CENTRAL NERVOUS AND PERIPHERAL NEROVUS SYSTEM TUMORS

Kenneth Alonso, MD, FACP

Incidence

- Anaplastic astrocytomas and glioblastomas (38% of primary brain tumors).
- Meningiomas and other mesenchymal tumors (27% of primary brain tumors).
- Schwannomas, meningiomas, and ependymomas (79% of primary spinal tumors)

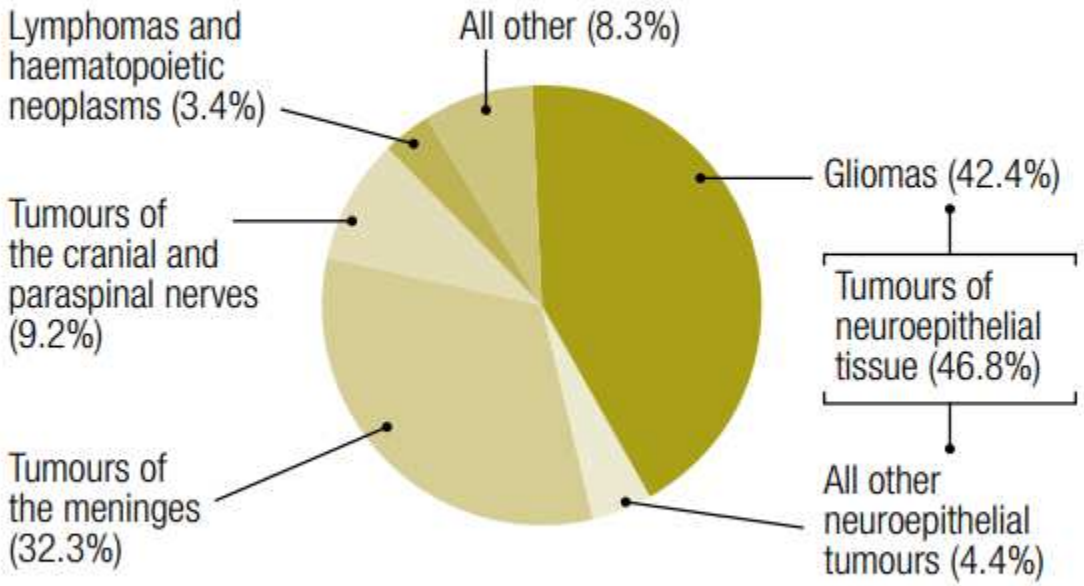
Table 2. 2016 World Health Organization (WHO) Classification and Histologic Grade of Astrocytic Tumors[a]

Type	WHO Histologic Grade
Diffuse Astrocytic Tumors:	
—Diffuse astrocytoma, *IDH*-mutant	II
—Anaplastic astrocytoma, *IDH*-mutant	III
—Glioblastoma, *IDH*–wild-type	IV
—Glioblastoma, *IDH*-mutant	IV
—Diffuse midline glioma, H3 K27M-mutant	IV
Other Astrocytic Tumors:	
—Pilocytic astrocytoma	I
—Pilomyxoid astrocytoma	Grade uncertain[b]
—Pleomorphic xanthoastrocytoma	II
—Anaplastic pleomorphic xanthoastrocytoma	III
—Subependymal giant cell astrocytoma	I
Other Gliomas:	
—Angiocentric glioma	I
—Choroid glioma of the third ventricle	II
—Astroblastoma	Grade uncertain

[a]Adapted from Louis et al.[2]

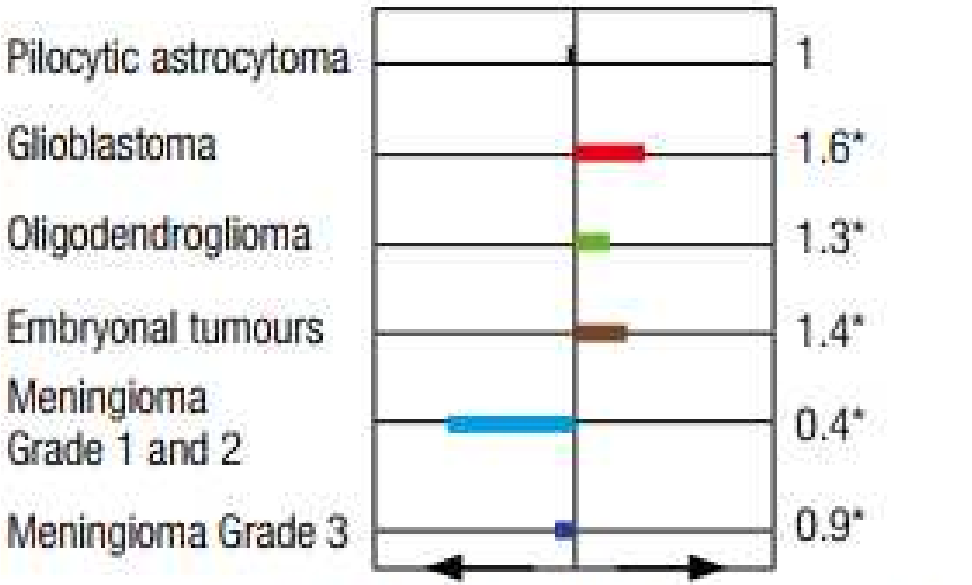
[b]In 2007, the WHO determined that the pilomyxoid variant of pilocytic astrocytoma may be an aggressive variant that is more likely to disseminate, and it was reclassified as a grade II tumor.[1,2,4,5] In 2016, the WHO suggested not grading the pilomyxoid variant until further studies clarify its behavior.[1,2]

Distribution of all primary CNS tumours by major histology groupings in France



CNS, Central nervous system.

Incidence rate ratios by gender (males/females) in USA



Higher incidence in females | Higher incidence in males

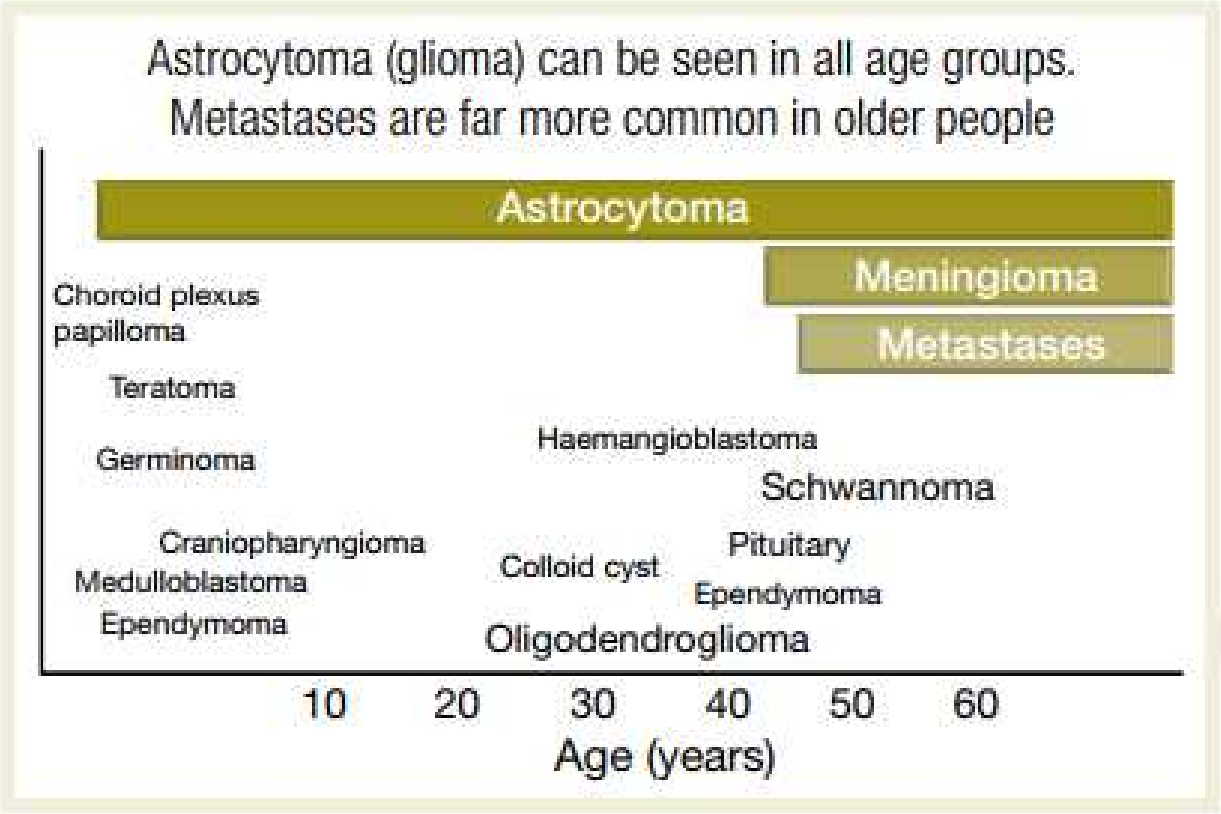
*Significant difference

Distribution of common tumors

- Tumors of the cerebrum are generally glial tumors.
- In childhood, glial tumors are found in the pons and cerebellum as well.
- Medulloblastoma occurs in the cerebellum.
- Non-glial tumors include dural based meningioma and schwannoma (CN VIII).
- Germ cell tumors occur in the pineal.
- Ependymoma occurs in the 4th ventricle.
- Hemangioblastoma occurs in the cerebellum.

Incidence

- Gliomas arise from a progenitor cell that preferentially differentiates down one of the cellular lineages.
- Anaplastic astrocytomas and glioblastomas (38% of primary brain tumors).
- Meningiomas and other mesenchymal tumors (27% of primary brain tumors).
- Schwannomas, meningiomas, and ependymomas (79% of primary spinal tumors)



Multiple tumors in the brain indicate metastatic disease. Some primary brain tumors like lymphomas, multicentric glioblastomas and gliomatosis cerebri can be multifocal.

Environmental risk factors

- High-dose ionizing radiation is the only unequivocal environmental risk factor that has been identified for glial and meningeal neoplasms.
- Mobile phone use and other radiofrequency electromagnetic fields as possible carcinogenic agents

Clinical presentations

- Weakness and sensory hemineglect (more prominent in right hemispheric lesions) are the hallmarks of tumors arising in the frontal or parietal lobes and thalamic region.
- Seizures of varying patterns (partial or generalized) are a common presentation of tumors in the frontoparietal regions and temporal lobe and are more often reported in low-grade glioma.

Clinical presentations

- Occipital lobe tumors may present with slow onset of visual field defects. Bilateral crossed neurological deficits (weakness on one side with contralateral cranial nerve palsy) can be an initial indicator of brainstem glioma.
- If the flow of cerebrospinal fluid is compromised (obstructive hydrocephalus), a Valsalva maneuver, coughing and position change of the head may cause sudden short- term intensive headache associated with nausea and loss of consciousness.

Clinical presentations

- Headache, rarely alone as initial symptom, can vary in intensity and quality. It is frequently more severe on awakening, due to pain-sensitive meninges and blood vessels.
- Psychiatric symptoms, e.g. anxiety and depression, seem to be underdiagnosed. Tumors in less critical areas (anterior frontal or temporal lobe) may be associated with subtle personality changes and memory problems.

Distribution of common tumors

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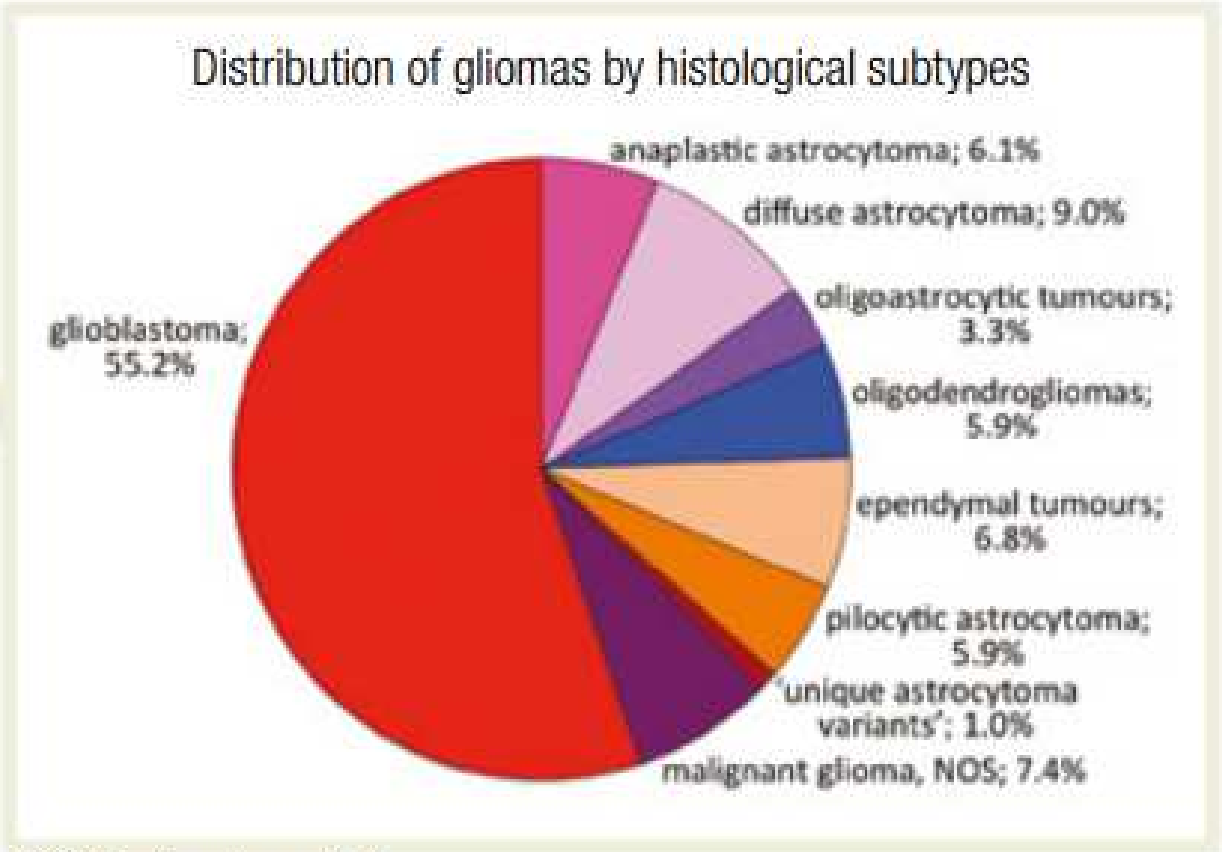
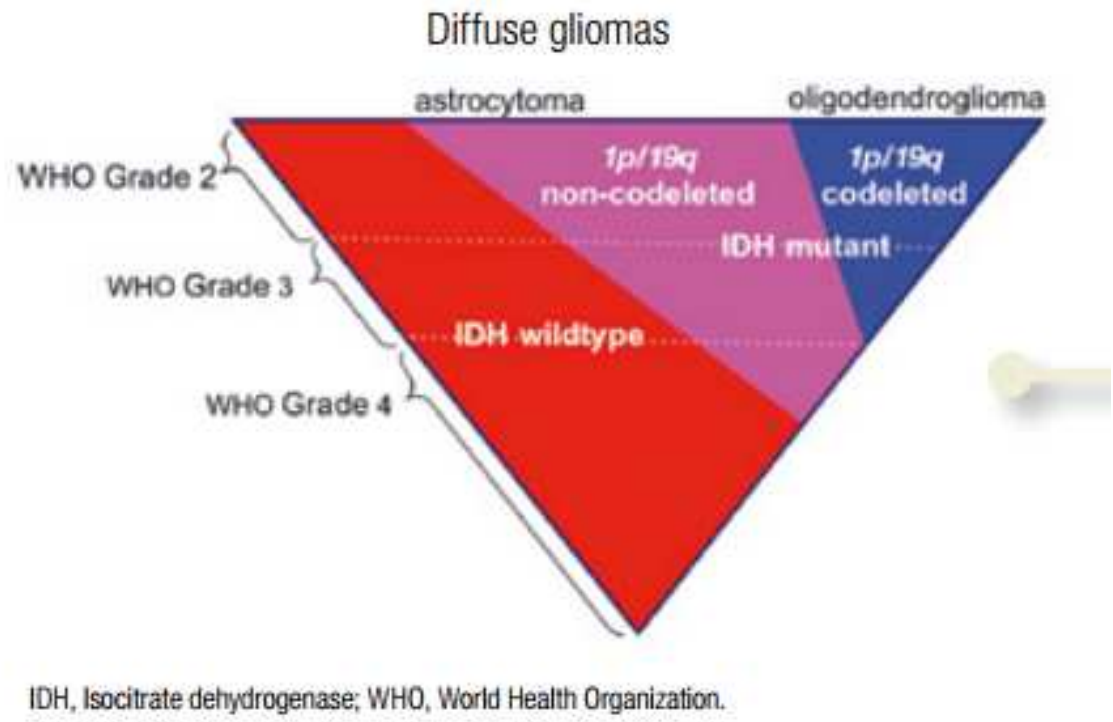
Table 3. Common Central Nervous System (CNS) Locations for Childhood Astrocytomas and Other Tumors of Glial Origin

Tumor Type	Common CNS Location
Pilocytic astrocytoma	Optic nerve, optic chiasm/hypothalamus, thalamus and basal ganglia, cerebral hemispheres, cerebellum, and brain stem; and spinal cord (rare)
Pleomorphic xanthoastrocytoma	Superficial location in cerebrum (temporal lobe preferentially)
Diffuse astrocytoma	Cerebrum (frontal and temporal lobes), brain stem, spinal cord, optic nerve, optic chiasm, optic pathway, hypothalamus, and thalamus
Anaplastic astrocytoma, glioblastoma	Cerebrum; occasionally cerebellum, brain stem, and spinal cord
Diffuse midline glioma, H3 K27M-mutant	Pons, thalamus, spinal cord, and other midline structures

