Update on Circumscribed Gliomas and Glioneuronal Tumors

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KEYWORDS

• Well-circumscribed • Glioma • Glioneuronal tumor • Benign • Low-grade

Key points

- Circumscribed intra-axial tumors are slow-growing and generally much more common in pediatric population as compared to their adult counterparts.
- Magnetic resonance imaging is critical for evaluation and particularly so in small biopsies.
- While molecular findings are distinct in some, *BRAF* alteration is common in the frequently occurring tumors and is shared across several histologic types.
- Neurofilament protein is a useful immunostain to illustrate the solid and infiltrative pattern, although a rapidly growing high-grade tumor can sometimes be expansile.
- Often contain dystrophic calcifications, perivascular chronic inflammatory infiltrate, Rosenthal material, and/or eosinophilic granular bodies. CD34 may be a good ancillary marker in glioneuronal processes.

ABSTRACT

Well-circumscribed intra-axial CNS tumors encompass a wide variety of gliomas and glioneuronal tumors, usually corresponding to WHO grades I and II. Nonetheless, sometimes high-grade 'diffuse' gliomas such as gliosarcoma and giant cell glioblastoma can be relatively circumscribed but are often found to have foci of diffuse infiltration on careful examination, harboring distinct molecular alterations. These tumors are excluded from the discussion in this chapter with the current review emphasizing on lower-grade entities to include a brief description of their histology and associated molecular findings. Like elsewhere in brain biopsy evaluation, imaging is crucial and acts as a surrogate to gross examination. Given the circumscribed nature of these tumors, surgery alone is the mainstay treatment in most entities.

CIRCUMSCRIBED ASTROCYTIC TUMORS

PILOCYTIC ASTROCYTOMA

Pilocytic astrocytoma is a well-circumscribed neoplasm (**Fig. 1**) frequently occurring in

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Surgical Pathology 13 (2020) 249–266
https://doi.org/10.1016/j.path.2020.02.004

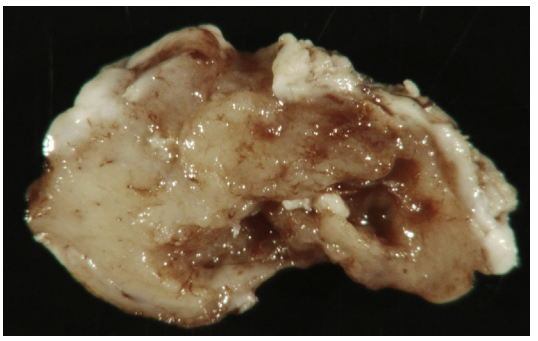

Fig. 1. Circumscribed glioma from a patient with pilocytic astrocytoma harboring predominantly solid and some cystic component.

children and young adults, with a predilection for the cerebellum. It also occurs in some other midline structures like the optic pathway ("optic pathway glioma," which is commonly associated with neurofibromatosis type I), hypothalamus, dorsal brain stem, spinal cord, and, rarely, cerebral hemispheres. Radiologically, classic pilocytic astrocytomas appear as a cystic mass with an enhancing mural nodule (**Fig. 2**A). Histologically, they often have a biphasic pattern with compact piloid areas intermixed with loose, microcystic areas. Rosenthal fibers and eosinophilic granular bodies are common (**Fig. 2**B). Mitotic activity is usually low. The blood vessels are often hyalinized with linear "glomeruloid" tufts of endothelial hyperplasia, sometimes making it challenging to differentiate from high-grade glioma. Glial fibrillary acidic protein (GFAP) is usually strongly and diffusely positive and highlights their long, hair-like (piloid) processes (**Fig. 3**). Molecularly, a majority of pilocytic astrocytomas are driven by alterations affecting the mitogen-activated protein kinase pathway. *BRAF–KIAA1549* fusion is the most common alteration in cerebellar pilocytic astrocytomas[1] and confers a better prognosis. These patients may also benefit from MEK/mammalian target of rapamycin (mTOR) inhibitor therapy.[2] Other fusions (*FAM131B–BRAF*,[3] *SRGAP3–RAF1*,[4] and *QK1–RAF1*[5]), mutations (*BRAFV600E*,[6] *KRAS*,[7] *FGFR1*, and *PTPN1*[8]), *NOTCH2* upregulation,[9] and *NF1* loss,[10] have also been reported infrequently. Pilocytic astrocytoma is a slow-growing, World Health Organization (WHO) grade I tumor with a 10-year overall survival rate of more than 95% after surgical resection alone.[11,12]

Key Features
Pilocytic Astrocytoma

- Pilocytic astrocytoma can be sporadic or inherited; the inherited form is associated with neurofibromatosis 1
- Corresponds to WHO grade I
- Although the posterior fossa (PF) is the preferred site in patients with sporadic tumors, optic pathway gliomas are often seen in association with neurofibromatosis type I and tend to have infiltrative pattern
- Classic MRI appearance features a cyst with mural enhancing nodule
- Biphasic histology with compact areas enriched in piloid cells (rendering its name pilocytic), Rosenthal material, and loose microcystic areas with variable eosinophilic granular bodies
- Typically low proliferation indices although glomeruloid type microvascular proliferation is common and infarct-like necrosis may be seen
- Differential diagnoses include high-grade gliomas owing to microvascular proliferation and pleomorphism including multinucleate cells (pennies on a plate), glioneuronal tumors (like a complex dysembryoplastic neuroepithelial tumor [DNET] and ganglioglioma) owing to the predominance of glial component harboring a pilocytic phenotype
- *BRAF* fusion is much more frequent than *BRAF* point mutations

PILOMYXOID ASTROCYTOMA

Pilomyxoid astrocytoma is a variant of pilocytic astrocytoma that preferentially presents in the hypothalamus and optic chiasm in infants and young children (median age, 10 months). Histologically, it is characterized by an angiocentric arrangement of monomorphous, bipolar cells in a markedly myxoid background (**Fig. 4**). Pilomyxoid astrocytoma does not have Rosenthal fibers or eosinophilic granular bodies, and nuclear atypia is uncommon. Mitoses may be present, as is vascular proliferation. Necrosis is rare. The tumor cells demonstrate strong and diffuse reactivity for GFAP (**Fig. 5**) with perivascular accentuated staining, as well as stain for S100, and vimentin. BRAF V600E immunostain is usually negative. Pilomyxoid astrocytoma is genetically similar to pilocytic

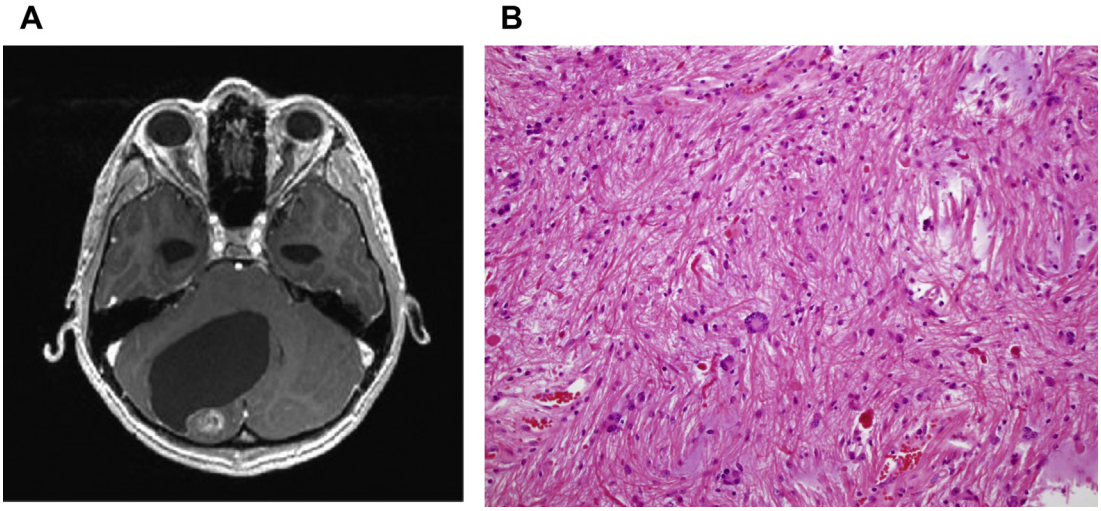

Fig. 2. Pilocytic astrocytoma. Cystic mass with mural enhancing nodule on T1-weighted postcontrast image (*A*). Predominance of compact areas in pilocytic astrocytoma with piloid and multinucleate cells (akin to pennies on a plate), rare microcyst with pale mucinous material, and abundant Rosenthal fibers in the background (*B*).

astrocytoma, and some of them show a *BRAF–KIAA1549* fusion.[13,14] Pilomyxoid astrocytomas are more aggressive than pilocytic astrocytomas with relatively frequent recurrences and cerebrospinal spread. However, it is unclear whether the aggressive behavior is related to its unfavorable hypothalamic/chiasmatic location. Therefore, the revised 2016 WHO classification[15] does not recommend a definitive grade for pilomyxoid astrocytoma.

