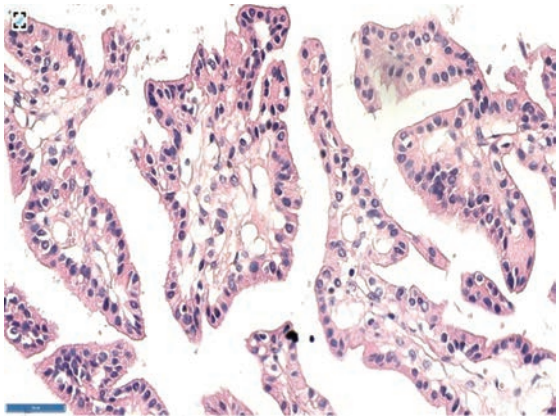


Fig. 2.13: Choroid plexus papilloma, CNS WHO grade 1

- Benign papilloma is composed of delicate fibrovascular connective tissue fronds covered by a single layer of uniform cuboidal to columnar epithelial cells with round to oval basal nuclei.
- Changes that they can undergo are oncocytic change, mucinous degeneration, melanization and xanthomatous changes with bone or cartilage formation.

Ancillary Tests

Immunohistochemistry: Vimentin and cytokeratin positive.

Differential Diagnosis

- ***Choroid plexus carcinoma:*** Anaplasia, necrosis, mitosis
- ***Papillary ependymoma:*** Pseudorosettes, GFAP positivity
- ***Metastatic papillary carcinoma:*** Atypia, mitosis, history and IHC to rule out possible primaries

Case History: A 35-year-old male with lesion in the base of skull.

Diagnosis: Chordoid meningioma, CNS WHO grade 2

Incidence and Localization

- Incidence rises with age.
- Common in clivus, sphenoid ridges and other sites common to all meningiomas.
- May be associated with Castleman's syndrome.

Imaging

MRI: Isodense dural masses which may be calcified.

Macroscopy

- Firm irregular masses.
- May be gritty with foci of calcification.

Microscopy

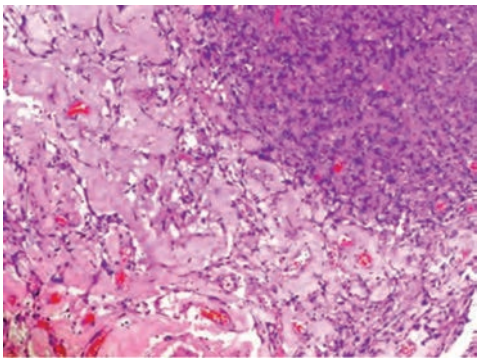


Fig. 2.14: Chordoid meningioma, CNS WHO grade 2

- Cells resembling chordoma cells.
- Cells arranged in trabeculae with eosinophilic, vacuolated cells in a myxoid background.
- Chordoid areas are interspersed by chronic inflammatory cell infiltrate.
- Permeates the bone.

Immunohistochemistry

EMA and S-100 positive.

Differential Diagnosis

Chordoma: Physaliferous cells, S-100 and brachyury positive.

Case History: A 40-year-old male with cystic SOL in the posterior fossa.

Diagnosis: Hemangioblastoma, CNS WHO grade 1

Incidence and Localization

- Account for <2% of all CNS tumors, typically occur in adults. VHL-associated tumors occur at a younger age than sporadic hemangioblastomas.
- Typically occur in cerebellum. Can also occur in brainstem and spinal cord.
- May occur sporadically (most commonly) or associated with von-Hipplel-Lindau (VHL).

Imaging

- Discrete highly vascular contrast enhancing masses.
- In the cerebellum seen as cystic lesion with mural nodules.

Macroscopy

Highly vascular, well circumscribed and pseudoencapsulated, solid or cystic lesion with mural nodule. Red with yellow/orange cut surface regions depending on lipid content.