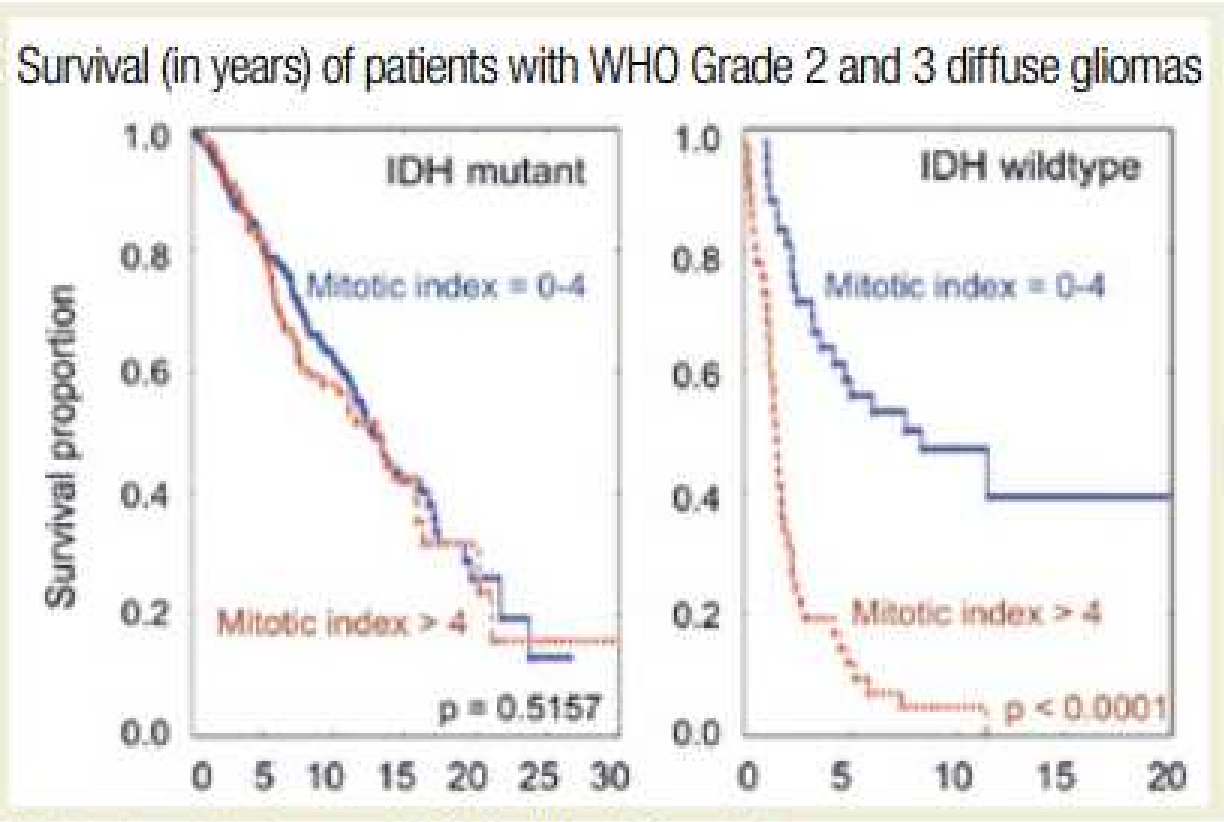


NOS, Not otherwise specified.



IDH, Isocitrate dehydrogenase; WHO, World Health Organization.

Three main molecular subgroups of diffuse gliomas are recognized: (1) IDH (isocitrate dehydrogenase) wildtype; (2) IDH mutant & 1p/19q non-co-deleted; (3) IDH mutant & 1p/19q co-deleted.



IDH, Isocitrate dehydrogenase; WHO, World Health Organization.

IDH mutants

- IDH1 and IDH2 hotspot regions (IDH1 R132, IDH2 R172) noted in diffuse gliomas
- Molecular features supporting the diagnosis of IDH mutant astrocytoma are: presence of TP53 and ATRX mutation, absence of TERT promoter mutation.
- The approximately 10% of glioblastomas that are IDH mutant are nowadays considered “secondary glioblastomas” (i.e. derived from a lower grade precursor tumor).

IDH Mutants

- Virtually all oligodendrogliomas are IDH mutant. As in diffuse IDH mutant astrocytomas, IDH1 R132H is by far the most common IDH mutation in oligodendrogliomas.
- Complete 1p/19q codeletion (loss of the entire chromosome arms) is the hallmark of oligodendrogliomas and indicates a better prognosis and therapy response.
- CIC and FUBP1 gene mutations (located on chromosome 19q and 1p, respectively) are found in a subset of 1p/19q co-deleted tumors; their impact on outcome is presently unclear.

Astrocytoma

- Increased glial cellularity with nuclear pleomorphism and an intervening network of astrocytic processes.
- Grading is dependent upon pleomorphism
- Low-grade astrocytomas have intact blood-brain barrier.
- Higher grade astrocytomas are infiltrative (between neuronal and glial processes).
- 80% of all astrocytomas
- There are no Grade I astrocytomas
- Fibrillary and pilocystic are principal histologic types

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Low-grade astrocytoma

- The O6-methylguanine-DNA methyltransferase (MGMT) promoter status in low-grade tumors was methylated in:
- All IDH mutations with co-deletion of 1p/19q (45/45).
- 86% of the IDH mutations without co-deletion of 1p/19q.
- Fifty-six percent of the IDH wild-type cases.
- p53 mutation and PDGF-A overexpression.

Low grade astrocytoma

- In pediatric grade II diffuse astrocytomas, the most common alterations reported (up to 53% of tumors) are rearrangements in the MYB family of transcription factors
- Also angiocentric gliomas
- BRAF activation in pilocytic astrocytoma occurs most commonly through a BRAF-KIAA1549 gene fusion, producing a fusion protein that lacks the BRAF regulatory domain.
- This fusion is seen in most infratentorial and midline pilocystic astrocytomas.
- Better clinical outcomes.

Diffuse astrocytoma

- Diffuse astrocytomas are poorly defined, gray, infiltrative tumors that expand and distort the invaded brain
- The cut surface of the tumor may be either firm or soft and gelatinous; cystic degeneration may be seen.
- The tumor may appear well demarcated from the surrounding brain tissue, but infiltration beyond the outer margins is always present.

WHO grade	Other astrocytic tumours	Ependymal tumours	Other gliomas
1	Pilocytic astrocytoma Subependymal giant cell astrocytoma	Subependymoma Myxopapillary ependymoma	Angiocentric glioma Chordoid glioma of the 3rd ventricle Astroblastoma
2	Pleiomorphic xanthoastrocytoma	Low-grade ependymoma	
3	Anaplastic pleiomorphic xanthoastrocytoma	Anaplastic ependymoma	

WHO, World Health Organization.

Apart from pilocytic astrocytomas and ependymomas, these gliomas are rare.

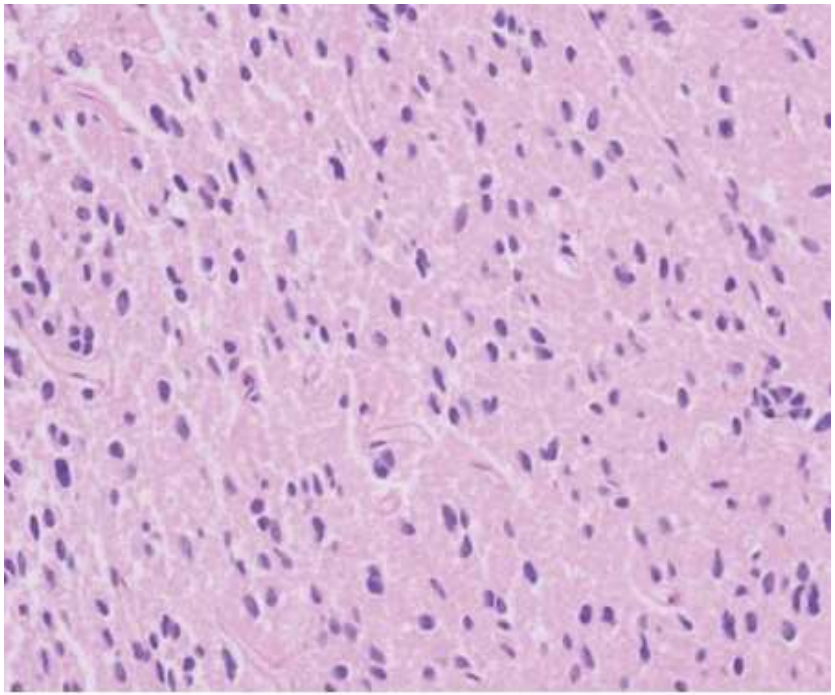
Fibrillary astrocytoma

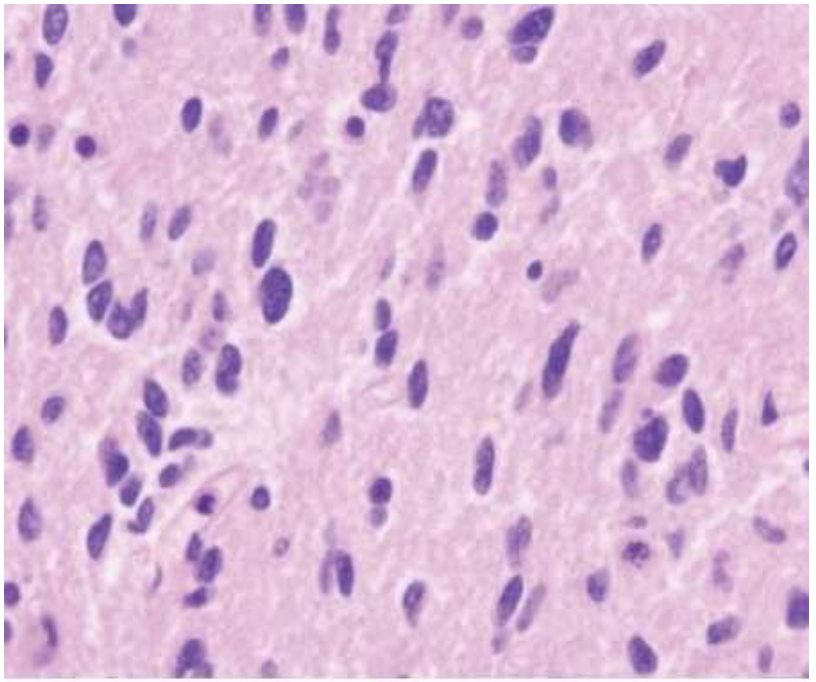
- 80% of adult brain tumors.
- Usually in cerebral hemispheres.
- 4^{th}-6^{th} decades.
- Gross:
- Poorly defined, gray, infiltrative tumors that expand and distort the brain.

Fibrillary astrocytoma

- Microscopic:
- Iincreased cell density.
- An extensive network of fine GFAP-positive astrocytic processes between tumor cell nuclei create a fibrillary background.
- Indistinct transition between involved and uninvolved areas.
- p53 mutation and PDGF-A overexpression.

Fibrillary astrocytoma





200x and 400x. (*Pathology slides courtesy of Dr. Gregory N. Fuller.*) Figs. 12-1, 12-2 Accessed 04/27/2010

Pilocystic astrocytoma

- Pilocystic (hairy) type is more common in children.
- Usually in 3rd ventricle, cerebellum.
- Slow growing.
- Usually solid, but may be cystic.
- Rare p53 mutations.
- May be found with NF1 mutations.

Pilocystic astrocytoma

- Histology:
- GFAP positive pili (hair like processes) extend from bipolar astrocytes.
- Rosenthal fibers (corckscrew intracytoplasmic inclusions).
- Eosinophilic granular bodies are also present.
- Tumors often biphasic with microcystic and fibrillary areas.

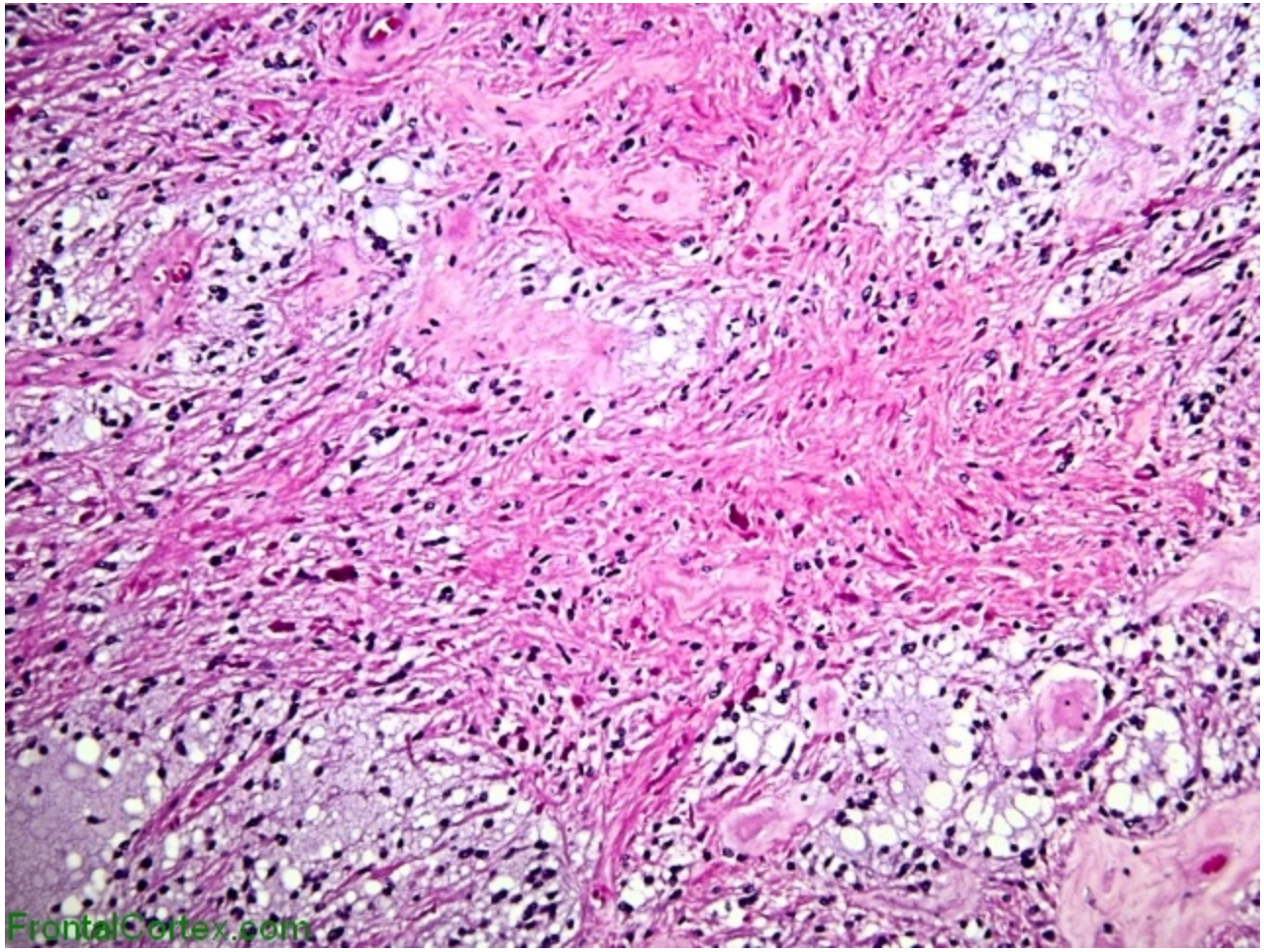
Pilocystic astrocytoma

- Tandem duplication at 7q34 leading to a fusion between KIAA1549 and BRAF is found in approximately 70% of pilocytic astrocytomas.
- An activating point mutation in BRAF (V600E) is found in an additional 5% to 9% of these tumors
- BRAF alterations occur in approximately 80% of pilocytic astrocytomas.
- Rare p53 mutations.
- May be found with NF1 mutations (usually in optic nerve gliomas)

Treatment of astrocytoma

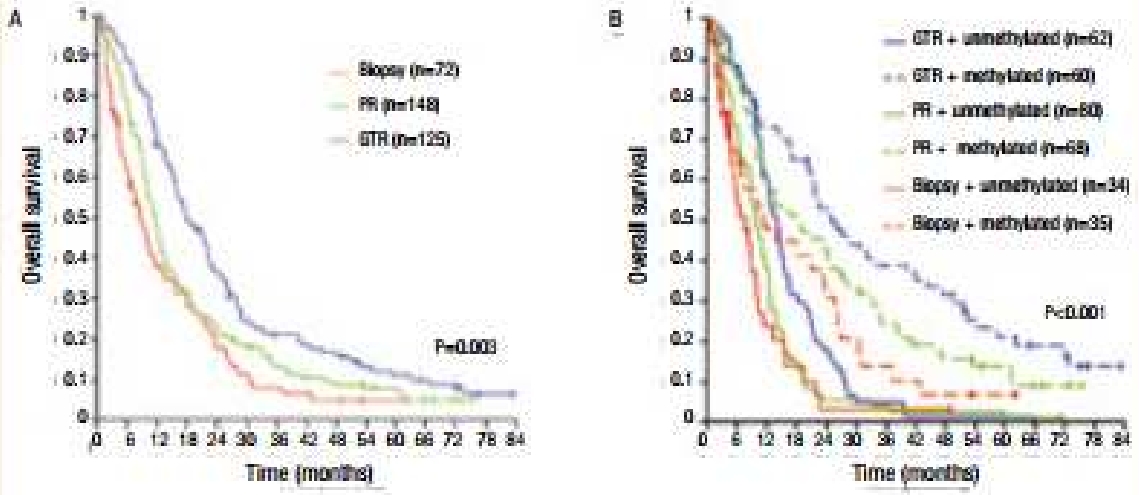
- Pilocytic astroctyoma is the only subset of low grade astrocytoma for which cure is possible with complete surgical resection.
- Low grade supratentorial astroctyoma of children responds for prolonged periods to procarbazine, carboplatin, and vincristine as well as to radiotherapy.
- Temozolide not needed
- High grade astrocytoma is treated with radiotherapy and nitrosourea.
- Temozolide may also be active.