Key Features
PILOMYXOID ASTROCYTOMA

- Pilomyxoid astrocytoma is a variant of pilocytic astrocytoma, albeit with more frequent cerebrospinal fluid dissemination
- Typically presents in a suprasellar/hypothalamic location
- Angiocentric arrangement of relatively monomorphous tumor cells is characteristic, which can be further highlighted by GFAP stain
- Generally lacks Rosenthal material and eosinophilic granular bodies

SUBEPENDYMAL GIANT CELL ASTROCYTOMA

Subependymal giant cell astrocytoma is a slow-growing tumor that usually arises in the wall of the lateral ventricles during the first 2 decades of life. It is seen in 5% to 15% of patients with confirmed tuberous sclerosis, a genetic disease caused by mutations in the *TSC1* or *TSC2* genes. The tumor is well-circumscribed, often calcified, contrast enhancing (**Fig. 6**A), and is composed of large ganglion-like to gemistocyte-like cells that are arranged in nests, fascicles, and sheets with dystrophic calcifications and mast cells in the background (**Fig. 6**B). Mitotic activity, endothelial proliferation, and necrosis are rare and are not indicative of anaplasia. The tumor cells show uniform immunoreactivity for S100, and variable immunoreactivity for GFAP and neuronal markers like synaptophysin and NeuN. CD34 is negative.

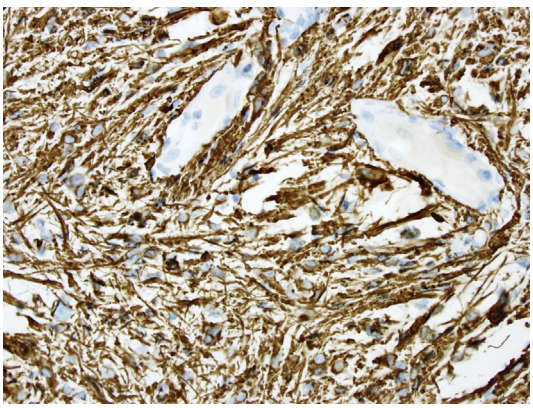

Fig. 3. Pilocytic astrocytoma. GFAP highlights long hairlike cytoplasmic processes.

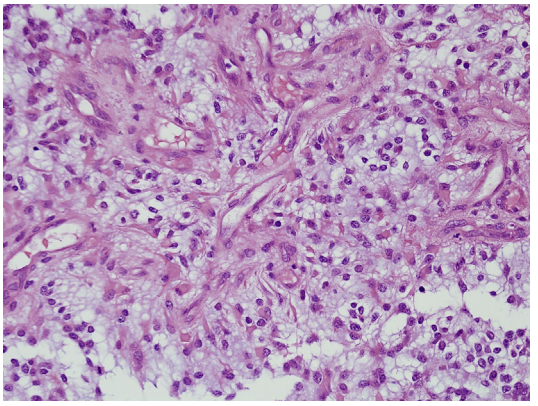

Fig. 4. Pilomyxoid astrocytoma. Angiocentric arrangement of tumor cells with myxoid matrix in the background.

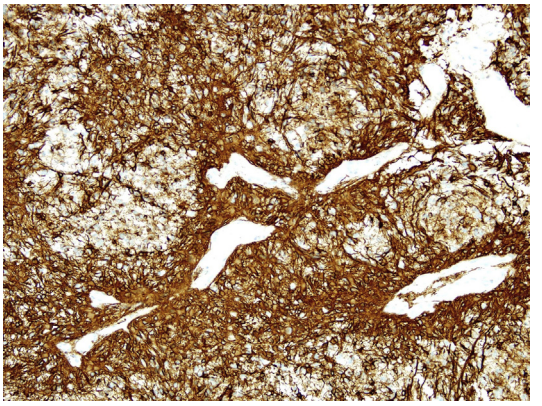

Fig. 5. Pilomyxoid astrocytoma. Diffuse reactivity with GFAP with accentuated staining around the blood vessels.

Subependymal giant cell astrocytoma is a WHO grade I tumor with a good prognosis when gross total resection is achieved.

Key Features
Subependymal Giant Cell Astrocytoma (SEGA)

- Mostly seen in association with tuberous sclerosis, where it can be the presenting feature
- Can rarely be sporadic
- Lateral ventricle most common site
- Contrast enhancing on imaging
- Variable expression of glial and neuronal markers
- Often CD34 negative
- Abundance of mast cells
- Falls under the umbrella of "mTORopathy" owing to the activation of mTOR pathway
- Corresponds to WHO grade I

PLEOMORPHIC XANTHOASTROCYTOMA AND ANAPLASTIC PLEOMORPHIC XANTHOASTROCYTOMA

Pleomorphic xanthoastrocytoma (PXA) is a rare epileptogenic astrocytic tumor that typically develops in the superficial cortical regions of children and young adults, most commonly in the temporal lobe. It is composed of large pleomorphic and frequently binucleated or multinucleated cells, spindled, and lipidized (xanthomatous) cells in a vaguely fascicular pattern (**Fig. 7**A). Eosinophilic granular bodies are almost always present (**Fig. 7**B). A dense reticulin network is another histologic hallmark (**Fig. 8**A). By definition, mitotic activity is low (<5 mitoses per 10 high-power field), and necrosis is rare. GFAP is consistently expressed (**Fig. 8**B) and reactivity for neuronal markers may be negligible to patchy. A *BRAF* V600E mutation occurs in approximately 60% to 66% of PXA[6,16] and has potential therapeutic implications.[17] The combination of *BRAF V600E* mutation and absence of an *IDH* mutation favors the diagnosis of PXA over diffuse astrocytoma. A *CDKN2A/B* deletion is another frequent alteration in PXA that is not associated with tumor grade or *BRAF* mutation.[18,19] PXA is a WHO grade II tumor with a relatively favorable prognosis compared with diffuse astrocytoma (90.4% overall survival at 5 years[20]).

Anapalstic PXA is a PXA with 5 or more mitoses per 10 high-power fields and frequent necrosis; microvascular proliferation is relatively uncommon. Anaplasia may be focal in a tumor and manifest at first diagnosis or at time of recurrence. It is important to see conventional PXA areas before labeling a tumor as anaplastic PXA. The frequency of *BRAF V600E* mutation is lower among anaplastic PXA than among PXA. Anaplastic PXA is a WHO grade III tumor with a 5-year overall survival of 55.6%.[20]

Key Features
Pleomorphic Xanthoastrocytoma (PXA) and Anaplastic PXA

- As the name implies, it is composed of highly pleomorphic and xanthic astrocytic cells
- Usually supratentorial and associated with chronic seizure disorder

- Variable expression of glial and neuronal markers
- Variable fascicular arrangement of tumor cells with enrichment of reticulin fibers
- Perivascular chronic inflammatory cell infiltrate is common
- CD34 is a good ancillary marker, which shows variable staining from scattered to bushy to diffuse
- *BRAF* point mutations are seen in around two-thirds of tumors with a frequency that decreases to approximately 50% in anaplastic examples
- Corresponds to WHO grade II with anaplastic examples corresponding to WHO grade III
- Differential diagnoses includes high-grade tumors such as conventional glioblastoma, gliosarcoma, and epithelioid glioblastoma and can be rather challenging especially to distinguish from anaplastic PXA, particularly so when conventional PXA areas are not conspicuous

ANGIOCENTRIC GLIOMA

Angiocentric glioma is another low-grade, well-circumscribed, epileptogenic glioma of childhood and young adults. It is a cortically based tumor, most often involving supratentorial areas such as the temporal, frontal, or parietal lobes. Histologically, it consists of monomorphic, bland spindle cells oriented parallel or radial (ependymoma like) to blood vessels, with frequent subpial palisading. Entrapped cortical neurons and neuropil can be present within the tumor, microscopically consistent with an infiltrative growth pattern. However, perineuronal satellitosis is rare, which is distinct from diffuse gliomas. The tumor cells are usually strongly positive for GFAP and S100. Some tumor cells show cytoplasmic dotlike reactivity for EMA and D2-40, resembling ependymoma. Recently, an *MYB-QKI* rearrangement was found to be a specific molecular alteration in angiocentric glioma.[21,22] Angiocentric glioma is a WHO grade I tumor and most cases can be cured by gross total resection with associated seizure control.