Microscopy

- Two main components (1) neoplastic stromal cells that are large and vacuolated,

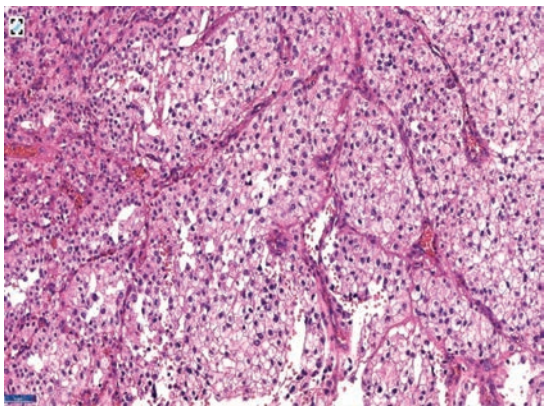


Fig. 2.15: Hemangioblastoma, CNS WHO grade 1

(2) abundant reactive vascular cells. Abundant stromal cells may reveal solid epithelioid aggregates associated with extramedullary hematopoiesis.
- Mitotic figures are rare.
- Adjacent astrocytic gliosis and Rosenthal fibers are frequently observed.
- *Variants:* Cellular (stroma cells > capillaries) and reticular (capillaries > stromal cells).

Ancillary Tests

Immunohistochemistry: Stromal cells immunoreactive for NSE, inhibin and GFAP weak positive. Factor VIIIa positive in vacuolated stromal cells.

Differential Diagnosis

- *Non-representative biopsy of gliotic cyst wall:* May be mistaken for pilocytic astrocytoma. Unlike hemangioblastomas, cerebellar astrocytomas are tumors of young age. Pilocytic astrocytoma has a biphasic histology.
- *Metastatic renal cell carcinoma:* This is entertained when hemangioblastoma lacks cystic areas. RCC shows epithelial characteristics. EMA will be positive in RCC.

Case History: A 60-year-old male with left cerebellar abscess.

Diagnosis: Pheohyphomycosis

Classification

Clinically, pheohyphomycosis has been classified according to the anatomical site involved, as:

- Cutaneous
- Subcutaneous
- Paranasal sinus
- Cerebral types
- Cerebral pheohyphomycosis is very rare, but the most serious form of disease, usually caused by *Cladophialophora bantiana*. The portal of entry is not known. Though inhabitation of spores into the lung and colonization and subsequent hematogenous spread has been suggested.

Common Fungal Infections of CNS

- Candidiasis
- Cryptococcosis
- Aspergillosis
- Mucormycosis

Forms of Fungi in CNS Infections

- Yeasts
- Branching hyphae
- Pseudohyphae

Microscopy

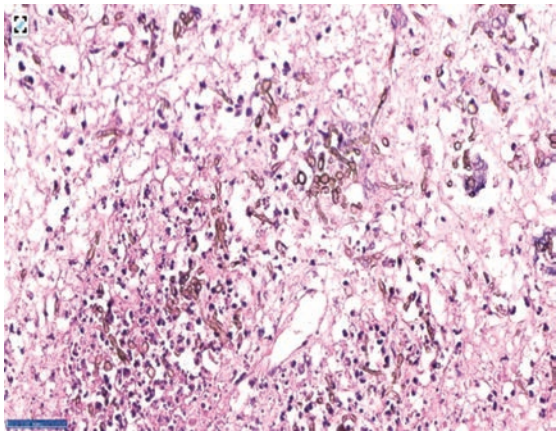


Fig. 2.16: Pheohyphomycosis

Have a characteristic appearance of irregularly swollen hyphae with yeast-like structures.

Special Stain

Masson-Fontana stain for melanin is used to confirm the presence of dematiaceous hyphae.

Case History: A 2-month-old infant with increase in circumference of head since one month.

Diagnosis: Melanotic progonoma of infancy (Melanotic neuroectodermal tumor of infancy)

Clinical Features

- It is an uncommon, rapidly growing pigmented, osteolytic tumor predominantly involving the maxilla or skull in infants.
- ***Histogenesis:*** Suggested neural crest origin with biphasic histology of melanin containing cells and neuroblast-like cells.
- 98% of them occur in infants less than 1 year.
- Most commonly affects the maxilla and jaw bones of infants.