Pilocystic astrocytoma

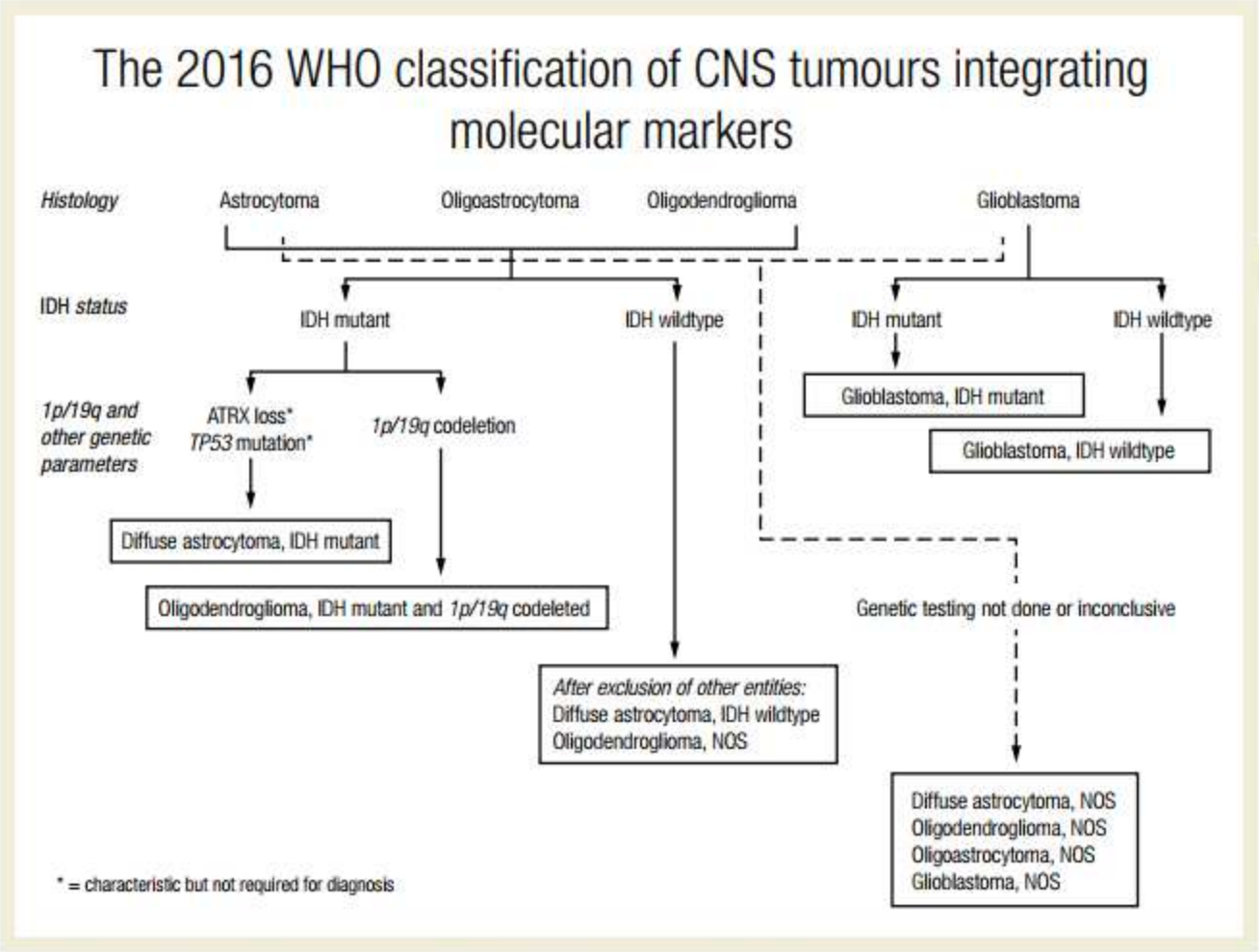


http://frontalcortex.com/gallery/pics/gliageek_Pilocytic%20Astrocytoma%20x200.jpg
Accessed 11/26/2019

Association of extent of resection (PR, partial resection, GTR, gross total resection) with overall survival in all patients (left) or by MGMT promoter methylation status



MGMT, O6-Methylguanine-DNA methyltransferase.



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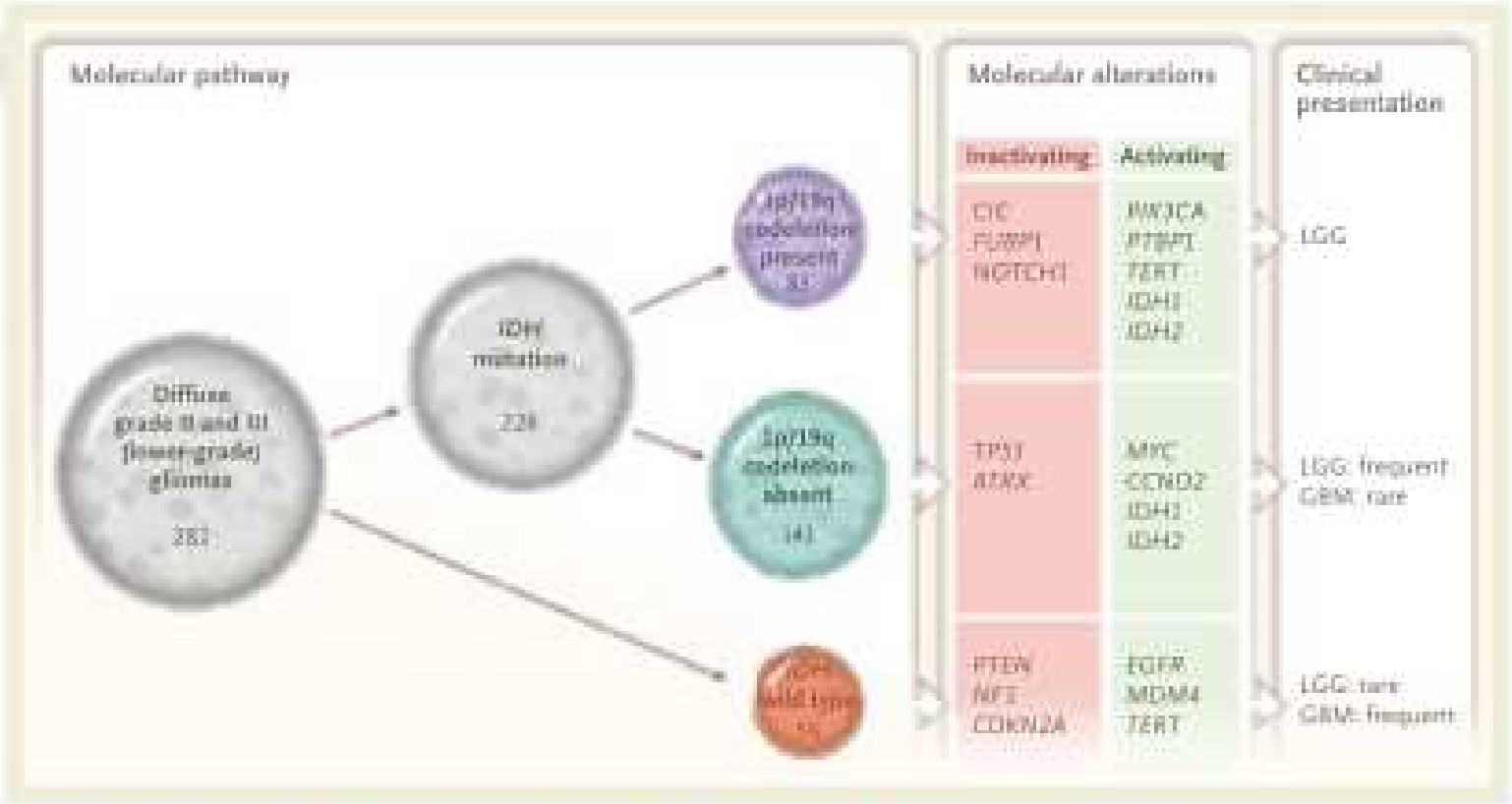


GBM, glioblastoma; IDH, isocitrate dehydrogenase; LGG, low-grade glioma.

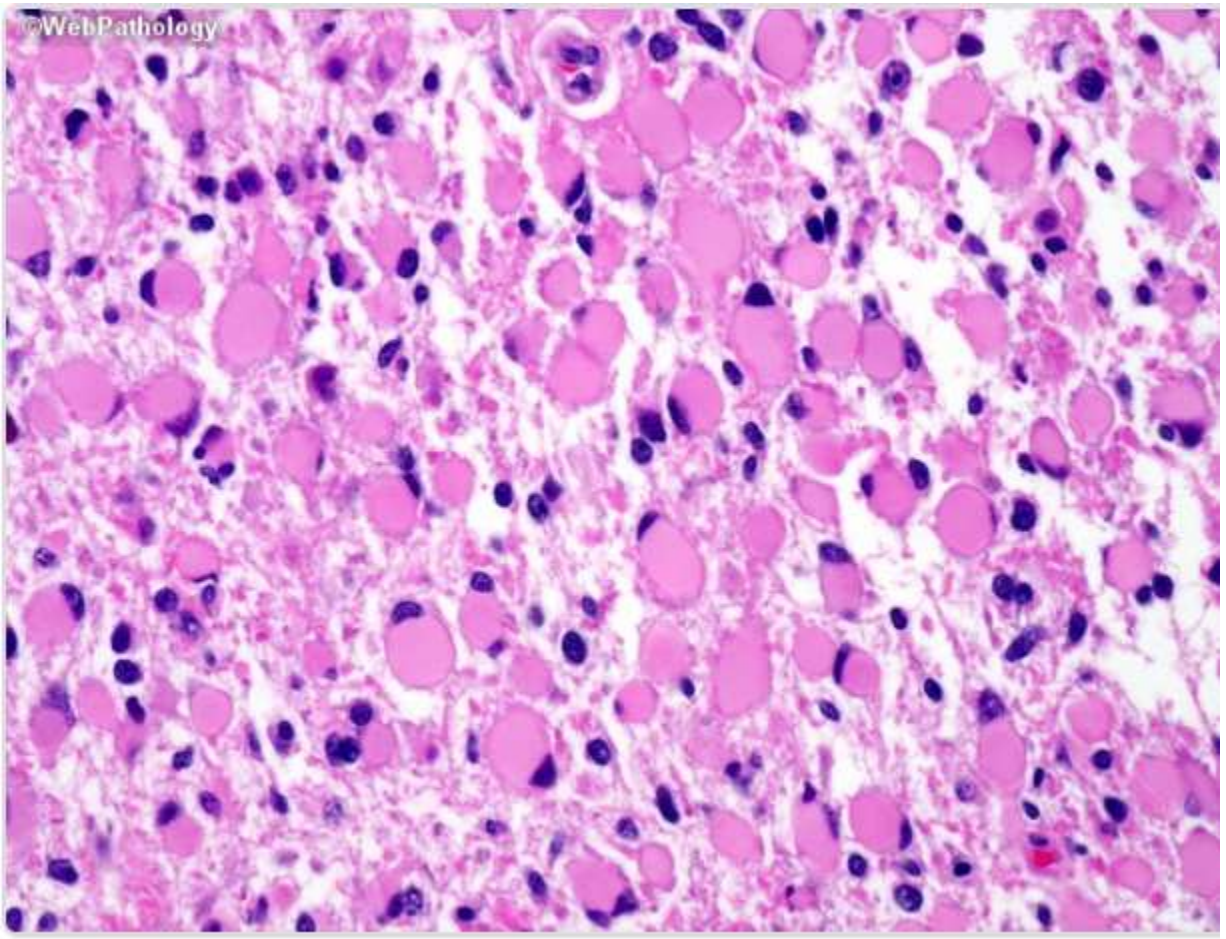
IDH mutations

- Mutations of IDH1 or 2 are gain of function mutations and result in the formation of a CpG island methylator phenotype (CIMP). This results in the silencing of numerous genes, including tumor suppressors.
- 1p/19q codeletion results from an unbalanced whole- arm translocation with loss of the derivative chromosome t(1p:19q).
- IDHmt and 1p/19q co-deleted tumors are usually associated with TERT promoter mutations.
- IDHwt LGGs are associated with intact alpha thalassemia/ mental retardation syndrome X-linked gene (ATRX) expression. This gene, like p53, is involved in telomere maintenance

Other astrocytomas

- Gemistocytic astrocytoma
- The predominant neoplastic astrocyte has a brightly eosinophilic cell body from which emanate abundant, stout processes
- May progress to glioblastoma
- Anaplastic astrocytoma
- Densely cellular with much nuclear pleomorphism.
- Behaves as does a glioblastoma

Gemistocytic astrocytoma



https://www.webpathology.com/image.asp?case=737&n=3
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Astrocytoma

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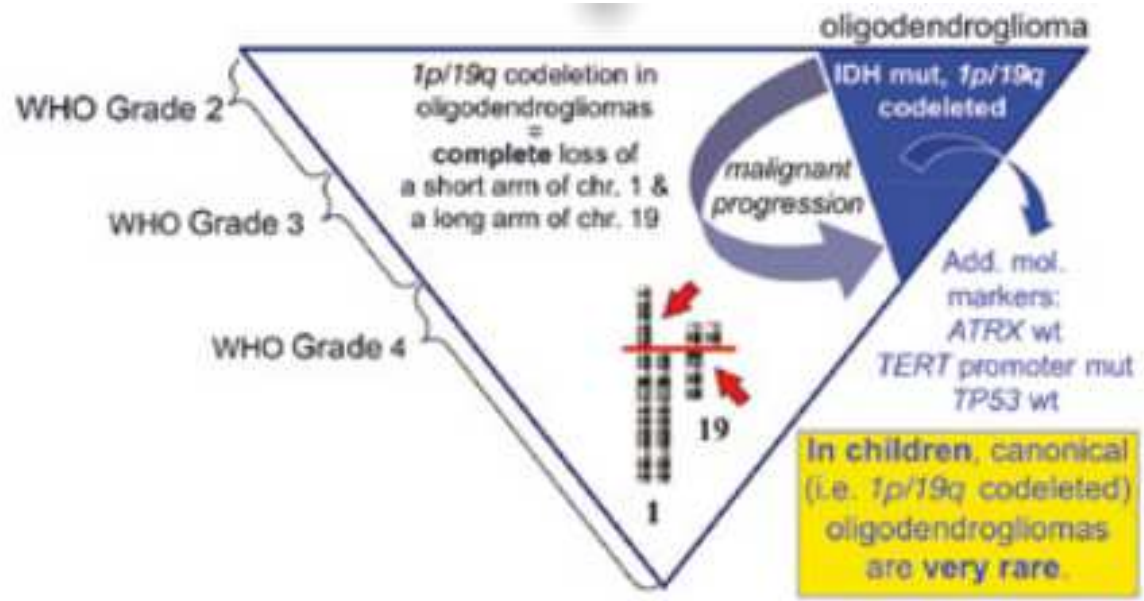
- Low grade supratentorial astroctyoma of children responds for prolonged periods to carboplatin and vincristine as well as to radiotherapy.
- Temozolide can slow tumor growth in low grade astrocytoma of adults.
- High grade astrocytoma is treated with radiotherapy and nitrosourea. Temozolide may also be active.



Chr, Chromosome; IDH, isocitrate dehydrogenase; mut, mutant; WHO, World Health Organization; wt, wildtype.

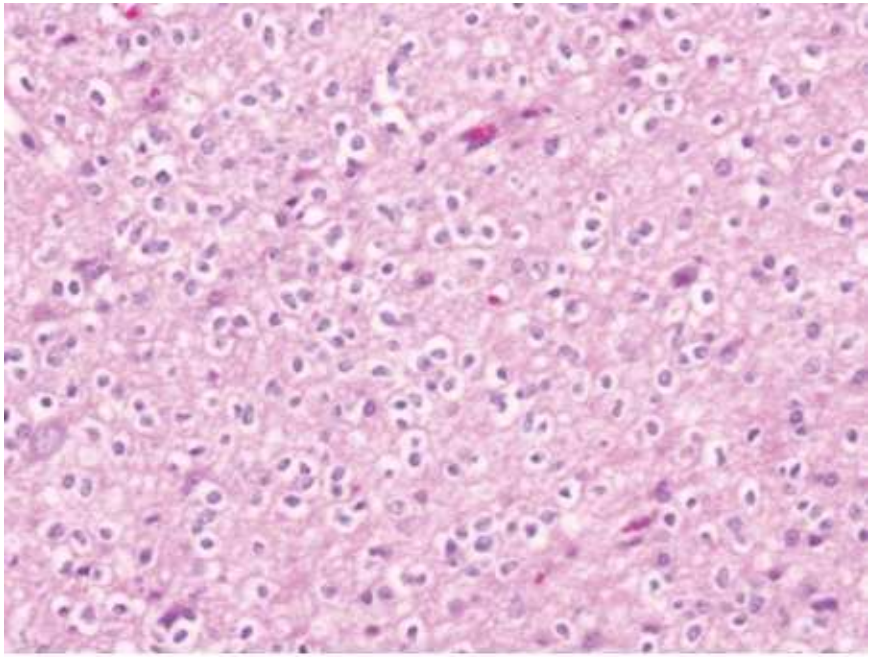
Oligodendroglioma

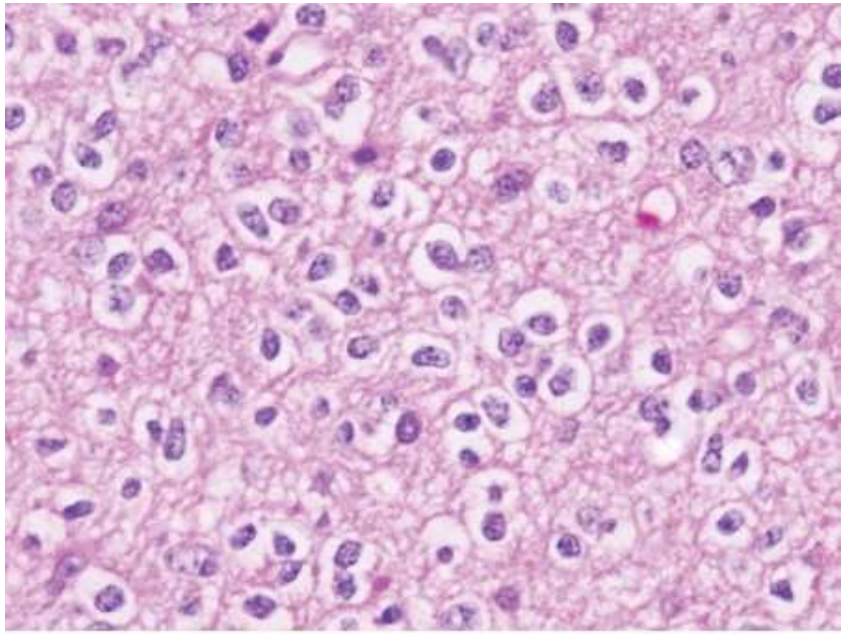
- 10% of all glial tumors.
- Cerebral hemispheres.
- More common in the 4th and 5th decades.
- Gross:
- Well circumscribed, gelatinous, gray mass often with cysts, focal hemorrhage, and calcification.
- Microscopic:
- Sheets of regular cells with spherical nuclei with fine chromatin surrounded by a clear halo of vacuolated cytoplasm ("Fried egg appearance")
- Tumor cells may satellite neurons, vessels.