Key Features
ANGIOCENTRIC GLIOMA

- Epilepsy-associated tumor
- Often cortically based
- WHO grade I
- Monomorphic bipolar glial cells with perivascular pseudorosetted arrangement
- Expression of glial (GFAP: diffuse cytoplasmic) and ependymal markers (EMA and D2-40: perinuclear dotlike or ringlike pattern)
- Differential diagnoses includes ependymoma, diffuse glioma, and astroblastoma (especially when epithelioid cells are present, which is relatively rare)
- *MYB* rearrangement is frequent with *MYB:QKI* fusion being a common event

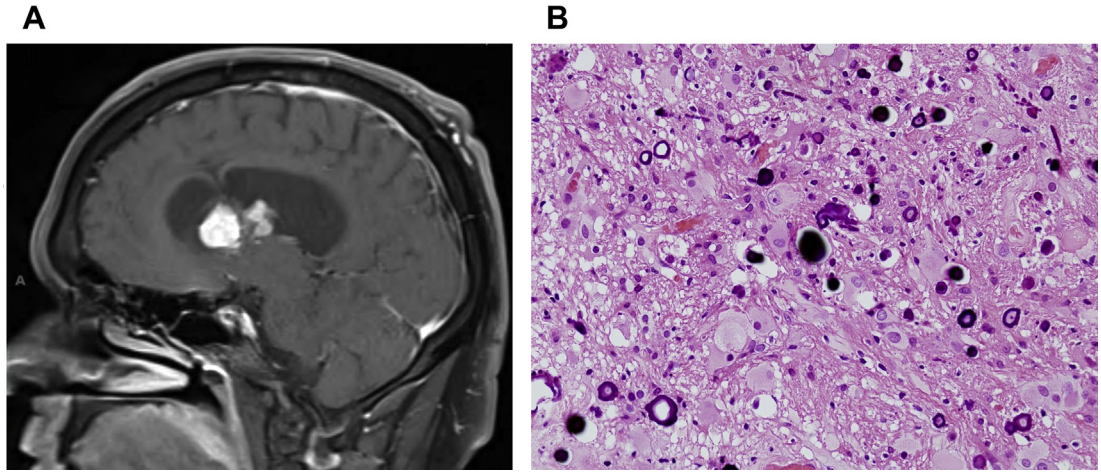

Fig. 6. Subependymal giant cell astrocytoma. A cystic mass with nodular areas of contrast enhancement arising from the ventricular wall of a patient with tuberous sclerosis (*A*). Numerous dystrophic calcifications, gemistocytic to ganglion-like cells, and spindled cells in subependymal giant cell astrocytoma (*B*).

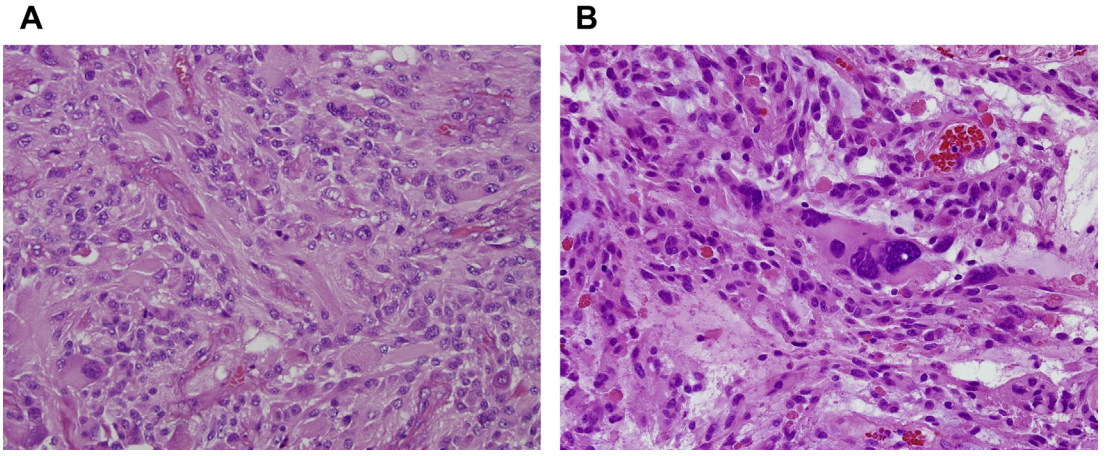

Fig. 7. Pleomorphic xanthoastrocytoma (PXA). Variable degree of fascicular arrangement of tumor cells is common in PXA (*A*). Large pleomorphic cells with several eosinophilic granular bodies in the background (*B*). Xanthic or lipidized cells may not always be present.

ASTROBLASTOMA

Astroblastoma is a rare, albeit another well-demarcated, glioma without clarity regarding its WHO grade at this time, typically seen in children and young adults, and often involving the supratentorial compartment.[23–26] It is generally characterized by glial cells with distinct cytoplasmic borders, arranged in conspicuous perivascular pseudorosetted to papillary architecture, harboring stouter cytoplasmic processes (**Fig. 9**A). Vascular hyalinization is frequent. Often positive, albeit variably, for GFAP (**Fig. 9**B) and lacks expression of epithelial markers. High-grade features constituted by dense cellularity, significant nuclear pleomorphism, increased mitotic activity, microvascular proliferation, and palisading necrosis have been reportedly associated with aggressive clinical behavior, although it has been questioned recently. Given the rarity of these tumors and challenges associated with accurate classification of these tumors, the molecular alterations are not as well-characterized; a relatively small series, however, has found frequent concomitant gains of chromosomes 19 and 20q.[27]

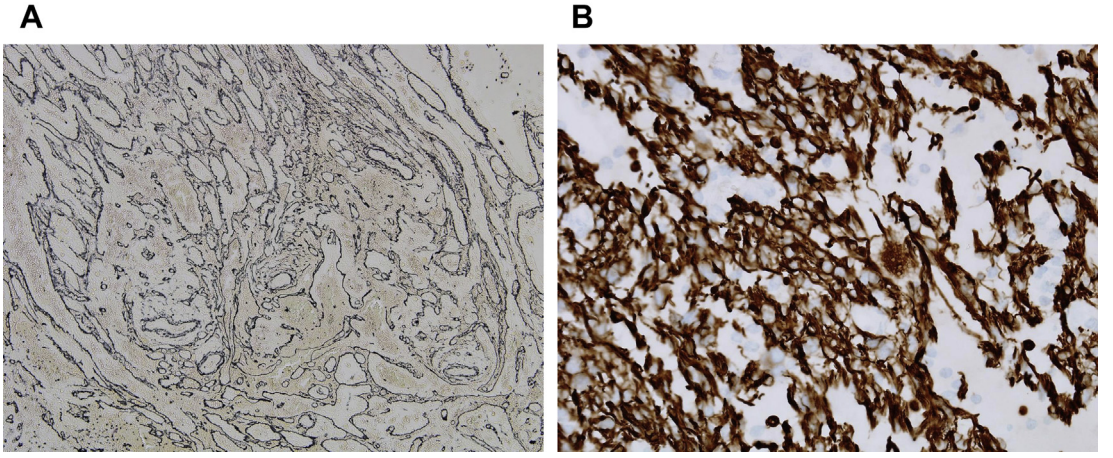

Fig. 8. Pleomorphic xanthoastrocytoma (PXA). There is usually a rich reticulin meshwork in PXA (*A*) and diffuse expression of GFAP (*B*).