Microscopy

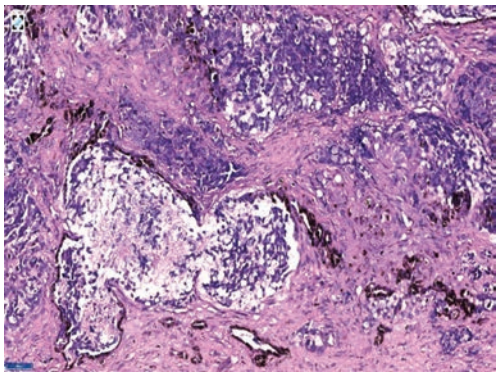


Fig. 2.17: Melanotic progonoma of infancy (melanotic neuroectodermal tumor of infancy)

- It is a biphasic tumor
- Composed of nodules of small round blue cell—neuroblast-like component
- Larger melanin producing epithelioid cells
- The background consists of dense fibrosis.

Ancillary Stains

- Larger cells are positive for keratin and HMB45, masson-fontana, a stain useful to demonstrate melanin pigment.

- Smaller cells are positive for CD57/Leu-7 and NSE.
- Both cell types are usually S-100 negative.
- ***Electron microscopy:*** Pigmented cells contain melanosomes, neuroblast-like cells contain neurosecretory granules and cytoplasmic processes.

Differential Diagnosis

- Neuroblastoma/other small round blue cell tumor: Typically lack the clinical presentation of a jaw or skull tumor in infants. Biphasic pattern, pigmented cells—rosettes present
- ***Melanocytoma:*** Well circumscribed lesion, no biphasic pattern
- ***Melanoma:*** Have prominent necrosis, atypia and mitotic figures.
- ***Melanotic medulloblastoma:*** Intraparenchymal lesion, rosettes present, hyperchromatic nuclei seen.

Case History: A 48-year-old male with known case of carcinoma lung.

Diagnosis: Metastatic tumor

Clinical Features

- Metastasis to brain affects both cerebrum and cerebellum.
- Most common tumors to metastasize are from lung and breast.

Macroscopy

- 80% located in arterial border zones of cerebral hemispheres.
- Well circumscribed—firm, granular, mucoid or necrotic, varying in color.
- Located at the junction of the gray and white matter.

Microscopy

- Discrete parenchymal lesion.
- Vascular proliferation may be seen adjacent to tumor area.
- Necrosis may be present.

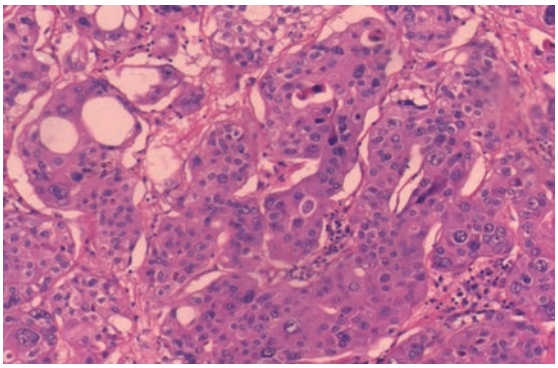


Fig. 2.18: Metastatic tumor

- Diffuse leptomeningeal infiltration may be seen.

Ancillary Studies

Immunohistochemistry: Immunoreactivity of the parent neoplasm.

Differential Diagnosis

- ***Glioblastoma multiforme:*** Endothelial proliferation, GFAP positive and cytokeratin negative.
- ***Papillary neoplasms:*** Have to be differentiated from choroid plexus carcinoma and other primary papillary tumors of CNS.
- ***Primary lymphomas:*** Are usually deep seated and angiocentric.

Case History: A 26-year-old male headache and seizures since 3 months, temporal lesion.

Diagnosis: DNET, WHO grade 1

Clinical Features

- Uncommon tumor
- Protracted history of partial seizures
- Onset before 20 years of age
- Majority localized to the cerebral cortex.

Imaging

- Well demarcated, T1 hypointense
- Internal nodularity
- Thin septations within the tumor
- Pseudocystic appearance due to mucoid accumulation.