Oligodendroglioma

- Loss of 9p, 10q, and mutation of CDKN2A associated with anaplastic change.
- Resection may be of benefit. Radiotherapy principal treatment.
- LOH 1p/19q common.
- Favorable if procarbazine, cyclophosphamide, vincristine added to radiotherapy as treatment.

Oligodendroglioma





200x, 400x. Figs. 30-13, 30-14 Accessed 04/27/2010

Pleomorphic xanthoastrocytoma

- Temporal lobes
- Children and young adults
- History of seizures
- Consists of neoplastic, occasionally bizarre, astrocytes, which are sometimes filled with lipids
- These cells express neuronal and glial markers
- The presence of abundant reticulin deposits, relative circumscription, and chronic inflammatory cell infiltrates, along with the absence of necrosis and mitotic activity, distinguish this tumor from more malignant types.

Brainstem gliomas

- Occur most often in the first 2 decades of life
- 10% to 20% of all brain tumors in this age group.
- Intrinsic pontine gliomas (the most common), with an aggressive course and short survival
- May be seen in adults
- Cervicomedullary junction tumors, often exophytic, with a less aggressive course
- Dorsally exophytic gliomas, with an even more benign course which may arise in the tectum of the midbrain, pons, or medulla.

Brainstem gliomas

- The term “optic pathway gliomas” (OPGs) indicates pilocytic astrocytomas arising in the optic nerves, chiasm and hypothalamus. They account for 3%–5% of pediatric intracranial tumors.
- Children with Type 1 neurofibromatosis (NF1) have an approximately 20% risk of developing an optic glioma. Patients with NF1 have a less aggressive clinical course than children without NF1.

Diffuse and focal brainstem glioma	
Diffuse tumours	**Focal tumours**
Majority (75%–80%)	20% remainder
Pons epicentre Diffuse growing with medulla-midbrain infiltration	Midbrain Pons: exophytic or intrinsic focal Medullary junction
Not surgically amenable	Possible surgery
Usually high grade	Usually low grade (not all)
2-year survival is less than 10%	Much better prognosis

Patient factors
Age (especially >75)
ABO blood type (A, AB)
Prior deep vein thrombosis or pulmonary embolism
Leg paresis, prolonged immobility
Multiple medical comorbidities
Obesity
Glioma-associated factors
Tumour grade (high > low-grade glioma)
Intraluminal thrombosis in surgical specimen
Recurrent disease
Tumour size (>5 cm)
Postoperative residual disease (biopsy>partial>gross total resection)
Treatment-associated factors
Postoperative period
Chemotherapy
VEGF-targeted treatment
Hormonal therapy
Venous access devices
Possible biomarkers

VEGF, Vascular endothelial growth factor.

Biomarker	Hazard ratio in multivariate analysis	p-value
Platelet count per $50x10^9$ L increase	0.73	0.019
Soluble P selectin per doubling	2.71	0.006
D-dimer per doubling	1.33	0.020

Leukocyte count (cutoff ≥11.5 × 109/L)
2. Platelet count (cutoff <196 × 109/L)
3. D-dimer (cutoff ≥1.66 µg/mL).

High grade pediatric gliomas

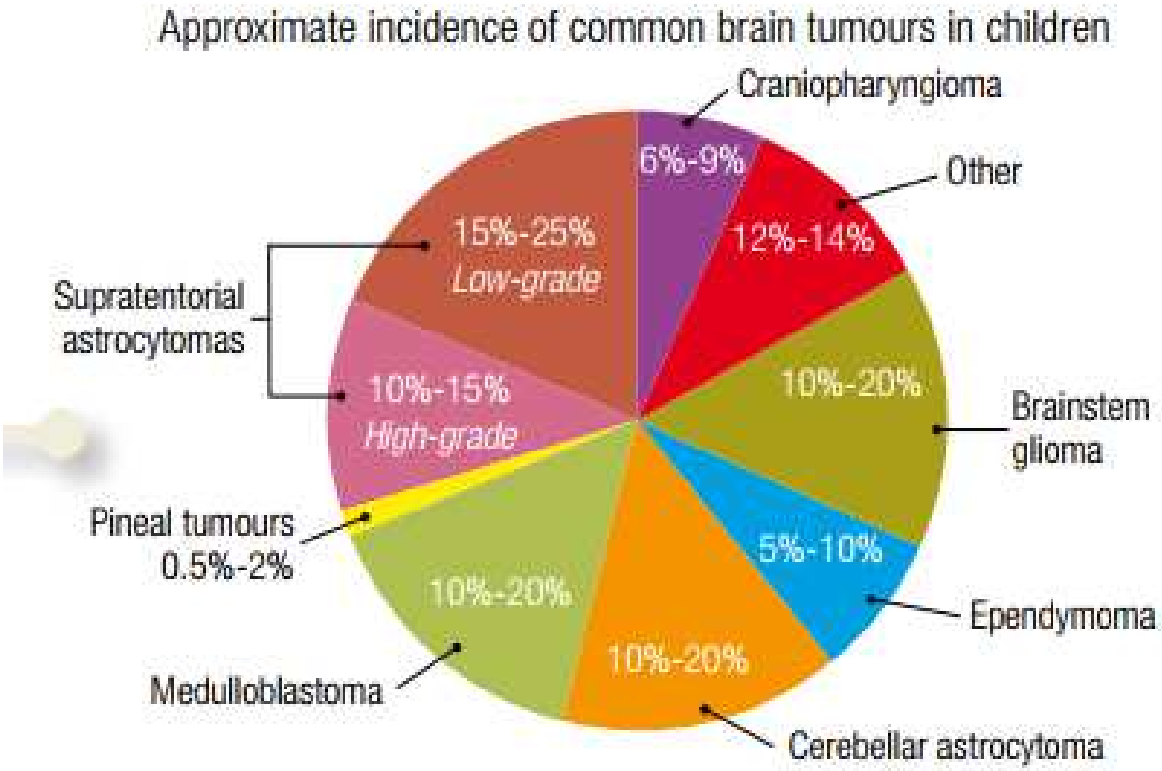
- Supratentorial HGGs represent 7%–11% of childhood CNS tumours. The median age at diagnosis is 9–10 years.
- Commonly altered genes in hemispheric high-grade astrocytomas of childhood are TP53 (in 30%–50% of cases), ATRX (in ~25%), SETD2 (in ~15%), CDKN2A (deletion; in ~30%), and PDGFRA (amplification and/or mutation; in ~30%)

High grade pediatric gliomas

- Mutations of the histone genes H3 (H3.1/H3.3) K27M are found exclusively in midline tumors as diffuse intrinsic pontine gliomas (DIPG) or thalamic lesions, whereas H3.3 G34 mutations are found exclusively in tumors of the cerebral hemispheres, more frequently seen in teenagers and young adults. In contrast, hemispheric glioblastomas in infants harbor NTRK fusions in approximately 40% of cases, and histone mutations have not been reported.

Syndrome	CNS tumour type
Cowden	Dysplastic gangliocytoma of the cerebellum
Li-Fraumeni	Multiple brain tumours, more frequently supratentorial primitive neuroectodermal tumour (PNET), medulloblastoma, astrocytoma
NF1	Neurofibromas, optic glioma
NF2	Schwannoma, meningioma, spinal ependymoma
Gorlin syndrome	Medulloblastoma, meningioma
Rubinstein-Taybi	Medulloblastoma, oligodendroglioma, meningioma
Tuberous sclerosis	Subependymal giant-cell astrocytoma
Turcot	Medulloblastoma
Von Hippel-Lindau	Haemangioblastoma

CNS, Central nervous system.


Approximate incidence of common brain tumours in children
Craniopharyngioma
6%-9%
Other
12%-14%
15%-25%
Low-grade
Supratentorial
astrocytomas
10%-15%
High-grade
10%-20%
Brainstem
glioma
Pineal tumours
0.5%-2%
5%-10%
Ependymoma
10%-20%
Medulloblastoma
10%-20%
Cerebellar astrocytoma

High grade pediatric glial tumors

- H3.3 (H3F3A) and H3.1 (HIST1H3B and, rarely, HIST1H3C) mutation at K27: The Histone K27–mutated cases occur predominantly in middle childhood (median age, approximately 10 years), are almost exclusively midline (thalamus, brain stem, and spinal cord), and carry a very poor prognosis.
- H3.3K27M cases occur throughout the midline and pons, account for approximately 60% of cases in these locations, and commonly present between the ages of 5 and 10 years.

High grade pediatric glial tumors

- Mutations in ACVR1, which is also the mutation observed in the genetic condition fibrodysplasia ossificans progressiva, are present in a high proportion of H3.1K27M cases. Primarily in pons.

High grade pediatric glial tumors

- H3.3 (H3F3A) mutation at G34: The H3.3G34 subtype presents in older children and young adults (median age, 14–18 years) and arises exclusively in the cerebral cortex. H3.3G34 cases commonly have mutations in TP53 and ATRX and show widespread hypomethylation across the whole genome.
- Patients with H3F3A mutations are at high risk of treatment failure.
- MGMT methylation rates >20%

High grade pediatric glial tumors

- IDH1 mutation: IDH1-mutated cases represent a small percentage of pediatric high-grade gliomas (approximately 5%), and pediatric high-grade glioma patients whose tumors have IDH1 mutations are almost exclusively older adolescents (median age in a pediatric population, 16 years) with hemispheric tumors.
- IDH1-mutated cases often show TP53 mutations, MGMT promoter methylation, and a glioma-CpG island methylator phenotype (G-CIMP).

High grade pediatric glioma

- Pleomorphic xanthoastrocytoma (PXA)–like:
- 10% of pediatric high-grade gliomas with specific DNA methylation patterns
- Commonly have BRAF V600E mutations and a relatively favorable outcome (approximately 50% survival at 5 years.
- Low-grade glioma–like:
- A small subset of pediatric brain tumors with the histologic appearance of high-grade gliomas show DNA methylation patterns like those of low-grade gliomas.

High grade pediatric glioma

- Pediatric glioblastoma patients whose tumors lack both histone mutations and IDH1 mutations represent approximately 40% of pediatric glioblastoma multiforme cases.
- The subtype characterized by high rates of MYCN amplification showed the poorest prognosis
- The subtype characterized by TERT promoter mutations and EGFR amplification showed the most favorable prognosis.
- The third group was characterized by PDGFRA amplification

High grade infant glioma

- Group 1 tumors were receptor tyrosine kinase (RTK) driven and primarily high grade (83%).
- These tumors harbored lesions in ALK, ROS1, NTRK, and MET.
- Median age at diagnosis was 3 months, and OS rates were approximately 60%.

High grade infant glioma

- Group 2 tumors were RAS/MAPK driven and were all hemispheric low-grade gliomas, representing one-fourth of hemispheric gliomas in infants.
- BRAF V600E was the most common alteration, followed by FGFR1 alterations and BRAF fusions.
- This group had a median age at presentation of 8 months and had the most favorable outcome (10-year OS rate, 93%).

High grade infant glioma

- Group 3 tumors were RAS/MAPK driven with low-grade histology and midline presentation (~80% optic pathway/hypothalamic gliomas).
- Most group 3 tumors showed either BRAF fusions or BRAF V600E. Median age at diagnosis was 7.5 months.
- The progression-free survival (PFS) rate at 5-years was approximately 20%, and the OS rate at 10 years was approximately 50% (far inferior to that of optic pathway/hypothalamic gliomas in children aged >1 year).

Anaplastic tumors

- Behave as glioblastomas
- Anaplastic astrocytoma
- Densely cellular
- Nuclear pleomorphism
- Mitotic figures are often observed.
- Anaplastic oligodendroglioma
- Densely cellular
- Nuclear pleomorphism
- Mitotic figures often observed
- Necrosis
- IDH mutations in 70%

Glioblastoma

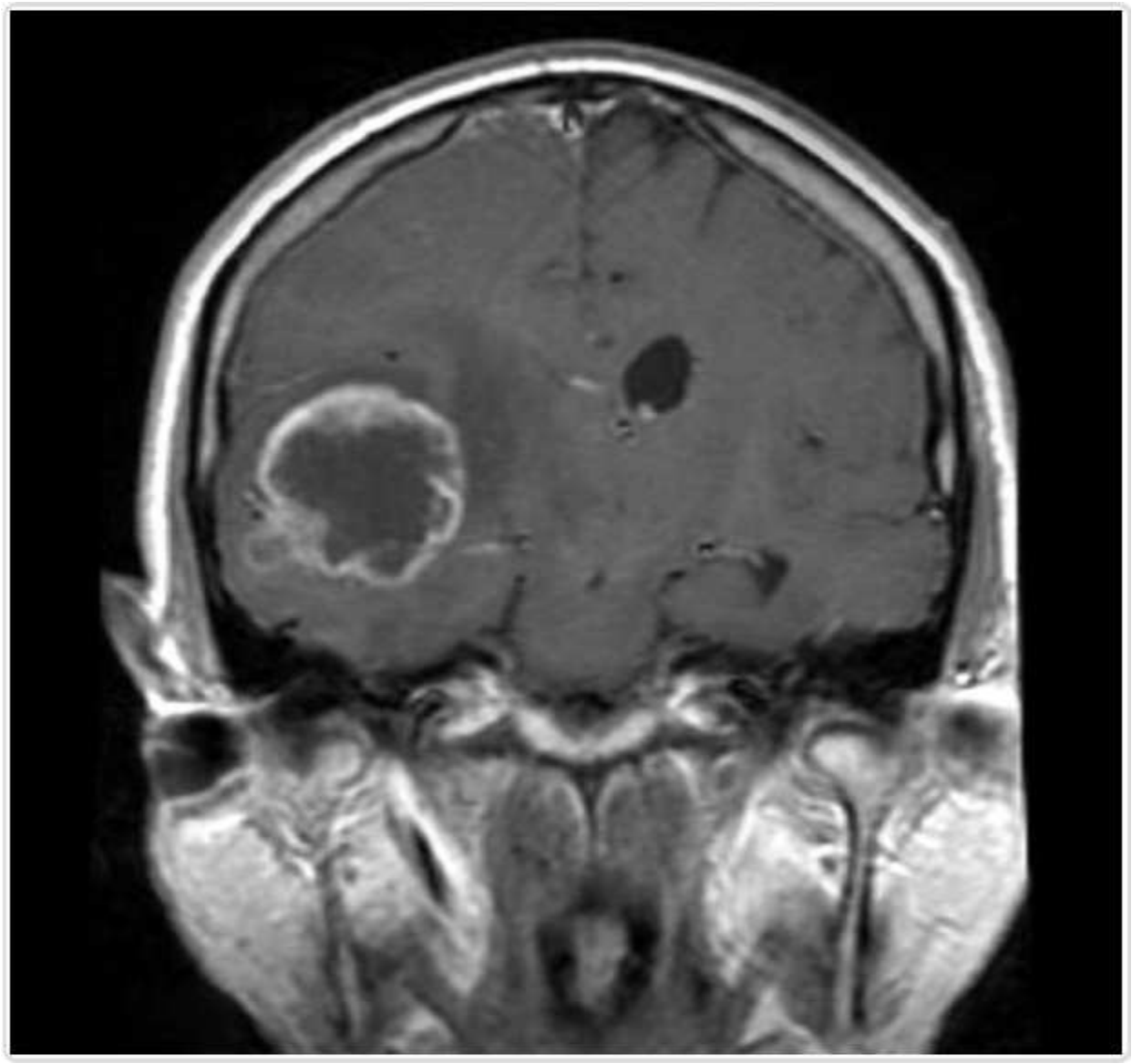
- May follow astroctyoma (younger patients) or present as primary lesion (older patients).
- Gross:
- Variation in the appearance of tumor from region to region:
- Firm and white to yellow and cystic or cystic with hemorrhage.

Glioblastoma

- Microscopic:
- Necrosis in a serpentine fashion along areas of hypercellularity.
- Tumor cells collect along edges of the necrotic regions ("pseudopalisade")
- Neoplastic vascular cell proliferation characterized by tufts lined by a double layer of endothelial cells.
- Glomeruloid body may be formed.