Key Features
Astroblastoma

- Contrast-enhancing, supratentorial mass
- Usually seen in children and young adults
- Not yet assigned a specific WHO grade
- Pseudorosetted to papillary architecture, stouter glial processes, and hyalinized blood vessels
- Differential diagnoses includes ependymoma (delicate cytoplasmic processes, lack of hyalinized blood vessels as well as absence of epithelial marker expression, and the location aid distinguish it)

CHORDOID GLIOMA OF THE THIRD VENTRICLE

Chordoid glioma of the third ventricle is a well-circumscribed, solid, homogeneously contrast-enhancing tumor usually seen in third ventricle of adults. Benign-appearing epithelioid cells with abundant eosinophilic cytoplasm, discrete cytoplasmic borders, arranged in a chordoid arrangement with or without mucinous/myxoid stroma, robust lymphoplasmacytic cell infiltrate, and rare mitoses characterize it on histologic examination (**Fig. 10**A). These often demonstrate strong expression of GFAP (**Fig. 10**B) and CD34 with variable TTF1 reactivity[28] (**Fig. 10**C), which help its distinction from other chordoid tumors such as chordoma and chordoid meningioma. A recurrent point mutation in *PRKCA* (D463H) has recently been identified as a consistent finding.[29] Long-term recurrence-free survival can be achieved through surgery alone, although the third ventricular location can make it challenging to attain a gross total resection.[30]

Key Features
Chordoid Glioma of the Third Ventricle

- Corresponds to WHO grade II
- Arises in the third ventricle of adults
- Epithelioid cells with or without myxoid/mucinous stroma, abundance of lymphoplasmacytic cell infiltrate, strong GFAP and TTF1 expression
- *PRKCA* (D463H) alteration is consistent
- Differential diagnoses include chordoma (physaliferous cells, bone involvement, brachyury reactivity, non-reactivity for TTF1 and GFAP) and chordoid meningioma (expresses EMA and PR, and lacks TTF1 and GFAP immunoreactivity)

POLYMORPHOUS LOW-GRADE NEUROEPITHELIAL TUMOR OF THE YOUNG

Polymorphous low-grade tumor of the young is a recently described tumor[31] in children and young adults with seizures, and is yet to make it to WHO classification scheme as a distinct

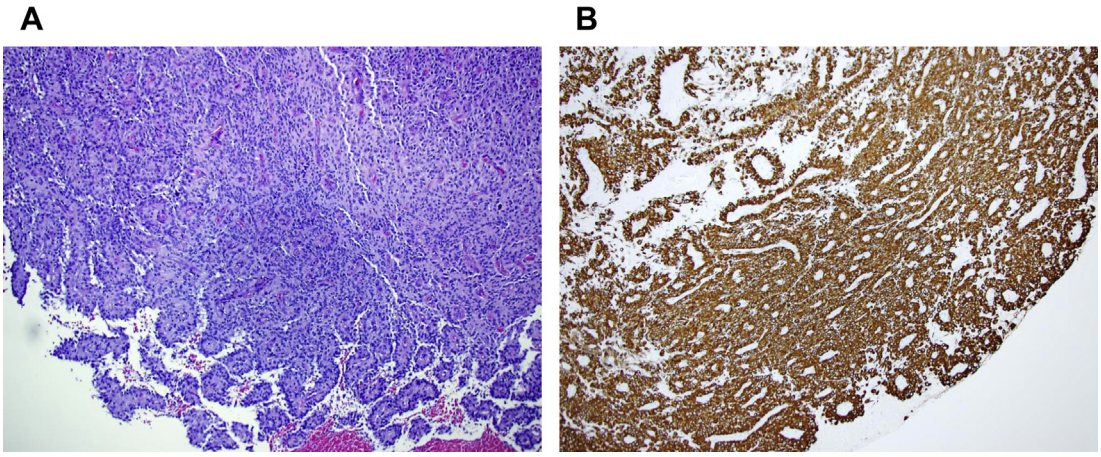

Fig. 9. Astroblastoma. Perivascular pseudorosetted to papillary arrangement of tumor cells with conspicuous hyalinized thickening of blood vessels (*A*) and strong reactivity for GFAP (*B*); the cytoplasmic processes are typically stouter.

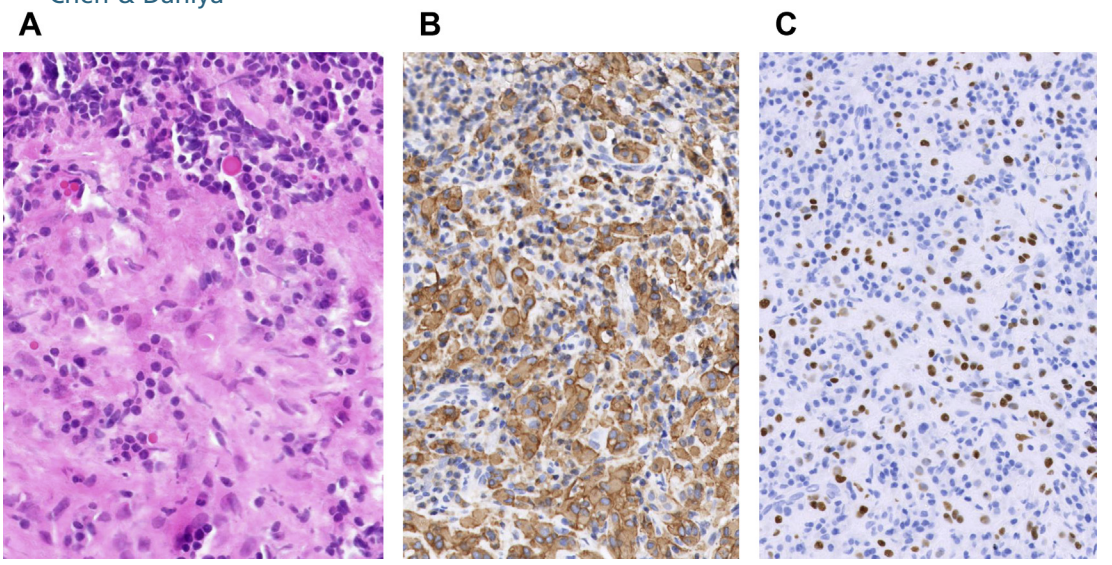

Fig. 10. Chordoid glioma of the third ventricle. Lack of fibrillar matrix and abundant lymphoplasmacytic infiltrate including few Russell bodies (*A*), strong GFAP (*B*) and variable TTF-1 (*C*) expression characterize chordoid glioma.

entity. It commonly presents in the superficial temporal lobe as a T2/fluid-attenuated inversion recovery hyperintense and calcified lesion without significant associated edema; infrequently enhances on postcontrast imaging. Its histology is characterized by relatively uniform appearing oligodendroglial cells with a diffuse growth pattern, thin capillary-sized vasculature and calcifications in the background, and an absence of concomitant dysmorphic neuronal component as well as Rosenthal material and eosinophilic granular bodies (**Fig. 11**A). CD34 (**Fig. 11**B) and OLIG2 (**Fig. 11**C) expression is usually strong and diffuse. GFAP expression is also common, albeit variable. Molecular alterations involving mitogen-activated protein kinase pathway ie, *FGFR2, FGFR3*, and *BRAF* genes are common.