Macroscopy

Multiple gelatinous nodules.

Microscopy

- Mucin-rich nodules
- Small oligodendroglia-like cells aligned in a columnar fashion along bundled axons and capillaries that are arrayed perpendicular to pial surface
- Myxoid matrix on which mature neurons float.

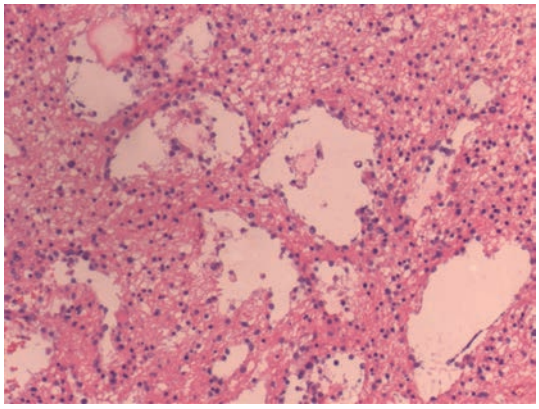


Fig. 2.19: DNET, WHO grade 1

Ancillary Test

Immunohistochemistry: GFAP positive astroglial cells with entrapped floating neurons positive for neuronal markers and S-100.

Differential Diagnosis

- ***Oligodendroglioma:*** IDH mutation and 1p19q codeletion
- ***Ganglioglioma:*** Neuronal dysmorphism/inflammatory infiltrates.

Case History: A 15-year-old male with subcortical well-circumscribed cystic and solid SOL in the temporal region.

Diagnosis: Papillary glioneuronal tumor, CNS WHO grade 1

Clinical Features

Arise in the cerebral hemispheres of adults.

Imaging

On MRI, they appear as well circumscribed, contrast enhancing lesions with little mass effect or surrounding edema.

Microscopy

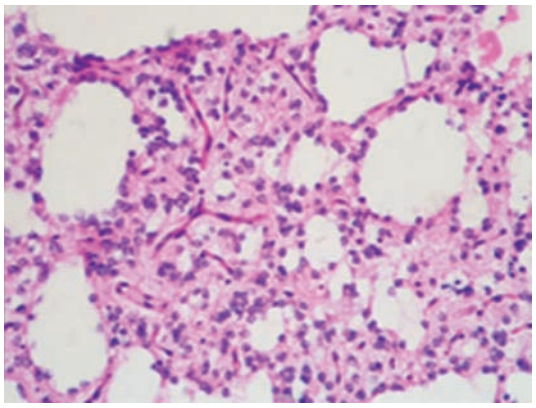


Fig. 2.20: Papillary glioneuronal tumor, CNS WHO grade 1

- Circumscribed, noninvasive
- Papillary/pseudopapillary architecture
- Central fibrovascular core surrounded by two distinct cell types
- Inner small cuboidal cells with outer larger clear cells with neurocytic or ganglioid appearance
- Rare to absent mitosis
- ***IHC:*** Strong GFAP of the inner layer and strong neuronal markers in the outer layers

Differential Diagnosis

- Papillary ependymoma: Rosettes, synaptophysin negative
- Extraventricular neurocytoma: No pseudopapillae lined by glial cells
- Rosette-forming glioneuronal tumor: 4th ventricle, neurocytic rosettes with synaptophysin positive cores.

Case History: A 62-year-old male presented with swelling over the frontal region of the scalp for the past one year.

Diagnosis: Solitary fibrous tumor (SFT), CNS WHO grade 2

Clinical Features

- 60% men, mean age 45 years
- Usually, single mass attached to meninges of brain or spinal cord (resembles meningioma radiographically)
- ***Sites:*** Dural based, supratentorial, 10% spinal

Imaging

CT-brain (contrast) well-defined lobulated extra-axial hyperdense frontal lesion causing indentation of cerebral parenchyma and destruction of adjacent bone.

Macroscopy

Variable sized, dural based, may be well circumscribed and appear gray to red.