Glioblastoma multiforme

Ring enhancement of necrotic lesion on MRI



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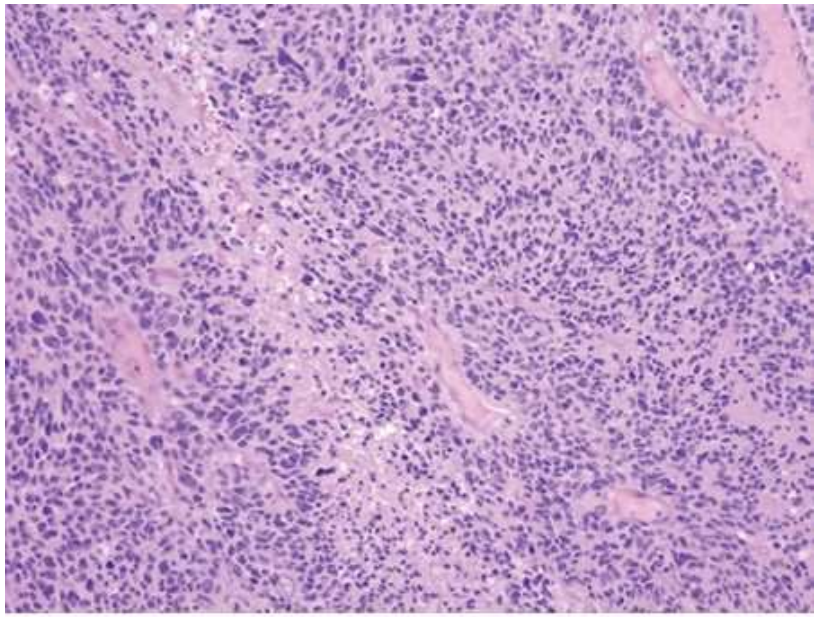
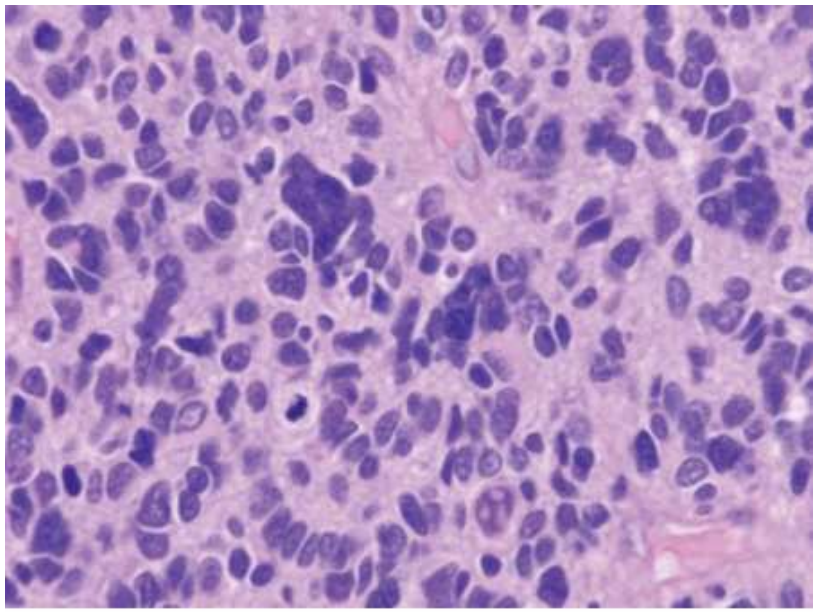
Glioblastoma



Source: Kantarjian HM, Wolff RA, Koller CA: *MD Anderson Manual of Medical Oncology*: http://www.accessmedicine.com



Source: Kantarjian HM, Wolff RA, Koller CA: *MD Anderson Manual of Medical Oncology*: http://www.accessmedicine.com

100x, 400x. Figs. 30-20, 30-21 Accessed 04/27/2010

Glioblastoma

- Primary lesion demonstrates:
- Amplification of EGFR and mutation or deletion of PETN, (activating RAS and PI_3K pathways),
- Deletion of checkpoint protein CDKN2A,
- MDM2 mutations (inhibiting p53)
- Pseudo-palisading cells are hypoxic, secrete VEGF, IL-8; over-express HIF-1.
- Promote angiogenic response, intracerebral migration (SRC activation).

Glioblastoma

- Histologic distinction between metastatic disease and primary glioma:
- Metastases to brain have associated tissue infiltrating lymphocytes (TIL)
- Gliomas demonstrate a reactive monocyte response
- IDH1 mutations elicit minimal response
- IDH2 mutations have associated TIL

Glioblastoma

- Five tumor subclasses:
- Neural class
- Proneural class.
- High frequency of IDH1 mutations and PDGFR amplifications.
- 10% of glioblastomas
- Predilection for frontal lobes
- Improved clinical outcomes.

Glioblastoma

- Mesenchymal class.
- NF1 mutations and deletions most common.
- 20% of children with NF1 mutations develop optic glioma
- ALDH1A3 mutation associated with radiation resistance.
- Classical class.
- EGFR amplifications common.
- MAPK class

Glioblastoma

- IDH mutations in 70% of anaplastic astrocytomas
- Longer progression-free survival (PFS) in patients with an IDH mutation without co-deletion of 1p/19q when treated with radiation therapy
- No significant treatment-dependent differences in PFS for patients with an IDH mutation with co-deletion of 1p/19q and IDH wild-type tumors.
- Patients with wild-type IDH tumors had the worst prognosis independent of treatment type.
- Patients with IDH-mutated tumors with co-deletion of 1p/19q had the best prognosis.

Glioblastoma

- Isocitrate dehydrogenase (IDH1) mutations favorable in glioblastoma.
- Tyrosine kinase inhibitors (tramatinib, dabafenib, vorasidenib) delay progression in IDH1 glioblastoma
- NFκB1A deletion (no inhibition of the EGFR pathway) associated with poor response to chemotherapy.
- Methylation of the promoter gene (silenced gene) encoding the DNA repair enzyme MGMT predicts response to alkylating drugs (e.g., sensitivity to temozolide).
- Silenced gene associated with longer survival.

Glioblastoma

- Poorly responsive tumor:
- 1p/19q intact
- Non-methylated MGMT promoter
- Wild-type IDH1/2 identify
- Treat with radiation alone.

Glioblastoma

- Radiation therapy with temozolide (followed by temozolide) demonstrates a clear survival benefit in those with silenced MGMT promoter gene.
- Procarbazine, cyclophosphamide, and vincristine with radiotherapy demonstrates durable responses in 50% of those patients with anaplastic oligodengrogliomas (1p/19q deletion), high-grade astrocytomas, and mixed gliomas.
- Bevacuzimab also effective as single agent. Limited duration of response.
- If CMV+, may respond to ganciclovir.

Medulloblastoma in children and adults	
Children	**Adults**
Peak age of incidence: 3-5 years	Median age: 24-30 years
Shorter clinical history: about 2 months	Longer clinical history: about 5 months
Classical MB is more common	Desmoplastic MB is more common
Biologically more aggressive	Biologically less aggressive
Usually median location	Usually lateral location
Higher surgical morbidity and mortality	Lower surgical morbidity and mortality
Poor RT tolerance	Better RT tolerance
Poor long-term survival	Better long-term survival

MB, Medulloblastoma; RT, radiotherapy.

Medulloblastoma

- Peak incidence at 7 years.
- 20% of tumors (second in occurrence to astrocytomas)
- Associated with Gorlin and Turcot syndrome.
- Granular cell origin.
- Occur in cerebellar vermis in children; cerebellar hemispheres in adults.
- Four types
- Three histological variants

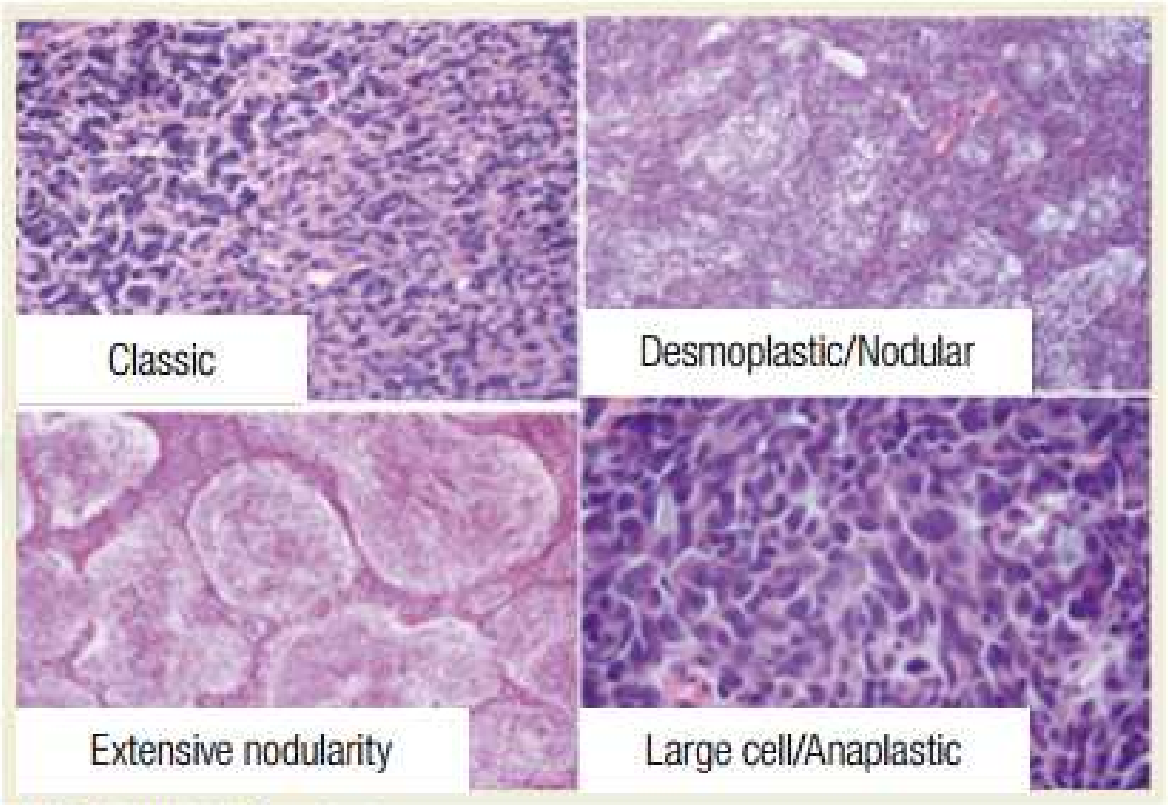
Medulloblastoma

- Four histologic types:
- Classic tumor, desmoplastic/ nodular (D/N), medulloblastoma with extensive nodularity (MBEN), anaplastic medulloblastoma and large cell medulloblastoma.
- Four molecular sub-groups:
- 1. WNT: Activation of WNT/beta-catenin signalling, overexpression of genes of the WNT pathway, with frequent mutations of the CNNTB1 gene, loss of chromosome 6 and accumulation of nuclear beta-catenin (favorable marker).

Medulloblastoma

- 2. Activation of the Sonic Hedgehog (SHH) pathway:
- For most desmoplastic MBs, which arise in a context of inactivating mutations in PTCH1 and SUFU genes, loss of 9q.
- 3. Group 3 tumors: High incidence of large cell/ anaplastic histology, very frequently metastatic, frequent MYC amplification.
- 4. Tumors of Group 4: Identified by isochromosome 17q as a frequent chromosomal alteration, mostly histologically of the classic variant.

2016 WHO classification of medulloblastoma

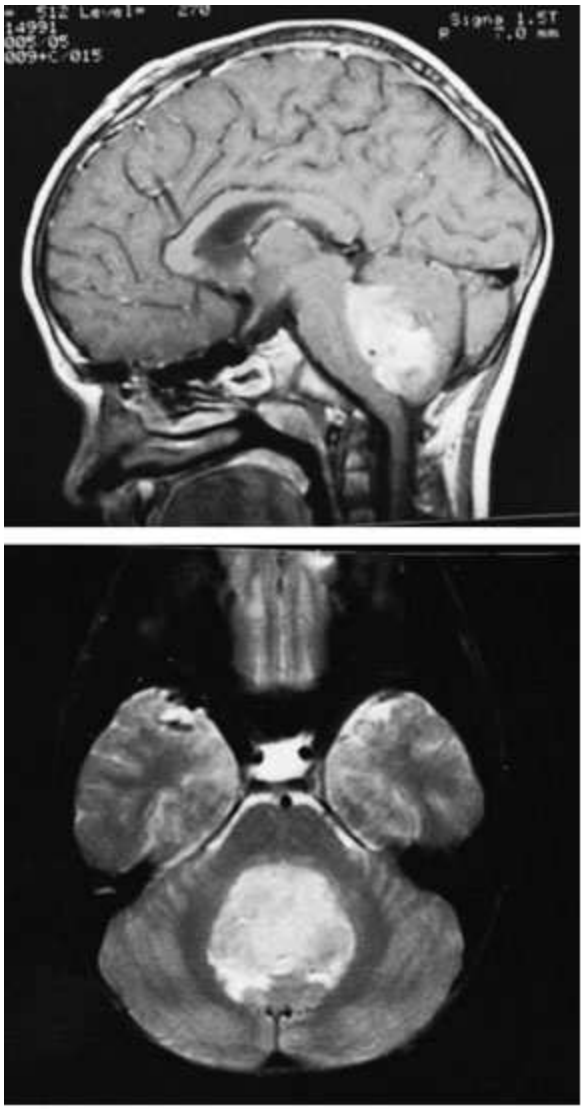


WHO, World Health Organization.

Medulloblastoma

- At the edges of the main tumor mass, medulloblastoma cells have a propensity to form linear chains of cells infiltrating through cerebellar cortex and penetrating the pia, spreading into the subarachnoid space.
- Dissemination through the CSF is a common complication, giving rise to nodular masses as far as the cauda equine (“drop metastases”).
- If the tumor occurs in the cerebral hemisphere, it is a primitive neuroectodermal tumor, not medulloblastoma

Medulloblastoma



MRI in the sagittal (*above*) and axial (*below*) planes, illustrating involvement of the cerebellar vermis and neoplastic obliteration of the fourth ventricle.

Fig. 34-11 Accessed 04/27/2010

Source: Ropper AH, Samuels MA: *Adams & Victor's Principles of Neurology 9th Edition*: http://www.accessmedicine.com

Medulloblastoma

- Gross:
- Well circumscribed, gray, friable, and may extend to cerebellar folia and involve the leptomeninges.
- Microscopic (classic):
- Densely cellular.
- Small, round cell tumor with Homer-Wright rosettes characterize tumor.
- A true rosette has cells around a central fibrillary core; pseudo-rosette is centered on a vessel
- May see mature neural elements as well.
- Express GFAP

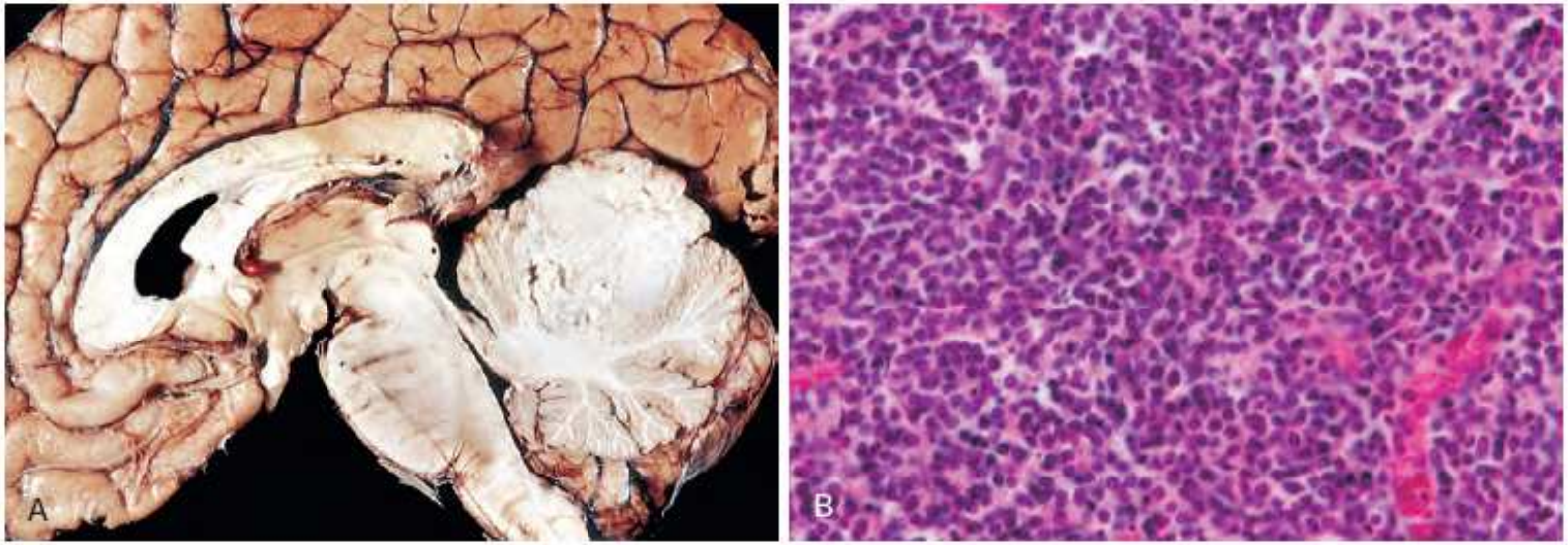
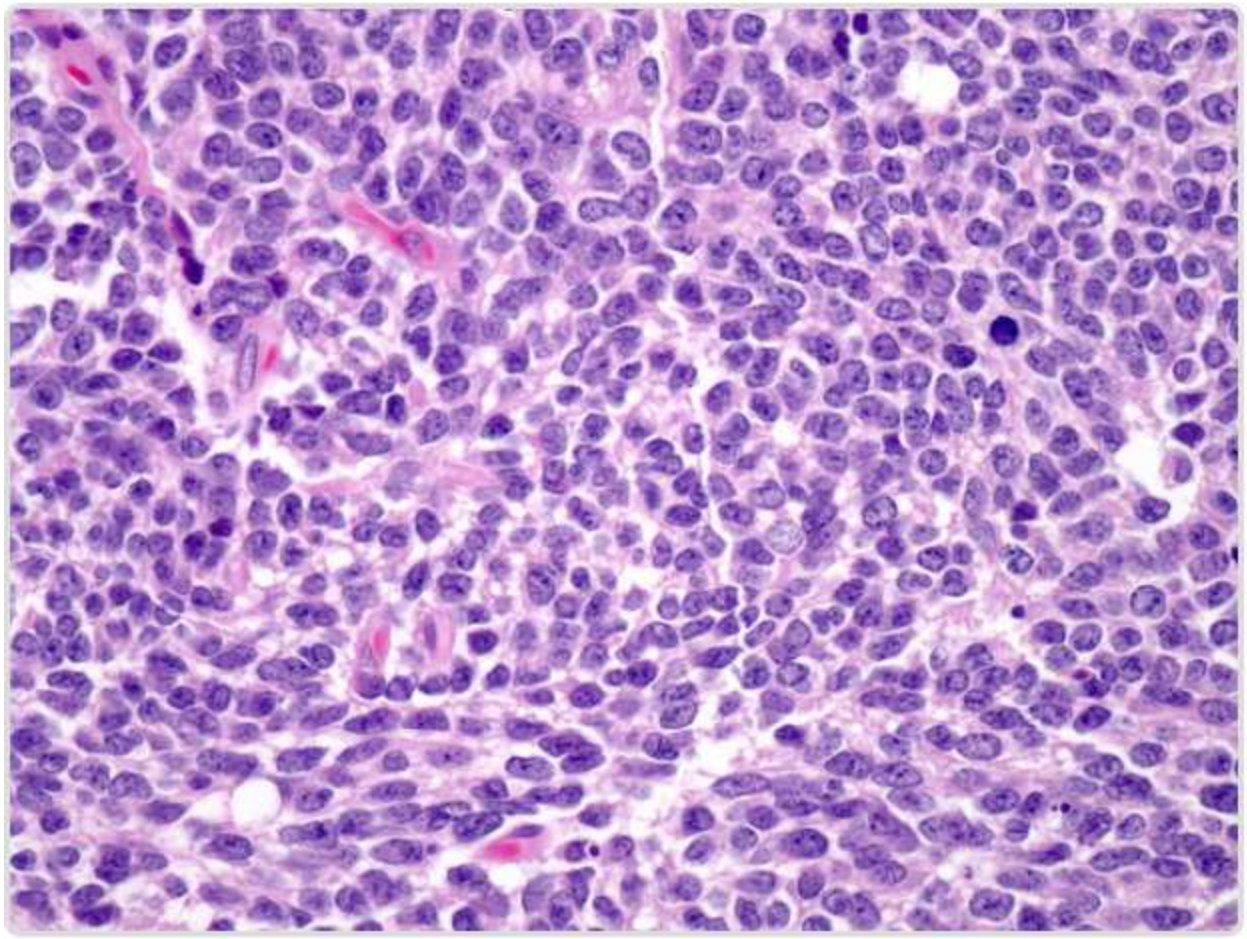


Figure 28-52 Medulloblastoma. **A,** Sagittal section of brain showing medulloblastoma destroying the superior midline cerebellum. **B,** Microscopic appearance of medulloblastoma.