Key Features
Polymorphous Low-grade Tumor of the Young

- Children and young adults
- Commonly involves the temporal lobe
- Epilepsy-associated tumor
- Oligodendroglial cells in a diffuse growth pattern, lack of dysmorphic neurons, strong and diffuse expression of OLIG-2 and CD34
- Not yet assigned a specific WHO entity and grade
- Differential diagnoses include DNET (specific glioneuronal element), diffuse glioma (typically lacks diffuse CD34 immunoreactivity), ganglioglioma with predominance of oligodendroglioma component (presence of dysmorphic neuronal component)
- *FGFR2*, *FGFR3*, and *BRAF* alterations are frequent

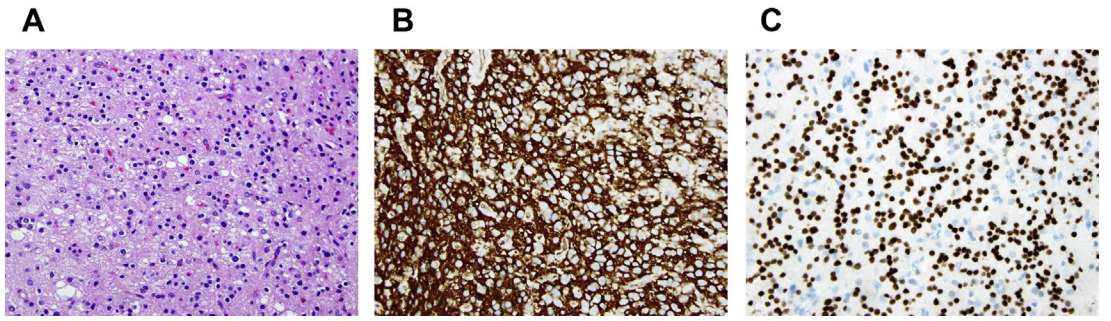

Fig. 11. Polymorphous low-grade tumor of the young. Relatively uniform appearing oligodendroglial cells with a diffuse growth pattern, lacking dysmorphic neuronal component and significant mitotic activity (*A*). Diffuse concomitant expression of CD34 (*B*) and OLIG-2 (*C*) is characteristic.

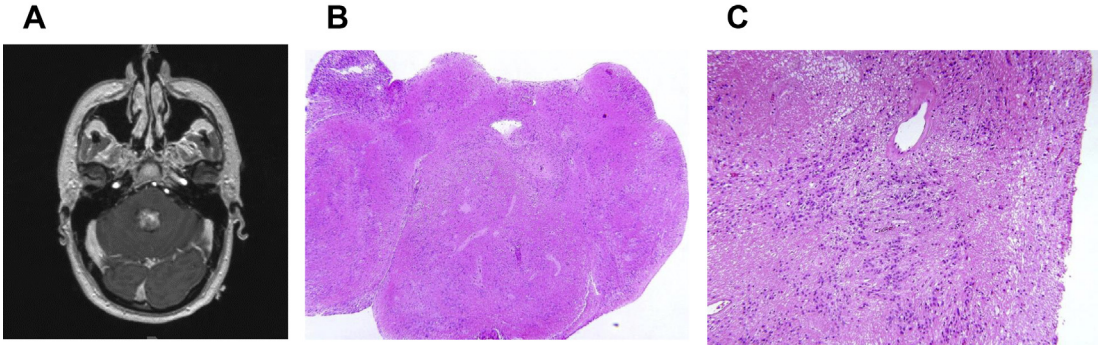

Fig. 12. Subependymoma. Slow-growing contrast-enhancing subependymoma of the fourth ventricle (*A*). Usually, these tumors are incidentally detected. Vaguely nodular architecture with acellular and paucicellular zonation highlighted on low power (*B*). Note the lack of true or pseudorosettes and hyalinization of the blood vessels (*C*). This tumor can sometimes have a microvascular proliferation.

EPENDYMAL TUMORS

SUBEPENDYMOMA

Subependymoma is a slow-growing, exophytic, intraventricular neoplasm that most frequently is found incidentally in the fourth ventricle in middle-aged and elderly patients, contrast enhancement is uncommon (**Fig. 12**A). Histologically, subependymoma is lobulated and well-demarcated, and is characterized by clusters of small, bland, uniform glial cells in a dense fibrillary matrix with frequent microcysts. Pseudorosettes and/or true rosettes are absent (**Fig. 12**B, C). Mitotic figures are rare and the blood vessels are often hyalinized. Because of their slow-growing nature, they are frequently associated with variable piloid gliosis in the surrounding tissue that is enriched in Rosenthal material and can be a diagnostic pitfall (**Fig. 13**). The tumor cells are usually immunoreactive for GFAP, and only rarely for EMA (in contrast to classic ependymoma). Subependymoma is a WHO grade I tumor with excellent prognosis after resection.[32]

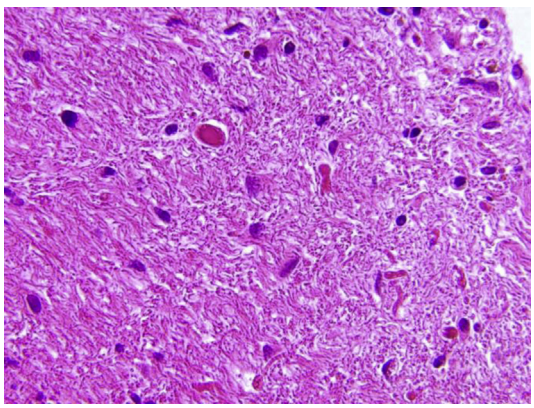

Fig. 13. Piloid gliosis with Rosenthal material is a frequent finding in the vicinity of a subependymoma owing to its slow-growing nature and can be a diagnostic pitfall.

Key Features
SUBEPENDYMOMA

- Often incidental
- Usually nonenhancing
- Fourth ventricle
- Middle aged and elderly
- Acellular and hypocellular regions with uniform nuclei and hyalinized blood vessels
- WHO grade I
- Differential diagnoses may include a conventional ependymoma (presence of rosettes) and pilocytic astrocytoma (biphasic pattern with piloid cells)

MYXOPAPILLARY EPENDYMOMA

Myxopapillary ependymoma is an ependymal neoplasm that occurs almost exclusively in the conus medullaris, cauda equina, and filum terminale. The tumor cells have characteristically elongate fibrillary processes arranged in radial patterns around blood vessels (**Fig. 14**), which frequently demonstrate mucoid/myxoid degeneration, a feature that can be further highlighted by Alcian blue stain (**Fig. 15**). Immunoreactivity for GFAP is often diffuse. Reactivity for EMA, S100, CD99, and vimentin is also frequent. Based on a recent study on ependymomas across different anatomic sites using DNA methylation profiles, myxopapillary ependymoma is characterized by chromosomal instability with frequent DNA copy number alterations.[33] Myxopapillary ependymoma is a WHO grade I tumor with a 5-year overall survival rate of more than 95% after resection.[33–35]

Key Features
Myxopapillary Ependymoma

- Commonly arise in cauda equina, and filum terminale of adults
- Frequently well-encapsulated
- Homogeneously contrast enhancing
- Perivascular mucoid/myxoid change, which can be highlighted by Alcian blue stain
- Corresponds to WHO grade I
- Anaplastic changes are extremely rare

EPENDYMOMA AND ANAPLASTIC EPENDYMOMA

Ependymoma is a circumscribed glioma in both children and adults that occurs mainly intracranially, and less frequently in the spinal cord. It is composed of small uniform cells with round nuclei and speckled chromatin in a fibrillary matrix. Pseudorosettes (tumor cells radially arranged around blood vessels forming perivascular anucleate zones) are frequent (**Fig. 16**A). Ependymal rosettes (tumor cells arranged around a central lumen) are another diagnostic feature, but these are less common. Perinuclear dot-like immunoreactivity for EMA (**Fig. 16**B) and D2-40 is typical in ependymomas. GFAP immunoreactivity is frequent in perivascular tumor cells, and may be variable in other areas of the tumor.

A histologically classic ependymoma is a WHO grade II tumor. When an ependymoma demonstrates high cellularity, elevated mitotic activity, widespread microvascular proliferation, and necrosis, it is considered an anaplastic ependymoma, which corresponds to a WHO grade III tumor. However, clinical outcome of an ependymoma primarily depends not on histologic grade, but on the extent of surgical resection, adjuvant radiation therapy, and molecular group.