Microscopy

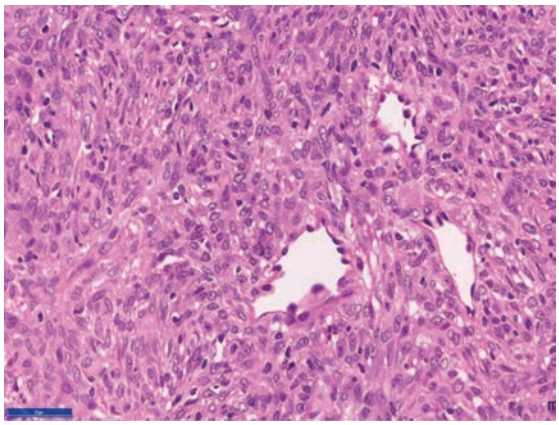


Fig. 2.21: Solitary fibrous tumor (SFT), CNS WHO grade 2

- Sheets of cells with uniform hypercellularity, cells are homogeneous with moderate amount of cytoplasm, round to oval nuclei and moderate pleomorphism
- Intratumoral staghorn vessels
- May have storiform pattern
- ***CNS WHO grade 1:*** <2.5 mitoses/mm^2 (<5 mitoses/10HPF)
- ***CNS WHO grade 2:*** ≥2.5 mitoses/mm^2 (≥5 mitoses/10HPF) without necrosis
- CNS WHO grade 2: ≥2.5 mitoses/mm^2 (≥5 mitoses/10HPF) with necrosis

Ancillary Test

IHC: STAT6 positive, CD34 positive, ALDH1 positive

Differential Diagnosis

- Fibrous meningioma—EMA positive, STAT6 negative
- Dural-based Ewing sarcoma/PNET—STAT6 negative
- Primary and metastasis synovial sarcoma—TLE1 positive

APPROACH TO CNS LESIONS I

WHO 5th Edition Nomenclature

Adult Diffuse Gliomas—Changes in Grading with Regards to Molecular Parameters

- The tumors according to WHO CNS5 are now "type specific" and grading is done "within-tumor-type" (No more "Anaplastic")
- WHO CNS5 has changed all CNS WHO tumor grades to Arabic numerals to avoid errors, and we now no longer use the term Anaplastic.
- Among the grading of astrocytomas that has been graded from 2 to 4 and grade 4 is a separate category from glioblastoma. There is no CNS WHO grade 1 IDH-mutant astrocytoma.
- The term "glioblastoma" is only used for adult IDH-wt tumors. Any high grade gliomas with MVP and necrosis which is IDHm needs to be called astrocytoma grade 4 or if it is having homozygous deletion of CDKN2A/B. You need not do CDKN2A/B to diagnose an obvious glioblastoma which is IDH mutant.
- In the oligodendroglioma, you have to have IDH mutant, and 1p19q codeleted. However, if you have expression of ATRX you need not do an FISH for 1p19q codeletion.
- In the ependymomas, you may or may not grade it histopathologically, depending on whether you have methylation profiling or not.

Paediatric Glioma

Paediatric diffuse low grade gliomas (grade 1 and 2)

- Diffuse astrocytoma, MYB1 or MYBL1—altered
- Angiocentric gliomas
- Polymorphous low-grade neuroepithelial tumor of the young
- Diffuse low-grade glioma, MAPK pathway— altered.

Paediatric diffuse high grade gliomas (grades 3 and 4)

- Diffuse midline glioma, H3 K27-altered
- Diffuse midline glioma, H3 G34-mutant
- Diffuse paediatric-type high grade glioma, H3 wild type and IDH wild type
- Infant-type hemispheric glioma

Meningiomas

No longer a meningioma is called "Atypical or Anaplastic. Just need to give a histopathological grade depending on its features, but you can also grade a meningiomas based on its molecular features.