Medulloblastoma



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Accessed 11/26/2019

Medulloblastoma variants

- Nodular desmoplastic variant
- Characterized by stromal response marked by collagen and reticulin deposition as well as pale islands of cells that show greater expression of neuronal markers.
- Large cell variant
- Large irregular vesicular nuclei, prominent nucleoli, frequent mitoses, apoptotic cells

Medulloblastoma types

- 1. WNT/β-catenin type
- Older children
- Classic medulloblastoma histology
- Monosomy 6 chromosome
- 90% 5 year survival
- 2. SHH-PTCH type
- Infants or young adults
- Cerebellar granule cell proliferation
- Nodular desmoplastic histology
- MYC-N amplification
- mTor activation

Medulloblastoma types

- Group 3
- Infants and children
- Large cell histology
- MYC amplification
- i17q
- Poor survival
- Group 4
- I17q without MYC amplification
- Possibly MYC-N amplification
- Classic or large cell histology

Medulloblastoma

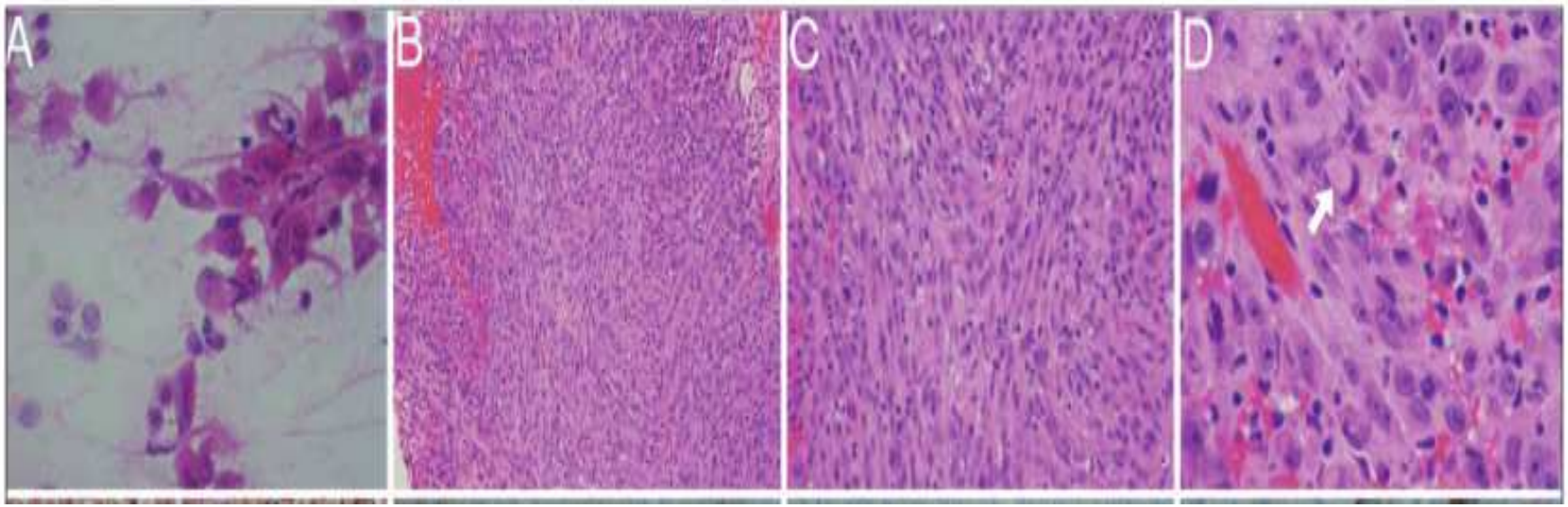
- MLL2 and MLL3 mutations involved in medulloblastoma development.
- Resect if possible.
- Radiosensitive.
- Adjuvant nitrosourea, cisplatin, vincristine with and following radiation.

Risk stratification for medulloblastoma	
Risk Stratification	
Low	Desmoplastic MB, beta-catenin
Standard	Total or near total resection, no metastasis
High	Post-surgical residual disease >1.5 cm^2, metastasis, CSF involvement
Very high	Large cell/anaplastic MB, *C-MYC/N-MYC* amplification

CSF, Cerebrospinal fluid; MB, medulloblastoma.

Typical teratoid/rhabdoid tumor

- Young children (<5 years-old)
- Supratentorial(50%), posterior fossa (50%)
- Large, soft, spread along brain surface
- Mesenchymal, epithelial, neuroglial elements present with islands of rhabdoid cells.
- High mitotic rate
- Rhabdoid cells have eosinophilic cytoplasm, sharp cell borders, and eccentric nuclei.
- Resemble striated muscle cells.
- Reactive for vimentin, epithelial membrane antigen
- 12 month survival



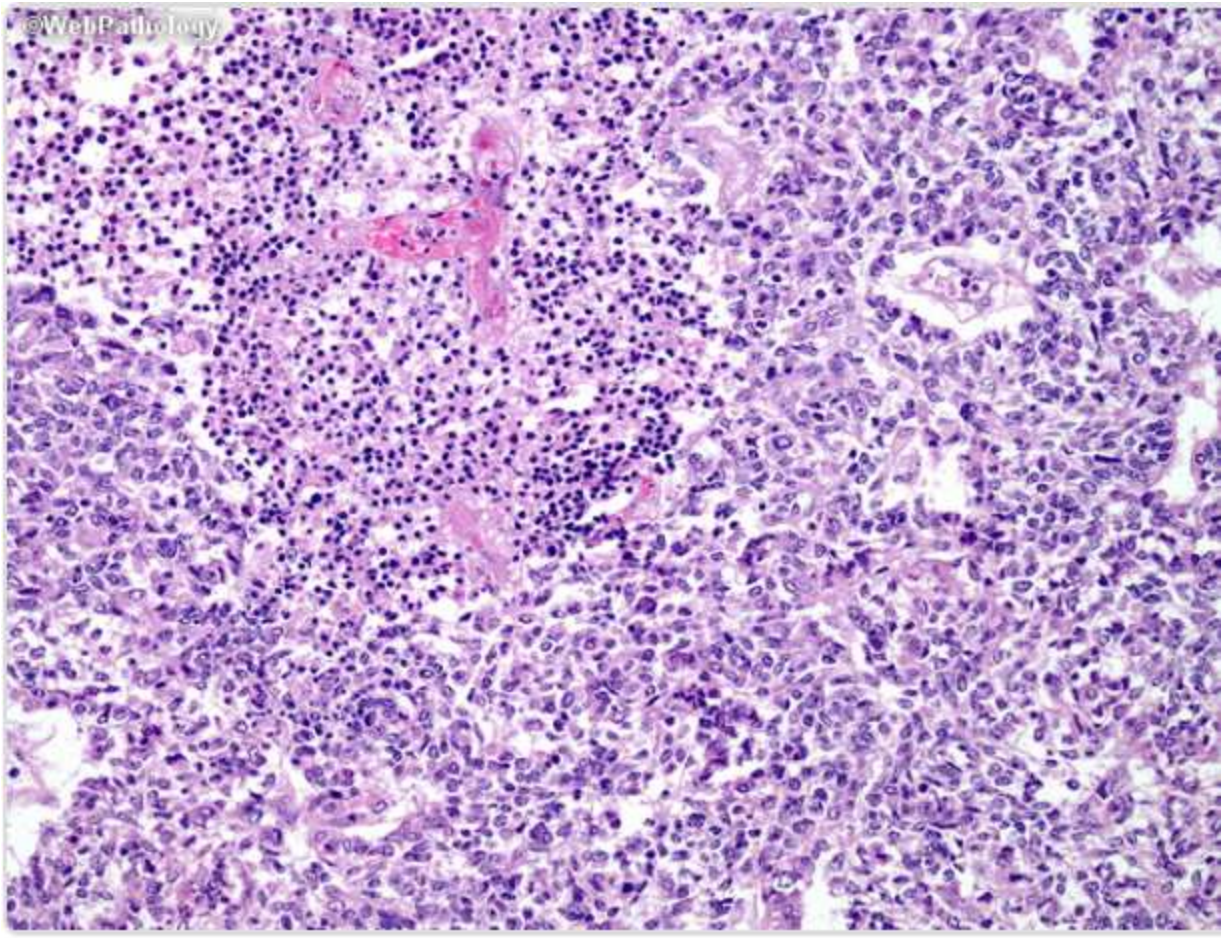
A, Tissue smear showing atypical epithelioid-like spindle cells with abundant pink cytoplasm, prominent nucleoli, and rhabdoid features, ×40. B, Atypical epithelioid-like spindle cells arranged in a fascicular pattern, ×10. C, Higher magnification showing epithelioid-like spindle cells with pink cytoplasm and prominent nuclei arranged in fascicular pattern, ×20. D, Focal tumor cells exhibiting rhabdoid features (arrow), ×40.

AACE Clinical Case Rep. 2015;1:e2-e7

Atypical teratoid tumor

- Posterior fossa and supratentorial origins in equal proportions.
- <5 years of age.
- Rhabdoid elements as defining characteristic of tumor.
- hSNF5/INI1 gene loss of function (chromosome 22) interferes with chromatin remodeling.
- Highly aggressive.

Atypical teratoid/rhabdoid tumor



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Primary CNS lymphoma

- Older patients as well as immunosuppressed patients.
- 5% of brain tumors
- May be seen in AIDS. (May be associated with EBV infection.)
- Very aggressive.
- Frequently multiple. Often involve deep gray matter as well as white matter and cortex.
- Uniform infiltration by neoplastic B-lymphocytes. Angiocentric growth.
- Reticulin stain demonstrate tumor cells separated one from another. ("hooping")

Primary CNS lymphoma

- 95% are diffuse large B-cell lymphomas which exhibit an activated immunophenotype with nearly all MUM1 positive (BCL6 positive, 50-80%; CD10 positive, 10%).
- MUM1 (Interferon regulatory factor 4) expressed late in B-cell development. Mutually exclusive with BCL6 expression.
- 6p21 locus involved (HLA).
- Affects NF_kB signalling.

Primary CNS lymphoma

- High dose methotrexate induction followed by cytarabine and thiotepa with stem cell harvest; then, high dose carmustine and thiotepa conditioning followed by stem cell transplant with later whole brain radiotherapy associated 5-year survival of >80%.
- If relapse, within 2 years.
- Steroid sensitive.
- Lelanomide effective in down-regulating MUM1.

Ependymoma

- Occur at any age.
- 10% of CNS tumors in children (usually before age 7).
- Usually periventricular, solid or papillary, arising from ventricle floor.
- In children, approximately 65%–75% of ependymomas arise in the posterior fossa. Children may present with signs and symptoms of obstructive hydrocephalus due to obstruction at the level of the fourth ventricle. They may also present with ataxia, neck pain or cranial nerve palsies.
- In adults, frequently in the spinal cord.
- Often the myxopapillary variant; tends to cause back pain, lower extremity weakness and/or bowel and bladder dysfunction.

WHO Grade	Corresponding tumour
1	Subependymoma
1	Myxopapillary ependymoma
2	Ependymoma
2 or 3	Ependymoma, *RELA* fusion-positive
3	Anaplastic ependymoma

WHO, World Health Organization.

Ependymoma

- Small, round cell tumor with gland like structures (rosettes, canals) that resemble embryological ependymal canal.
- More frequent are pseudo-rosettes in which the tumor cells are arranged around vessels with an intervening zone consisting of ependymal processes directed toward the vessel wall.
- Ependymal processes express GFAP.

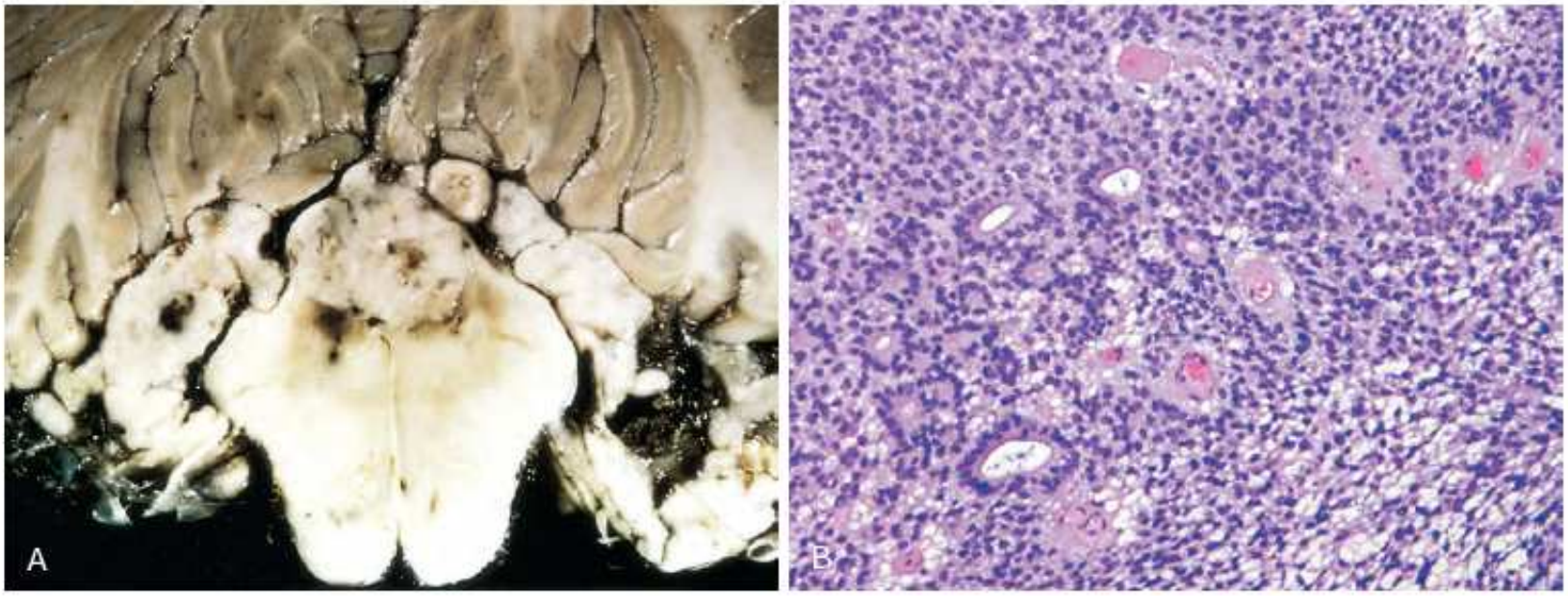
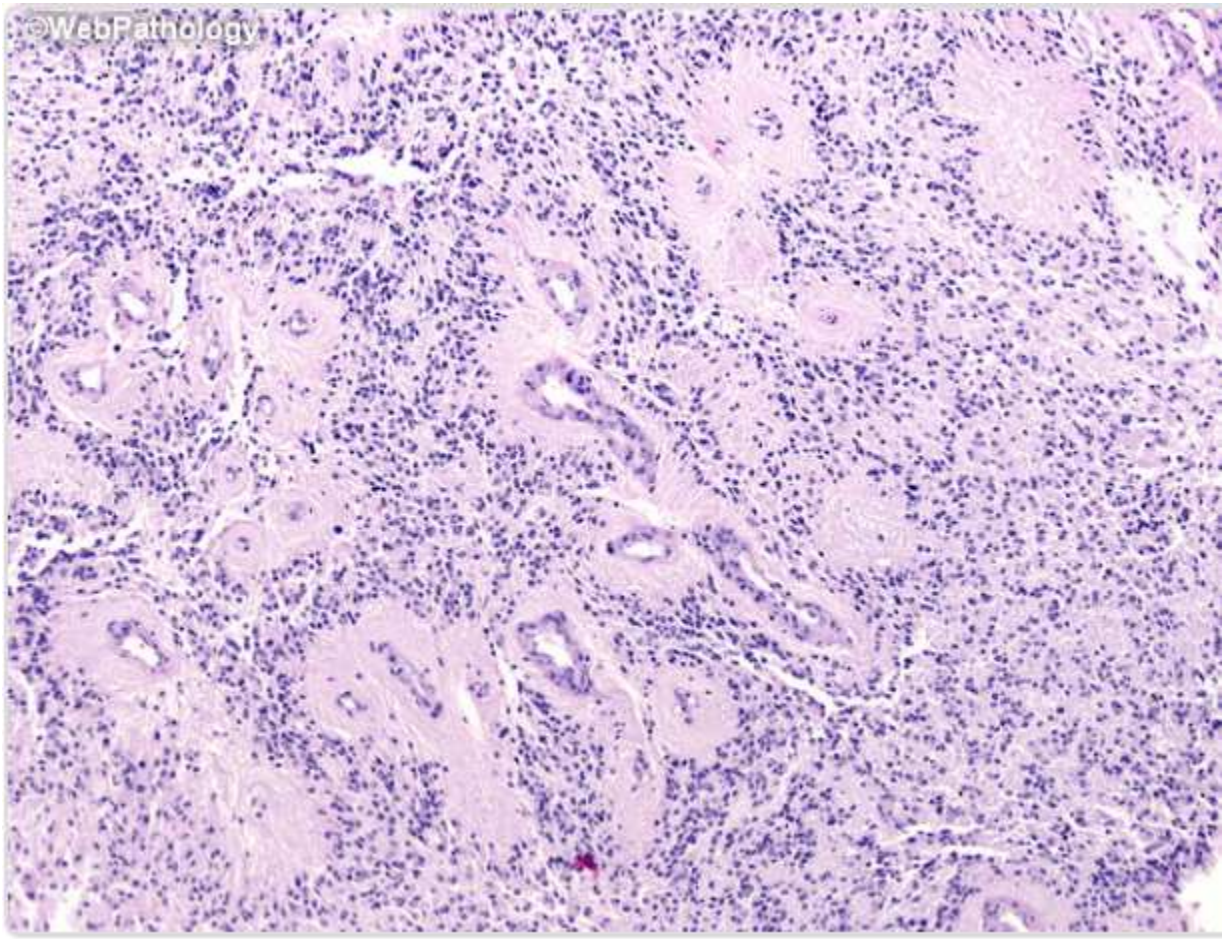


Figure 28-51 Ependymoma. **A,** Tumor growing into the fourth ventricle, distorting, compressing, and infiltrating surrounding structures. **B,** Microscopic appearance of ependymoma.