A recent DNA methylation profiling study of 500 ependymomas across 3 main central nervous system compartments, supratentorial brain (ST), posterior fossa (PF), and spine (SP), has identified 9 molecular subgroups of ependymomas, 3 from each anatomic compartment.[33] Among the 9 subgroups, PF-EPN-A or supratentorial RELA-positive ependymomas (discussed elsewhere in this article) show dismal prognosis. The PF-EPN-A subgroup accounting for about 74% of PF ependymomas, predominantly occur in the lateral PF in infants and young children (median age 3 years), and demonstrate a relatively balanced genome with widespread epigenomic alterations, including DNA CpG island hypermethylation, global DNA hypomethylation, and H3K27me3 loss with poor prognosis.[36–38] Much more recently, a subset of spinal ependymoma harboring *MYCN* amplification have been shown to be associated with poor prognosis.[39]

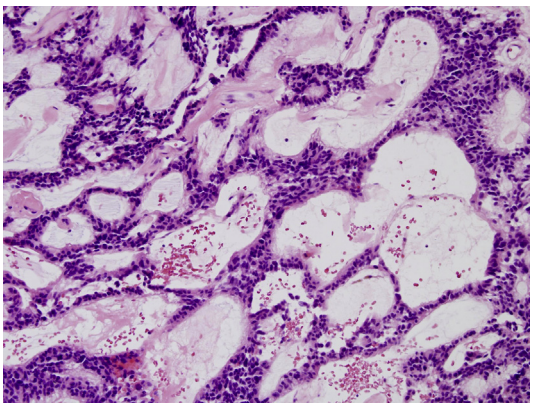

Fig. 14. Myxopapillary ependymoma with marked mucinous/myxoid change in the blood vessel walls.

Key Features
Ependymoma

- Posterior fossa (PF) common site
- PF-A is frequent in infants with H3 K27me3 loss and is associated with poor prognosis
- Supratentorial examples often have *RELA* fusion and are associated with a worse prognosis
- Perivascular pseudorosettes are characteristic with delicate cytoplasmic processes; true rosettes are "hallmark" but are infrequent
- Often GFAP positive and show perinuclear dot-like reactivity with EMA and D2-40
- Differential diagnoses includes oligodendroglioma (diffuse growth pattern, IDH mutant and 1p19q-codeleted) and central neurocytoma (lack of true or pseudorosettes and expression of neuronal markers) for the clear cell variant of ependymoma

EPENDYMOMA, *RELA* FUSION POSITIVE

Ependymoma, *RELA* fusion positive is a new entity in the 2016 updated WHO, and accounts for approximately 70% of childhood supratentorial tumors.[33] It does not have a specific morphology,

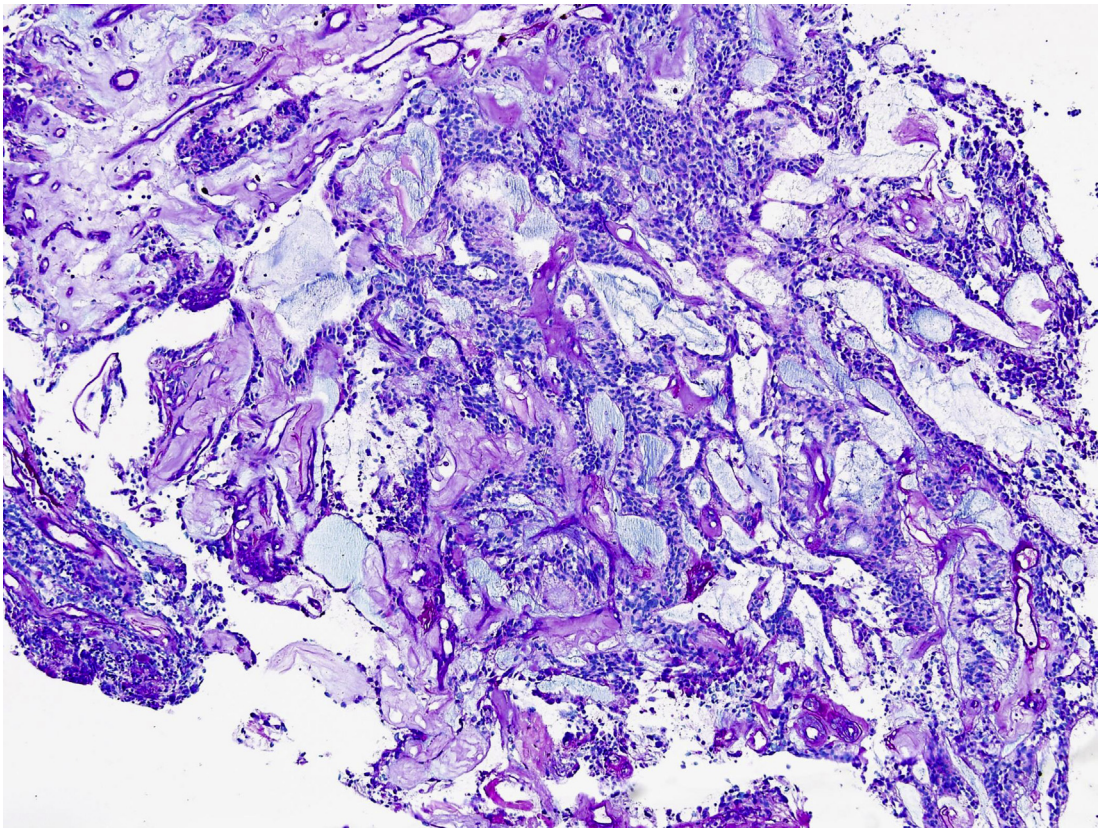

Fig. 15. Myxopapillary ependymoma. Alcian blue-PAS stain highlights the abundance of myxoid change within the vascular walls, partially rendering its name.

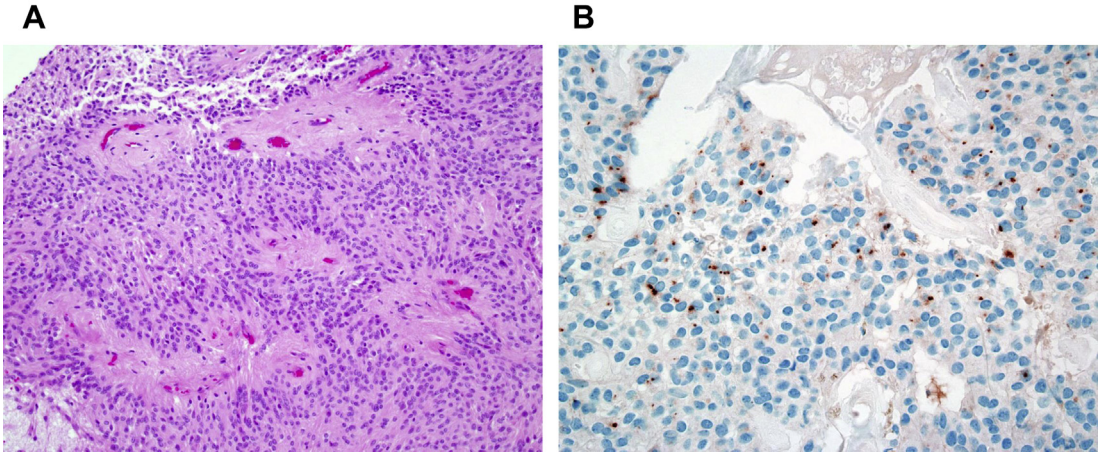

Fig. 16. Ependymoma with a perivascular pseudorosetted arrangement of neoplastic cells (*A*). True rosettes are rather infrequent but when present are diagnostic. Typically express both glial (GFAP; diffuse cytoplasmic) and epithelial markers (perinuclear dotlike). Shown is perinuclear dotlike intracytoplasmic reactivity for epithelial membrane antigen (*B*). D2-40 also shows a similar staining pattern to that of an EMA, but is generally slightly more widespread.

but is rather defined by the presence of *RELA* fusion, most commonly *C11orf95-RELA*, which can be detected by interphase fluorescence in situ hybridization with break-apart probes. *C11orf95-RELA* fusion is caused by a local chromosome shattering event (chromothripsis) on chromosome 11, and this fusion leads to constitutive activation of the nuclear factor-κB pathway. RELA-fused ependymoma is associated with different chromosomal copy number changes and molecular alterations compared to non–*RELA*-fused ependymomas.[40] *RELA* fusion-positive ependymomas have the worst prognosis of the 3 supratentorial molecular groups.