CNS WHO grade 2
4–19 mitotic figures in 10 consecutive HPF
OR
Brain invasion
OR
Specific morphological subtype (chordoid or clear cell)
OR
At least 3 of the following:
- Increased cellularity
- Small cells with high N:C ratio
- Prominent nucleoli
- Sheeting
- Foci of spontaneous (non-iatrogenic) necrosis

CNS WHO grade 3
20 or more mitotic figures in 10 consecutive HPF
OR
Frank Anaplasia
OR
TERT promoter mutation
OR
Homozygous deletion of CDKN2A and/or CDKN2B

Medulloblastoma

- Medulloblastoma, Wnt activated
- Medulloblastoma, SHH activated, p53wt
- Medulloblastoma, SHH activated, p53mt
- Medulloblastoma, non-Wnt, non-SHH
- *Medulloblastoma, histologically defined*

Molecularly defined using IHC:
beta Catenin, GAB1, YAP1

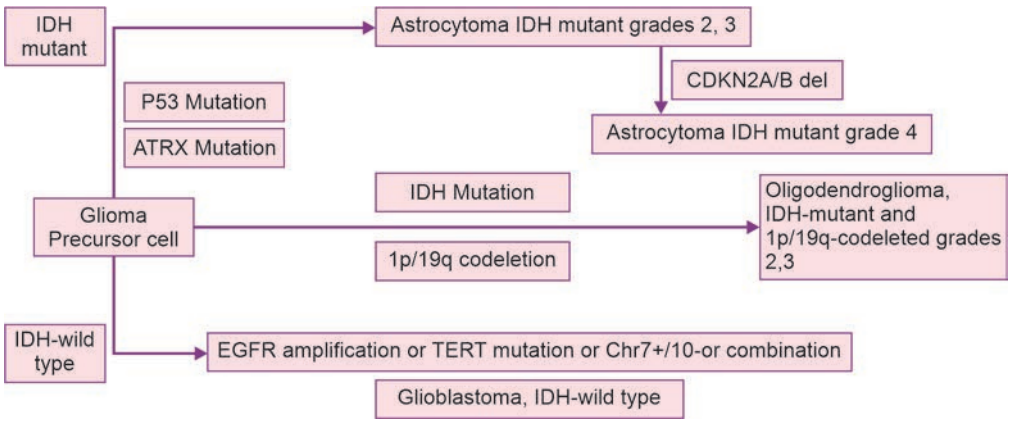
13 Entities with Revised Nomenclature

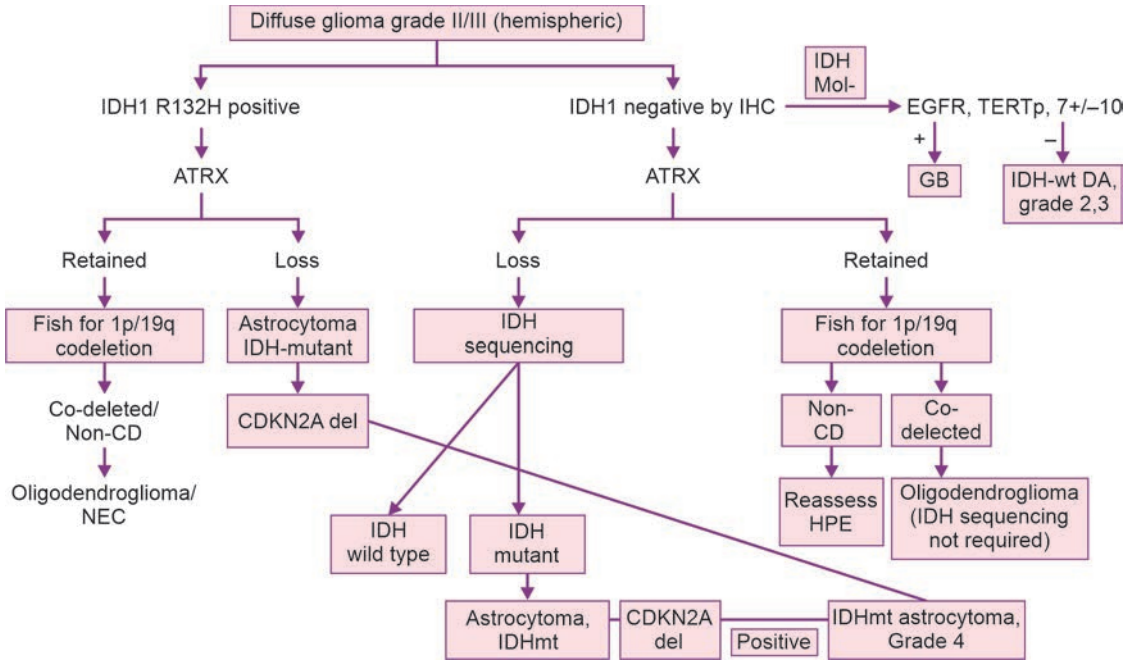
1. Astrocytoma, IDH-mutant (covers grades 2–4; eliminates the term "Glioblastoma, IHD-mutant")
2. Diffuse midline glioma, H3 K27-altered (changes "mutant" to altered" given multiple mechanisms)
3. Chordoid glioma (removes site designation)
4. Astroblastoma, MN1-altered (adds genetic modifier)
5. Supratentorial ependyoma, ZFTA fusion-positive (reflects changes in fusion partner and gene nomenclature; see text)
6. Embryonal tumor with multilayered rosettes (removes genetic modifier to allow for genetic subtypes)
7. Malignant melanotic nerve sheath tumor (conforms to terminology in soft tissue pathology literature)
8. Solitary fibrous tumor (removes the term "hemangiopericytoma" to conform fully with soft tissue pathology nomenclature)
9. Mesenchymal chondrosarcoma (formerly a subtype)
10. Adamantinomatous craniopharyngioma (formerly a subtype)
11. Papillary craniopharyngioma (formerly a subtype)