Ependymoma



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Ependymoma

- CSF dissemination common.
- Associated with loss of both NF2 alleles in spinal cord location; loss of one TSC1 allele if supratentorial.
- Resect if possible.
- Craniospinal radiation may be indicated.
- The myxopapillary ependymoma occurs in the filum terminale of the spinal cord.
- Contaiins papillary elements in a myxoid backround (acid mucopolysaccharides).

WHO Grade	Corresponding tumour
1	Subependymoma
1	Myxopapillary ependymoma
2	Ependymoma
2 or 3	Ependymoma, *RELA* fusion-positive
3	Anaplastic ependymoma

WHO, World Health Organization.

Other peri-ventricular tumors

- Subependymoma.
- Slow growing nodules.
- Usually in lateral and 4th ventricles.
- Choroid plexus papilloma.
- Usually in lateral (children) and 4th (adults) ventricles.
- Resect.
- Radiation if anaplastic.
- Choroid plexus tumors associated with von Hipple-Lindau and Li-Fraumeni syndromes.

Colloid cyst of 3rd ventricle

- Occur in young adults.
- Non-neoplastic.
- Attached to roof of 3rd ventricle.
- May cause non-communicating hydrocephalus.

- Positional headache as clue.
- May be rapidly fatal.

Germ cell tumors

- Generally occur along midline.
- Pineal (male predominance) or suprasellar sites.
- 90% in first two decades.
- “Fried egg” appearance to cells if germinoma (50% in pineal location)
- Mesenchymal elements as well if teratoma (15% in pineal location).
- Resect if possible.
- Germinoma highly radiosensitive.
- Radiation with chemotherapy including cisplatin, etoposide, and bleomycin, or carboplatin, etoposide, vinblastine for non-seminomatous tumor

Pineal

- Dysgerminomas most common tumor.
- Often positive for placental alkaline phosphatase, c-kit, and OCT4.
- May cause precocious puberty, particularly in boys.
- Pineocytomas resemble paragangliomas
- Benign
- No secretory function.

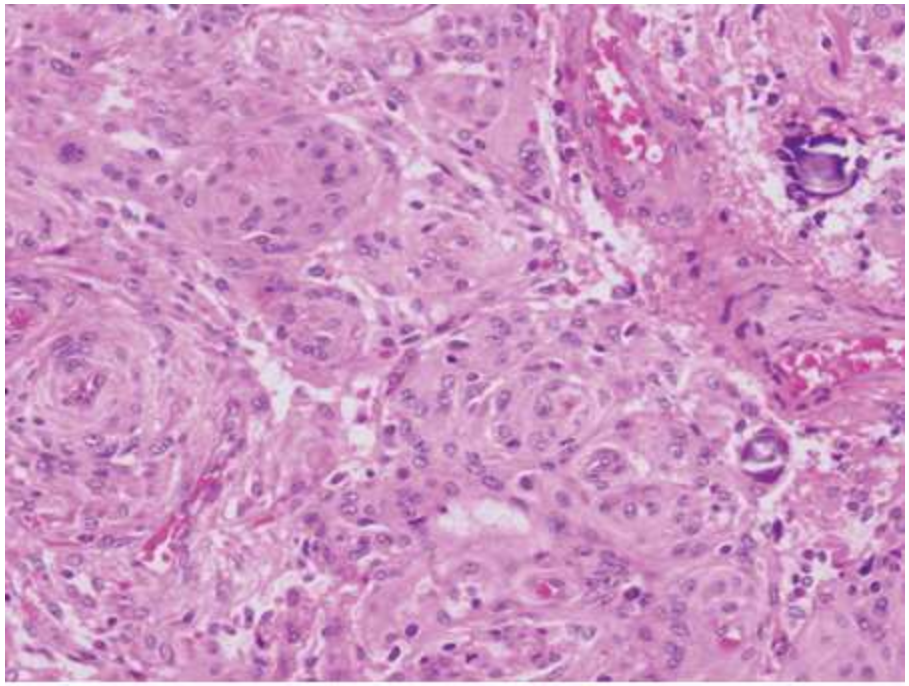
Pineal

- Pineoblastomas resemble medullobastoma or neuroblastoma
- Mitoses common.
- Positive for synaptophysin but negative for glail fibrillary acidic protein.
- Mass effect.
- Surgical excision difficult.
- Dysgerminoma is radiosensitive.

Meningioma

- Usually in women (3:2 cerebrum; 10:1, spine)
- Rounded masses with well defined dural bases that compress underlying brain.
- May extend to overlying bone, particularly if plaque like growth.
- Arise from meningothelial cells of the arachnoid
- Nine histologic patterns
- 80% contain Progesterone receptors; 40% estrogen receptors; 40% androgen receptors.
- 50-60% associated with NF2 deletion (22q12); are high grade.
- TRAF7 mutation associated with low grade lesion

Meningioma



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Meningioma

- Syncytial Pattern
- Whorled clusters of cells in tight groups without visible membranes
- Fibroblastic Pattern
- Elongated cells with abundant collagen deposition between them
- Transitional pattern

Meningioma

- Psammomatous pattern
- Presence of calcified syncytial nests (Psammoma body)
- Secretory pattern
- PAS positive intracytoplasmic droplets
- TRAF7 mutation at 16p13.3 affects MAPK, NF-kB
- Microcystic pattern
- Spongy appearance
- NF2 mutations at 22q12.2 common in meningioma;
- May see overexpression of FAK at 8q24.3, leading to extension

Meningioma

- Atypical meningioma
- 4-10 mitoses per high power field, or
- Patternless growth with increased cellularity and small cells with high nuclear to cytoplasm ratio
- Clear cell pattern also possible
- Chordoid pattern also possible
- Papillary meningioma
- Rhabdoid meningioma
- Highly aggressive meningiomas.
- May require radiation therapy.

Neurofibromatosis 1

- More common
- Characterized by:
- Neurofibromas of peripheral nerve
- Gliomas of the optic nerve
- Pigmented nodules of the iris (Lisch nodules)
- Cutaneous hyperpigmented macules (café au lait spots).
- NF1 (17q22) loss leads to constitutive activation of RAS as inhibitory GTPase (neurofibromin) is lost.

Neurofibromatosis 1

- Solitary neurofibroma presents in soft tissues. Not invasive; however, adnexal structures often enwrapped by the edges of the lesions.
- A plexiform neurofibroma involves peripheral nerve; difficult to distinguish nerve from neoplasm; locally invasive.
- Malignant transformation of plexiform neurofibroma or multiple neurofibromata are seen.
- Triton tumors contain epithelial, mesenchymal, and neural elements.

Neurofibromatosis 2

- Schwann cell tumor
- Present at the cerebello-pontine angle. (CN VIII)
- NF2 (22q12) mutation with loss of gene product, merlin, related to red cell cytoskeletal protein 4.1 (ERM family)

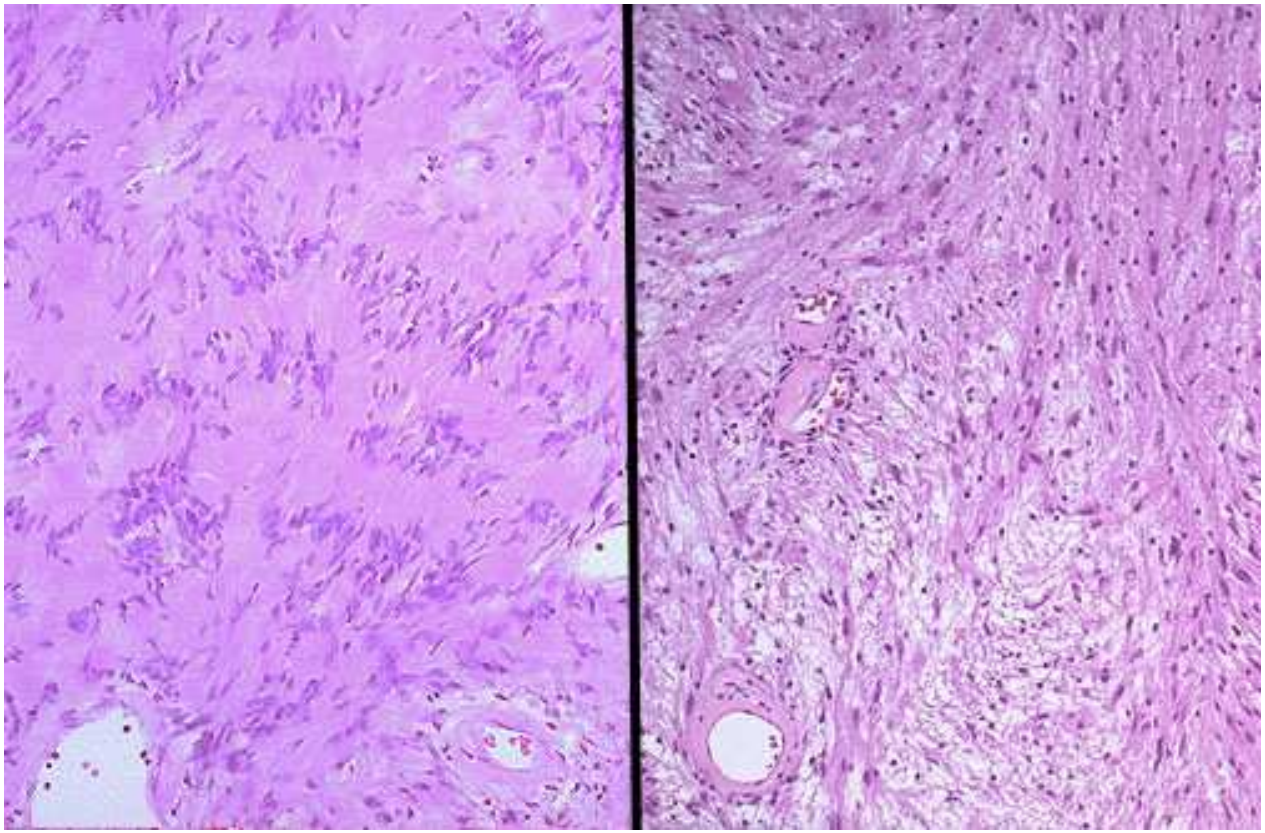
  Does not establish stable cell-cell junctions

Schwann cell tumor

- Present at the cerebello-pontine angle. (CN VIII)
- Antoni A pattern:
- Spindle cells in palisade.
- Verocay body formation (Acellular areas between palisading nuclei)
- Rare mitoses.
- Antoni B pattern:
- Looser stroma and myxoid change
- Fewer cells
- Schwann cell origin.
- Associated with NF2 (22q12)

  Loss of gene product, merlin.
- Resect.

Schwann cell tumor



Left: Antoni A pattern

Right: Antoni B pattern

https://webpath.med.utah.edu/CNSHTML/CNS187.html
Accessed 04/27/2010

Schwann cell tumor

- Solitary neurofibroma presents in soft tissues. Not invasive; however, adnexal structures often enwrapped by the edges of the lesions.
- Plexiform neurofibroma involves peripheral nerve; difficult to distinguish nerve from neoplasm; locally invasive.
- NF1 (17q22) loss leads to constitutive activation of RAS as inhibitory GTPase (neurofibromin) is lost.
- Malignant transformation of plexiform neurofibroma or multiple neurofibromata are seen.
- Triton tumors contain epithelial, mesenchymal, and neural elements.

Spinal tumors

- 50% extradural, 40% intradural–extramedullary and 10% intramedullary manifestation.
- Ninety-five percent of extradural tumors are metastases and the remaining 5% are primary bone tumors.
- Intradural neuromas, ependymomas and meningiomas are most frequently found. Intra-axial ependymomas, astrocytomas and hemangiomas are also diagnosed.

Tumour	Axial pain	Lumbar pain	Radicular symptoms	Ataxia	Myelopathy	Vegetative dysfunction	Intracranial pressure
Extradural	++	+	+	–	–	+	–
Intradural–extramedullary	–	+	++	+	+	+	(+)
Intramedullary	–	–	++	++	++	+	+

Common extradural spine tumours

Origin	Tumour	Biological behaviour	Preferred therapy
Bone	Osteoidosteoma	Benign	Intralesional curettage
	Osteoblastoma	Benign	Marginal en-bloc resection
Cartilage	Osteochondroma	Benign	En-bloc resection
Blood vessels	Aneurysmal bone cyst	Semi-malignant	Interventional embolisation, intralesional curettage
Notochordal	Chordoma	Malignant	Aggressive en-bloc resection + radiotherapy
Haematopoietic system	Multiple myeloma	Malignant	Radiotherapy + chemotherapy
	Ewing sarcoma	Malignant	

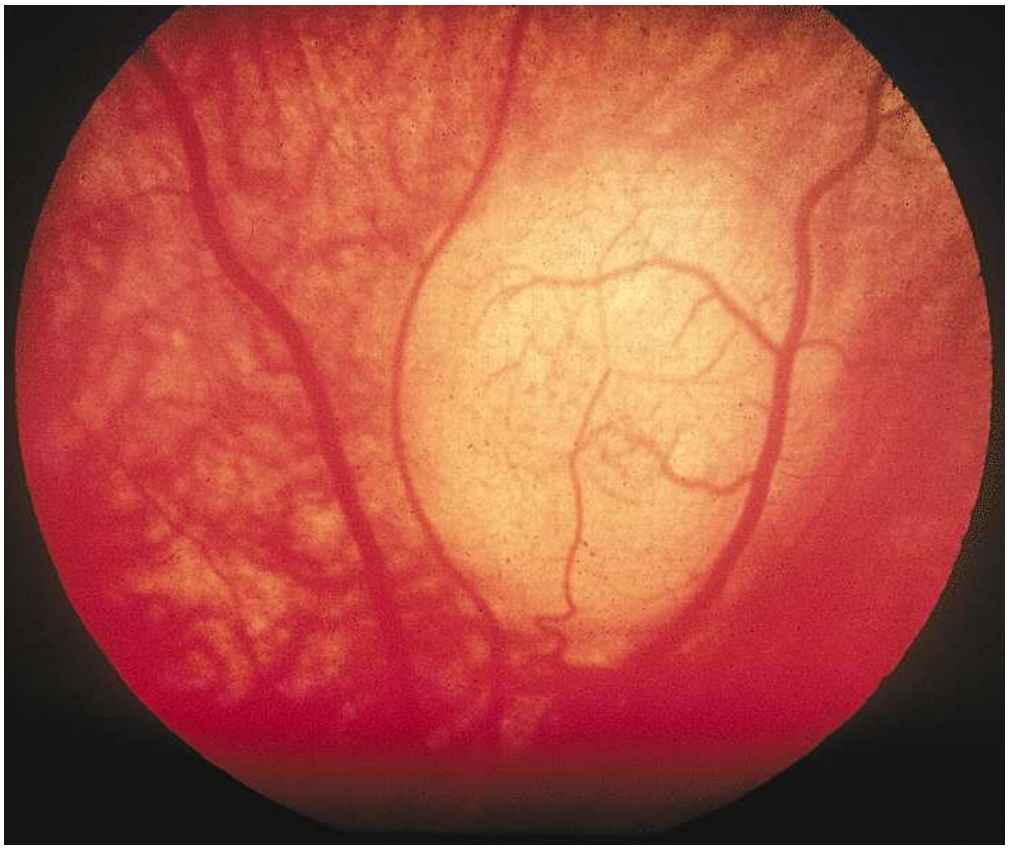
Retinoblastoma

- Most common ocular tumor in children.
- 70% sporadic
- Loss of light reflex; “red” eye
- Neuronal origin
- Primitive embryonal tumor characterized by small cells with large nuclei.
- Flexner-Wintersteiner pseudo-rosettes identified about vessel.
- 13q14 (Rb) germline mutation essential for development of tumor.
- Germline mutation associated with bilateral disease as well as pinealoblastoma.

Retinoblastoma

- Spread is usually to brain and bone marrow.
- Enucleation if eye not salvageable.
- Carboplatin, vincristine, etoposide chemotherapy in attempt to reduce tumor burden and salvage eye
- Risk of osteosarcoma and melanoma as secondary cancers

Retinoblastoma

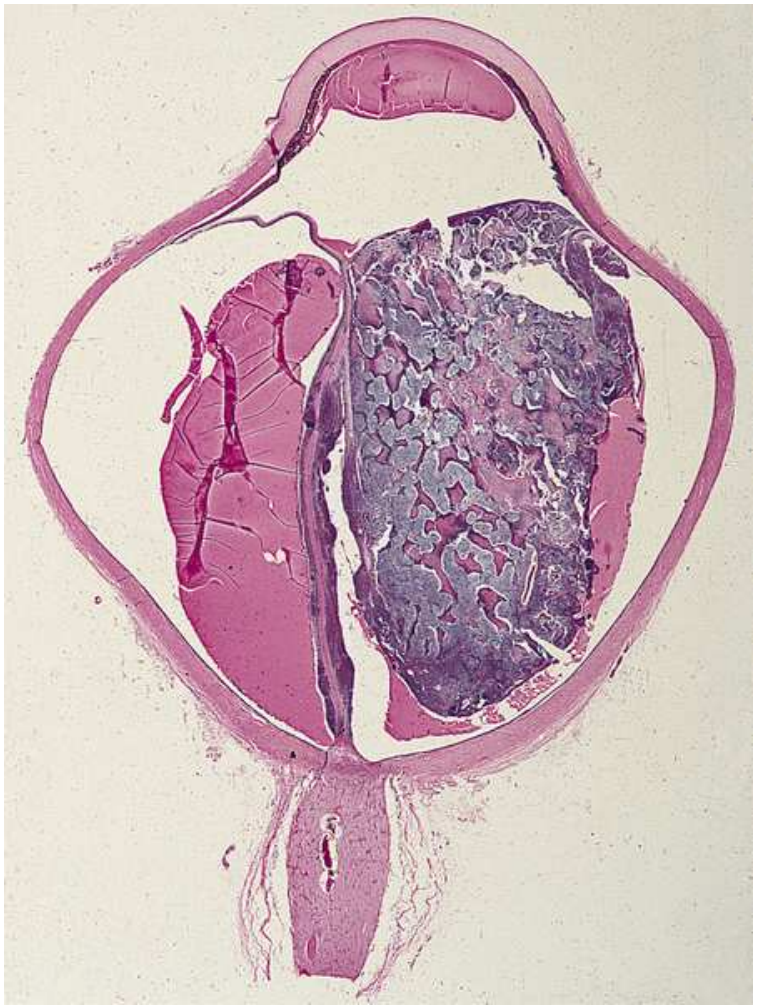


Fundus photograph of retinal tumor that has grown into the subretinal space. Retinal blood vessels pass over the tumor.