CIRCUMSCRIBED GLIONEURONAL TUMORS

DYSEMBRYOPLASTIC NEUROEPITHELIAL TUMOR

Dysembryoplastic neuroepithelial tumor (DNET) is a benign, predominantly cortically based glioneuronal neoplasm that most frequently occurs in the temporal lobe of children or young adults. Patients usually present with medically refractory focal epilepsy before the age of 20 years. The tumor presents as T2-hyperintense single or multiple pseudocysts on MRI, and typically has a multinodular character. Histologically, simple DNET shows a multinodular growth pattern with a specific glioneuronal element demonstrated by columns of axons oriented perpendicularly to the cortical surface. These columns are further surrounded by small uniform oligodendrocyte-like cells in a myxoid background, and bland-appearing neurons seem to float in the mucin-rich matrix (**Fig. 17**). In complex DNET, specific glioneuronal element is present together with glial nodules, which have histologic features of pilocytic astrocytoma, ganglioglioma, diffuse glioma or other glial neoplasms. Dystrophic microcalcifications are common. Cortical dysplasia may be present in the surrounding brain parenchyma. The oligodendrocyte-like cells in DNET show immunoreactivity for OLIG-2, but not for GFAP or MAP2. DNET lacks an *IDH1/IDH2* mutation and 1p19q co-deletions. Instead, they often harbor germline or somatic *FGFR1* mutations.[41,42] These features help distinguish DNET from a diffuse glioma. DNET is a WHO grade I tumor with an excellent prognosis after surgery.

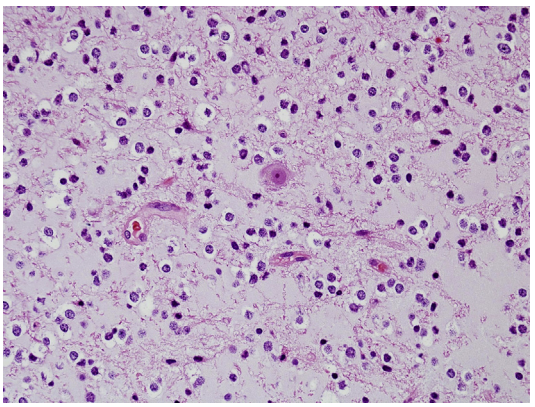

Fig. 17. DNET. Pools of pale mucin with uniform oligodendroglial cells and bland-appearing floating neurons.

Key Features
DYSEMBRYOPLASTIC NEUROEPITHELIAL TUMOR (DNET)

- Most common chronic seizure disorder
- Corresponds to WHO grade I
- Often cystic, multinodular, and cortically based tumor on imaging; can show contrast enhancement
- Simple and complex forms
- Pools of pale mucin with oligodendroglial-like cells and floating neurons
- *FGFR1* alterations are frequent with lack of *IDH* mutation
- Differential diagnoses includes oligodendroglioma (lacks "floating neurons"), ganglioglioma (absence of specific glioneuronal elements), and pilocytic astrocytoma (lacks neuronal elements)

GANGLIOGLIOMA AND ANAPLASTIC GANGLIOGLIOMA

Ganglioglioma is a slow-growing, most common epileptogenic glioneuronal tumor, predominantly occurring in the temporal lobe of children and young adults. They often present as intracortical cysts with a contrast-enhancing nodule on imaging, sometimes with associated calcifications. Ganglioglioma is a biphasic tumor with variable dysplastic neurons and neoplastic glial cells. Dysplastic neurons may be clumped or haphazardly arranged, and may show binucleation or multinucleation, cytomegaly, pale or vacuolated cytoplasm, abnormal distribution of Nissl substance, or disoriented processes. The glial component may resemble pilocytic astrocytoma, diffuse astrocytoma, or oligodendroglioma. Ganglioglioma frequently exhibits dense perivascular

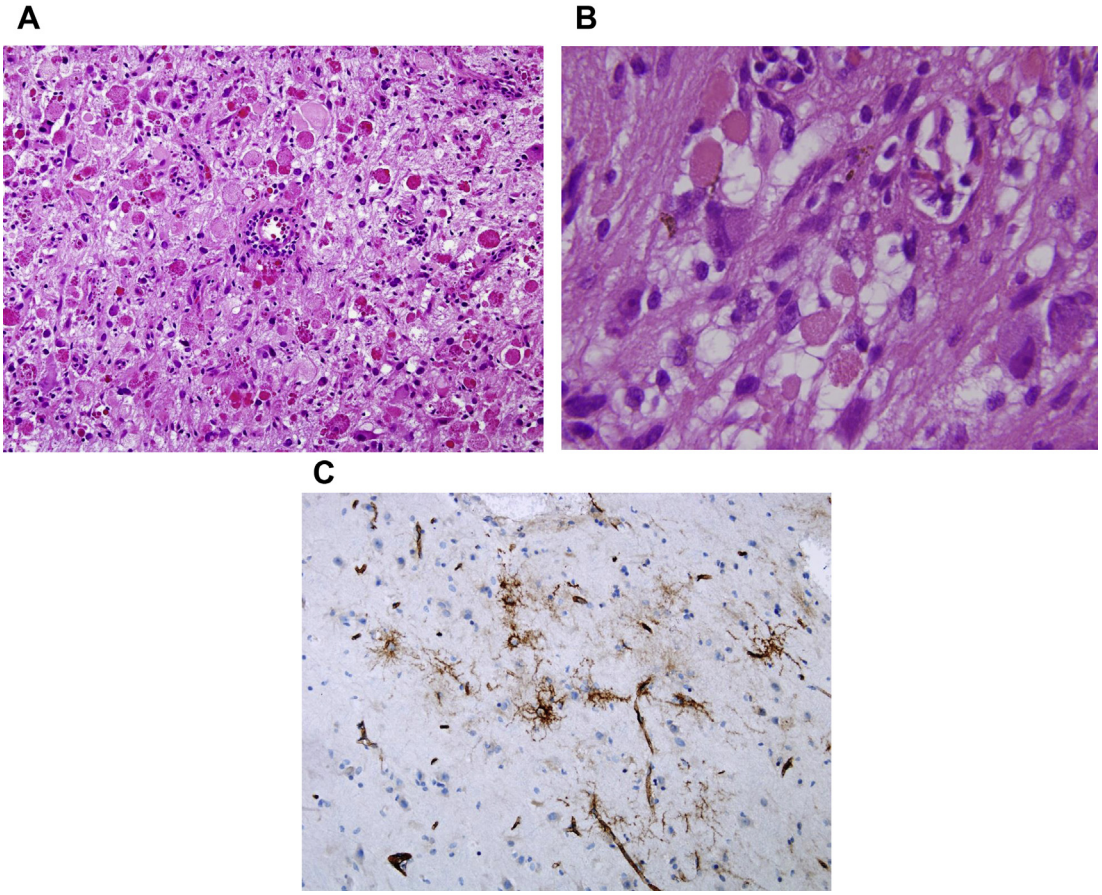

Fig. 18. Ganglioglioma. Dysmorphic ganglion cells and glial elements with numerous eosinophilic granular bodies and perivascular chronic inflammatory cell infiltrate (*A*). High power with better illustration of dysmorphic ganglion cells (*B*). CD34-positive spider cells characterized by highly ramified cytoplasmic processes are seen in the surrounding brain parenchyma with cortical dysplasia (*C*).

lymphocytic infiltrates and dystrophic calcification. Eosinophilic granular bodies are more often encountered than Rosenthal fibers (**Fig. 18**A, B). Patients with these tumors also have associated focal cortical dysplasia, which can be furthermore highlighted by CD34 (**Fig. 18**C) immunostain. The neoplastic glial cells are immunoreactive for GFAP (**Fig. 19**). Dysplastic neurons or ganglionic cells are immunoreactive for neurofilament (**Fig. 20**A), synaptophysin (**Fig. 20**B), chromogranin, and CD34 (**Fig. 21**). About 20% to 60% of gangliogliomas harbor a *BRAF* V600 E mutation.[6,43–45] The presence of this alteration in pediatric patients has been shown to be associated with a poor prognosis.[46] Gains of chromosomes 5, 6, and 7, and *CDKN2A* homozygous deletion have also been reported.[43,47] Ganglioglioma corresponds to WHO grade I with a good prognosis after surgical resection.