12. Pituicytoma, granular cell tumor of the sellar region, and spindle cell oncocytoma (grouped rather than separate)
13. Pituitary adenoma/PitNET(adds the term "PitNET")

NEW ENTITIES

Diffuse astrocytoma. MYB or MYBL1- altered Polymoprhous low-grade neuroepithelial tumor of the young Diffuse low-grade glioma, MAPK pathway altered Diffuse hemispheric glioma, HE.E G34-mutant Diffuse pediatric type high grade glioma, H3-wildtype and IDH- wildtype Infant type hemispheric glioma High-grade astrocytoma with piloid features (Methylation only dx)	*7 Gliomas*
Diffuse glioneuronal tumour with oligodendroglioma like features and nuclear clusters (provisional entity) Myxoid glioneuronal tumor Multinodular and vacuolating neuronal tumour	*3 Glioneuronal*
Supratentorial ependyoma, YAP1 fusion-positive Posterior fossa ependymoma, PFA Posterior fossa ependyoma, PFB Spinal ependyoma, MYCN-Amplified	*4 Ependymomas*
Cribriform neutroepithelial tumor (provisional entity) CNS neuroblastoma, FOXR2- activated CNS tumour with BCOR internal tandem duplication Desmoplastic myxoid tumour, SMARCB1- mutant	*4 Embryonal*
Angiomatoid fibrous histiocytoma/ intracranial myxoid mesenchymal tumor CIC-rearranged sarcoma Primary intracranial sarcoma, DICER 1-mutant	*3 sarcomas*
Pituitary blastoma	*1 Pituitary*

APPROACH TO CNS LESIONS II




Diffuse glioma grade II/III (hemispheric)
IDH1 R132H positive
IDH1 negative by IHC
IDH Mol-
EGFR, TERTp, 7+/–10
+
–
GB
IDH-wt DA, grade 2,3
ATRX
ATRX
Retained
Loss
Loss
Retained
Fish for 1p/19q codeletion
Astrocytoma IDH-mutant
IDH sequencing
Fish for 1p/19q codeletion
Co-deleted/ Non-CD
CDKN2A del
Non-CD
Co-delected
Oligodendroglioma/ NEC
Reassess HPE
Oligodendroglioma (IDH sequencing not required)
IDH wild type
IDH mutant
Astrocytoma, IDHmt
CDKN2A del
Positive
IDHmt astrocytoma, Grade 4