Fig. PL-04A

McLean, IW, Burnier, MN, Zimmerman, LE, Jakobiec, FA., “Tumors of the eye and ocular adnexa.” Atlas of Tumor Pathology,Third Series, Fascicle 12. Armed Forces Institute of Pathology, Washington, D.C. 1994.

Retinoblastoma

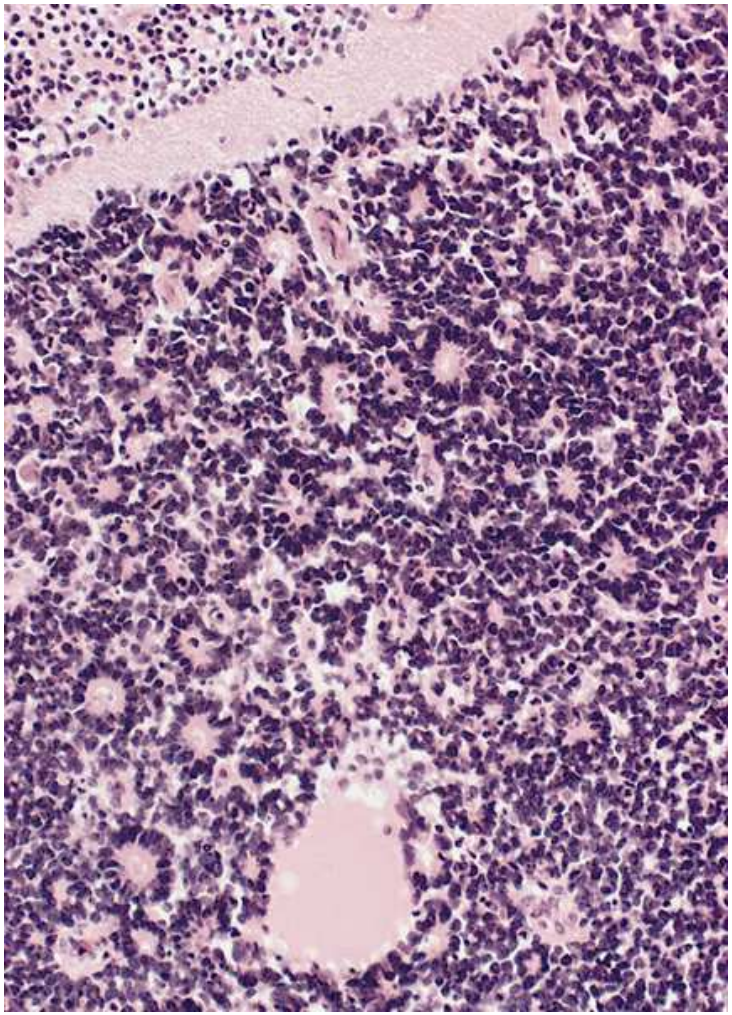


Total retinal detachment and collapse of the anterior chamber caused by a partially necrotic tumor with viable cells surrounding blood vessels in a sleeve pattern. There is no invasion of choroid, sclera, or optic nerve.

Fig. PL-04C

McLean, IW, Burnier, MN, Zimmerman, LE, Jakobiec, FA. , “Tumors of the eye and ocular adnexa.” Atlas of Tumor Pathology,.Third Series, Fascicle 12. Armed Forces Institute of Pathology, Washington, D.C. 1994.

Retinoblastoma



Flexner-Wintersteiner rosettes.

Fig. 23-23L

Lack, EE., “Tumors of the Adrenal Gland and Extra-Adrenal Paraganglia.” Atlas of Tumor Pathology, Third Series, Fascicle 19. Armed Forces Institute of Pathology, Washington, D.C. 1997.

Intra-ocular melanoma

- 10% of white population have uveal nevi. Rarely progress to melanoma.
- Peak incidence in 7th decade.
- May arise in anterior (iris) or posterior (ciliary body or choroid) uveal tract.
- There is loss of light reflex. An area of pigmentation is noted in fundus.
- Pigmented neoplasm that present with spindle cells or with epithelioid cells.
- Epithelioid cells are characteristic of poorer tumor prognosis.

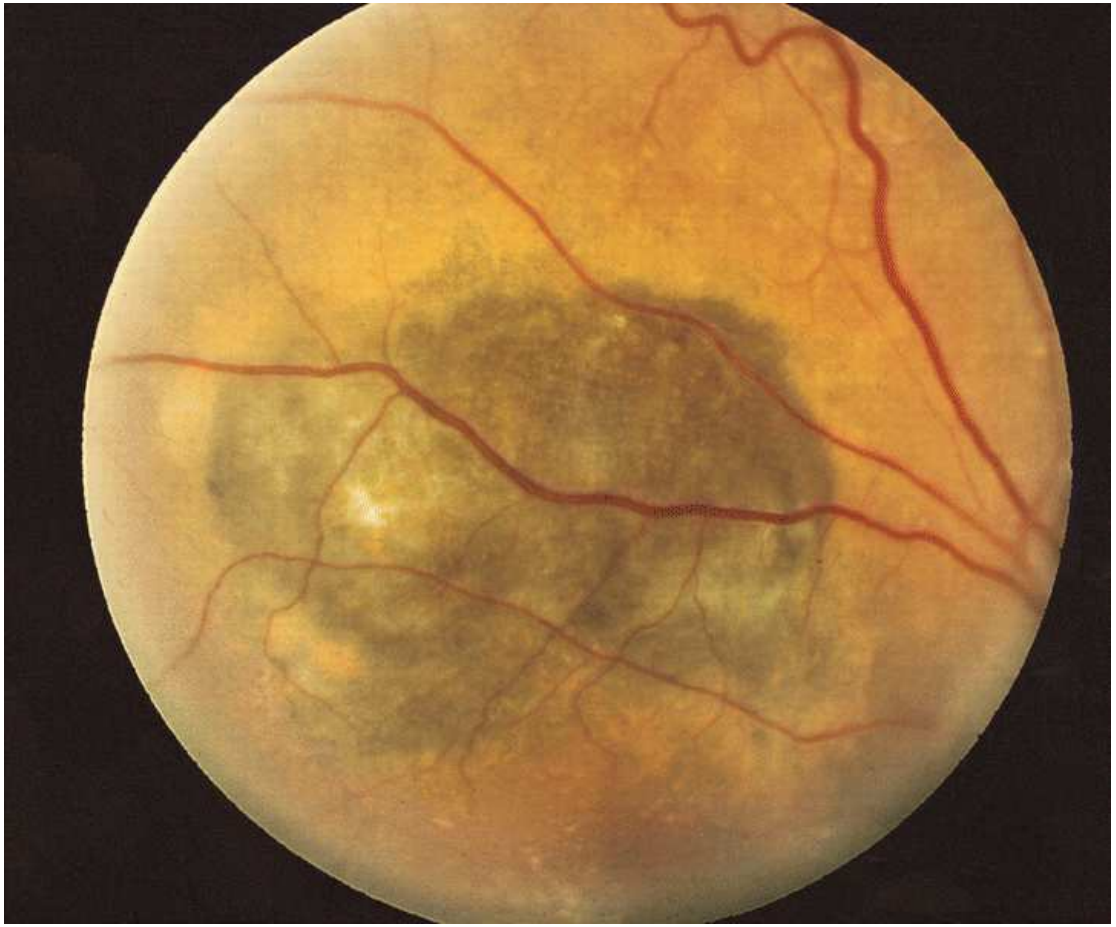
Intra-ocular melanoma

- Hematogenous spread (no lymphatics in uvea). Liver prime metastatic site.
- Iris melanoma (best prognosis)
- Ciliary body melanoma (worst prognosis)
- May be treated with plaque brachytherapy (^{125}I)
- or charged particle (protons, α-particles) therapy
- Large tumors are enucleated.

Malignant melanoma

- End and limited-stage ocular melanoma managed by close observation.
- Radiation may be employed.
- Enucleation:
- If tumor is growing in a blind eye
- Involves more than half the iris or involves the anterior chamber
- Extraocular extension.

Malignant melanoma



Pigmented choroidal lesion noted. Irregular borders.

Fig. PL-10A

McLean, IW, Burnier, MN, Zimmerman, LE, Jakobiec, FA. , “Tumors of the eye and ocular adnexa.” Atlas of Tumor Pathology,.Third Series, Fascicle 12. Armed Forces Institute of Pathology, Washington, D.C. 1994.

Malignant melanoma

Heavily pigmented, mushroom-shaped choroidal tumor.

PL-XIIB

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Neuronal tumors

- Gangliоglioma is a glial neoplasm resembling a low grade astrocytoma in which also are found mature-appearing ganglion cells.
- Binculeate forms often are present.
- Cystic change may be noted centrally.
- Slowly growing but may progress.
- Often present with seizures.
- Generally found in temporal lobe.

Neuronal tumors

- MAPK pathway activation.
- BRAF alterations are observed in approximately 50% of ganglioglioma cases, with V600E being by far the most common alteration;
- Cortical neurocytoma consists of cells resembling oligodendrocytes and islands of neuropil.
- Most commonly found in the ventricular system.

Neuronal tumors

- Dysembryoblastic neuroepithelial tumor
- Temporal lobe.
- Presents with seizure.
- Septal lesions associated with hydrocephalus.
- Multiple discrete intracortical nodules of small, round cells in columns about central cores of processes and associated with a myxoid background.
- Low grade astrocytoma may surround the nodules in complex lesions.

Neuronal tumors

- FGFR1 mutation in 80%
- PDGFRApK385 mutation in corpus callosum
- Demoplastic
- MAPK pathway involved
- Rosette-forming glioneuronal tumor (RGNT)
- adolescents and adults
- FGFR1 hot spot mutations
- 30% PI3KCA and NF1 mutations as well
- Good prognosis

Neuronal tumors

- Diffuse leptomeningeal glioneuronal tumor (DLGNT)
- Patients with DLGNT-MC-1 were diagnosed at an earlier age than were patients with DLGNT-MC-2 (5 years vs. 14 years, respectively).
- The 5-year overall survival was higher for patients with DLGNT-MC-1 than for those with DLGNT-MC-2 (100% vs. 43%, respectively)
- loss of 1q in MC-1; gain, in MC-2
- 1p/19q deletions in MC-1
- MAPK activation

Complications of elevated intracranial pressure

- Papilledema.
- Herniation of the uncus of the temporal lobe
- Leads to compression of CN III, causing an ipsilateral fixed, dilated pupil, with paralysis of all extra-ocular movements except abduction (CN VI).
- Tonsillar herniation
- Causes brainstem compression and compromises vital respiratory and cardiac centers in the medulla oblongata.

Familial tumor syndromes

- Neurofibromatosis type 1
- Associated with hyperpigmented macules (Café au lait spots) and pigmented iris nodules (Lisch).
- Variably penetrating.
- NF1mutation
- Neurofibromatosis type 2
- Bilateral schwannomas of CNVIII
- Multiple meningiomas
- Spinal cord ependymomas are spectrum of neurofibromatosis type 2.
- Autosomal recessive.
- NF2.

Tuberous sclerosis

- Manifest as seizures, autism, mental retardation.
- Characterized by the development of hamartomas in the brain as well as glial nodules in the retina.
- Express both neurofilaments and GFAP.
- Cysts may be seen in the liver or pancreas.
- Renal angiomyolipma, cardiac rhabdomyoma, and pulmonary lymphagioleiomyomatosis may be found.
- Angiofibromas and subungual fibormas may also be found.
- Hypopigmented skin areas (ash-leaf patches) or localized leathery thickening of skin (shagreen patches) are cutaneous manifestations of the disorder.

Tuberous sclerosis

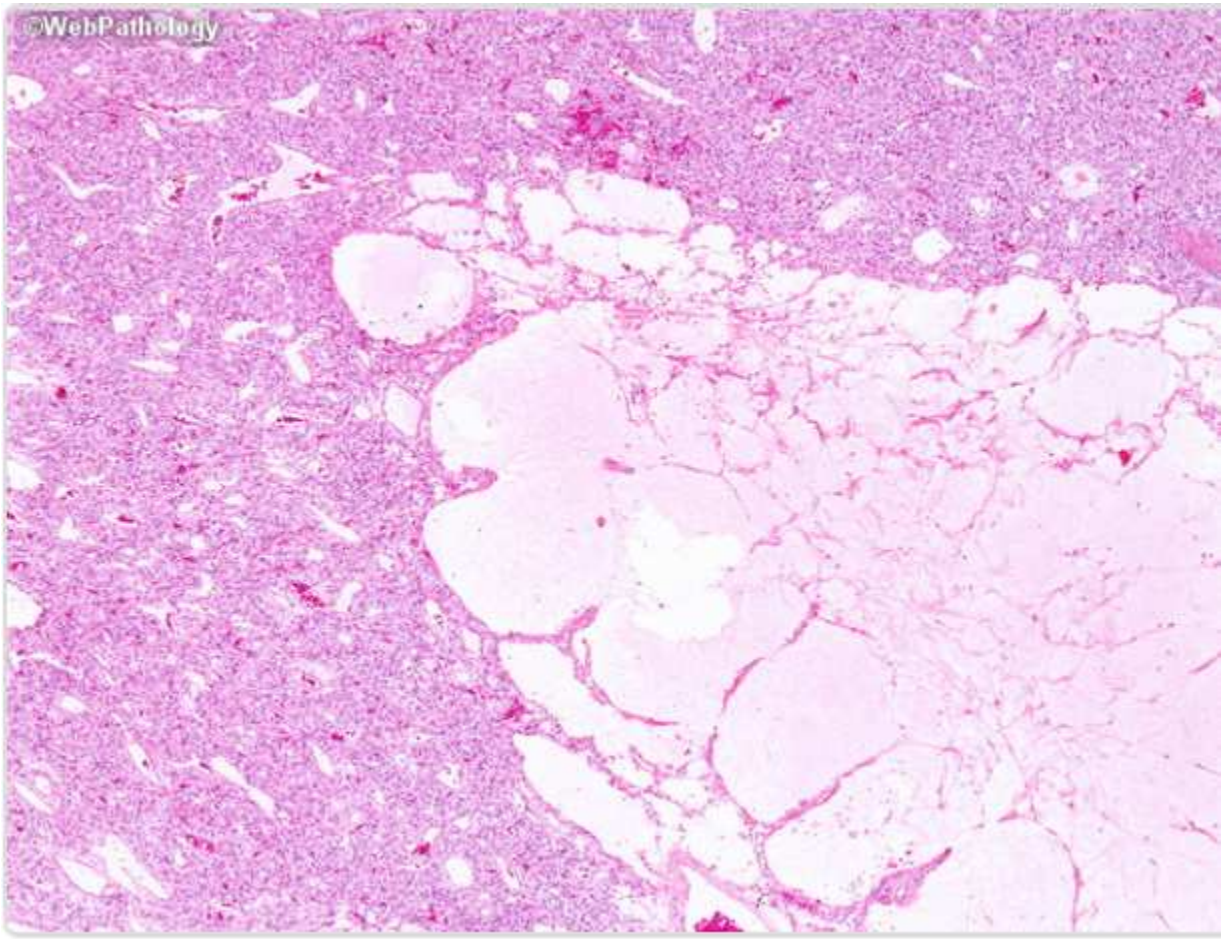
- TSC1 (9q34) encodes hamartin; TSC2 (16p13.3) encodes tuberin. The two proteins bind to form a complex that inhibits the kinase in mTOR.
- Autosomal dominant.
- Cortical and subependymal tumors are associated with loss of only one allele.
- Subependymal giant cell astrocytoma has loss of both alleles.
- Hamartomatous nodules bulge into the ventricular system (“candle-gutting”).
- Surgical resection of hamartomatous eliptogenic foci may be beneficial.

Von Hippel-Lindau disease

- Hemangioblastoma (vascular tumor) of cerebellum and retina.
- May see cysts of pancreas, liver, kidneys. Renal carcinoma may also develop.
- Autosomal dominant.
- VHL gene (3p25-26) encodes a protein that is a component of a ubiquitin ligase complex that downregulates HIF-1.
- Polycythemia present in 10% of cases.
- Mis-sense mutations alone in VHL are highly likely to be associated with pheochromocytoma in this syndrome.

Hemangioblastoma

Well-formed vascular tumors with abundant lipid content.



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Paraneoplastic syndromes

- Lambert-Eaton syndrome
- Proximal muscle weakness
- Orthostatic change
- Diplopia but no ptosis (distinguish from myasthenia gravis)
- Improves during the day (distinguish from myasthenia gravis)
- Due to antibodies to presynaptic voltage gated (P/Q) calcium channel

Paraneoplastic syndromes

- Subacute cerebellar degeneration
- Presents with dizziness, nausea, and vomiting
- Ataxia
- Dysarthria
- Vertigo
- Diplopia
- Antibody to Purkinje cell
- May coincide with Lambert-Eaton syndrome
- Also seen in thiamine deficiency
- Optic neuritis
- Anti-CV2 antibody (to oligodendroglia)

Paraneoplastic syndromes

- Limbic encephalitis
- Short-term memory defects
- Seizures
- Psychiatric disturbances
- Anti-Hu antibody
- May also be seen with germ cell tumor of testis (anti-Ma2) or ovarian teratoma (anti-NDAR)
- Indistinguishable from Herpes simplex or HSV-6 encephalitis
- (There are non-neoplastic variants associated with antibody to voltage gated potassium channels)