Key Features
GANGLIOGLIOMA

- Mesial temporal lobe is common site
- Mostly in children, and young adults with chronic seizure disorder
- Corresponds to WHO grade I
- Composed of glial and neuronal components with frequent perivascular chronic inflammatory cell infiltrate, and eosinophilic granular bodies
- *BRAF* point mutations are seen in around half of cases
- Differential diagnoses includes pilocytic astrocytoma (lack of dysmorphic neuronal component), diffuse glioma (contains entrapped native neurons highlighted by NeuN rather than dysmorphic/dysplastic neuronal elements that are highlighted by synaptophysin and neurofilament), and complex DNET (lacks substantial neuronal dysmorphism and chronic inflammatory cell infiltrate)

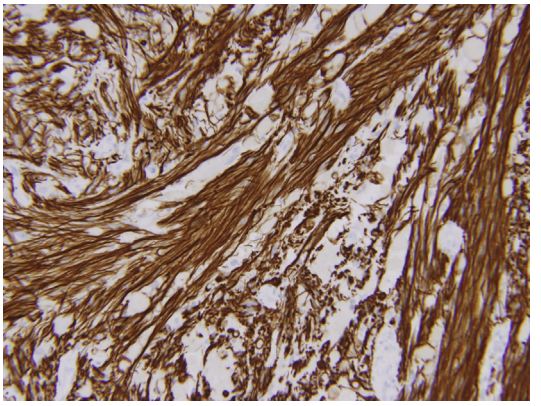

Fig. 19. Glial cells with long piloid cytoplasmic processes highlighted by a GFAP immunostain in a ganglioglioma with predominant pilocytic astrocytoma–like areas within the glial component.

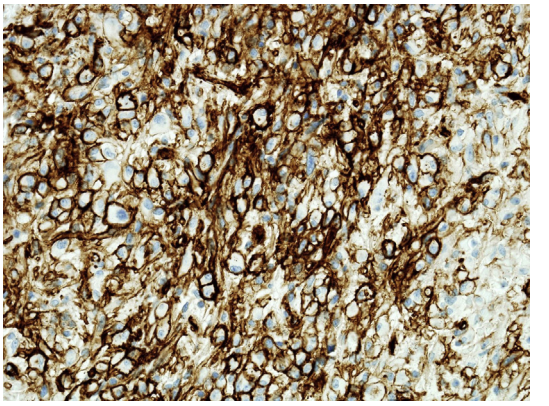

Fig. 21. Ganglioglioma. Widespread CD34 immunoreactivity within the tumor cells.

DESMOPLASTIC INFANTILE ASTROCYTOMA AND GANGLIOGLIOMA

Desmoplastic infantile astrocytoma (DIA) and desmoplastic infantile ganglioglioma (DIG) are rare neoplasms that occur in infants and young children (median age, 6 months). They often present as superficial, large, cystic lesions in the frontoparietal region. Histologically, DIA is composed of a prominent desmoplastic stroma admixed with spindled or gemistocytic astrocytes in a fascicular or storiform pattern. In DIG, besides the neoplastic astrocytes, there are also neoplastic neuronal cells with variable differentiation (**Fig. 22**A). Both DIA and DIG may have a poorly differentiated, small blue cell component (**Fig. 22**B). Although dystrophic calcifications are often present, perivascular chronic inflammatory cell infiltrate is generally absent. In both DIA and DIG, there is a prominent reticulin-positive network in the desmoplastic stroma (**Fig. 22**C). The neoplastic astrocytes are immunoreactive for GFAP (**Fig. 22**D), the neuronal cells are positive for neuronal markers like synaptophysin (**Fig. 22**E), and the poorly differentiated neuroepithelial component reacts with both GFAP and neuronal markers. Mitotic activity and necrosis may be present in the poorly differentiated neuroepithelial component, but do not seem to influence prognosis. A recent study revealed somatic *BRAF* mutations in more than 40% of DIA/DIG,[48] most frequently *BRAF* V600E mutation. DIA and DIG are WHO grade I tumors with long-term survival after gross total resection.[49,50]

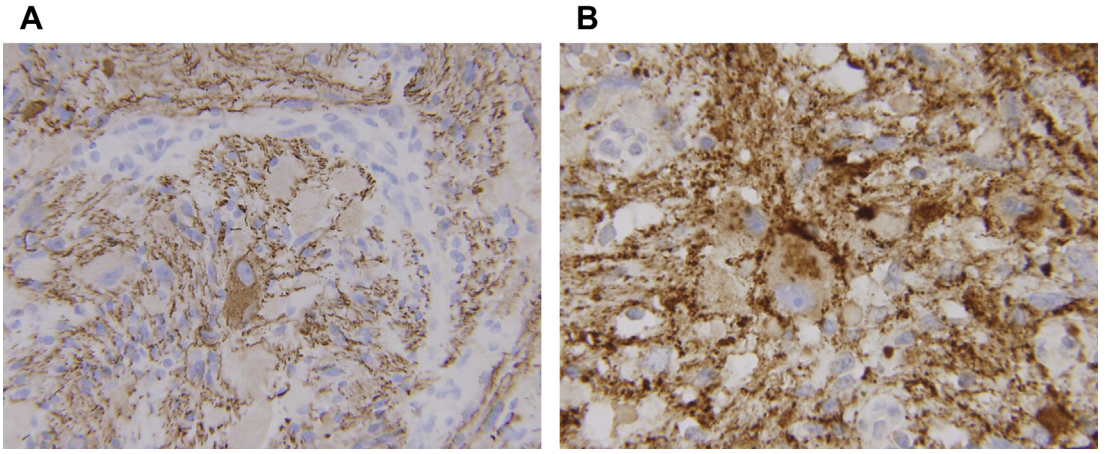

Fig. 20. Ganglioglioma. Dysmorphic neurons highlighted by neurofilament staining of their soma (*A*). Strong synaptophysin reactivity within dysplastic neurons (*B*).

Key Features
Desmoplastic Infantile Astrocytoma (DIA) and Desmoplastic Infantile Ganglioglioma (DIGG)

- Corresponds to WHO grade I
- Large, superficial, cerebral hemispheric, cystic masses in infants
- Composed of glial with or without neuronal elements in a robust desmoplastic background which can be highlighted by a reticulin stain
- *BRAF* point mutations are frequent
- Differential diagnoses includes PXA (presence of xanthic or lipidized cells, perivascular chronic inflammatory cell infiltrate and lack of small blue cells) and ganglioglioma (devoid of desmoplasia)

PAPILLARY GLIONEURONAL TUMOR

Papillary glioneuronal tumor (PGNT) is a rare, circumscribed, cystic or solid contrast-enhancing tumor that preferentially locates in the periventricular white matter of the temporal lobe in young adults. Histologically, it is characterized by pseudopapillary structures with hyalinized blood vessels, lined by flat to cuboidal astrocytes. Neurocytes and occasional ganglion cells are present in the interpapillary regions. The glial component is immunoreactive for GFAP or Olig2, and the neuronal component is positive for synaptophysin and NeuN. Recent studies have demonstrated that PGNT exhibits a characteristic methylation profile and fusions involving *PRKCA*, most frequently an *SLC44S1-PRKCA* fusion.[51–53] PGNT is a WHO grade I tumor with a good prognosis.[54]

Key Features
Papillary Glioneuronal Tumor (PGNT)

- Corresponds to WHO grade I
- Generally presents as solid and cystic enhancing temporal lobe mass in young adults
- Pseudopapillary architecture with surrounding glial cells reactive for GFAP or OLIG-2 and presence of neuronal elements (neurocytic in nature) outside of glial cells which are seen immediately around the blood vessels
- Fusions involving *PRKCA* gene is a frequent molecular alteration
- Differential diagnoses includes extraventricular neurocytoma (lack of pseudopapillary architecture, much more uniform cells, paucity of glial processes, widespread expression of neuronal marker such as synaptophysin), astroblastoma (pseudorosetted architecture is rendered by perpendicular stouter cytoplasmic processes rather than parallel processes seen in PGNT as well as presence of hyalinized vasculature), ependymoma (absence of dysmorphic neuronal component) and rarely ganglioglioma (conspicuous dysmorphic ganglion cells and perivascular chronic inflammatory cell infiltrate, lack of pseudopapillary architecture, hyalinized vessels, and neurocytic elements)

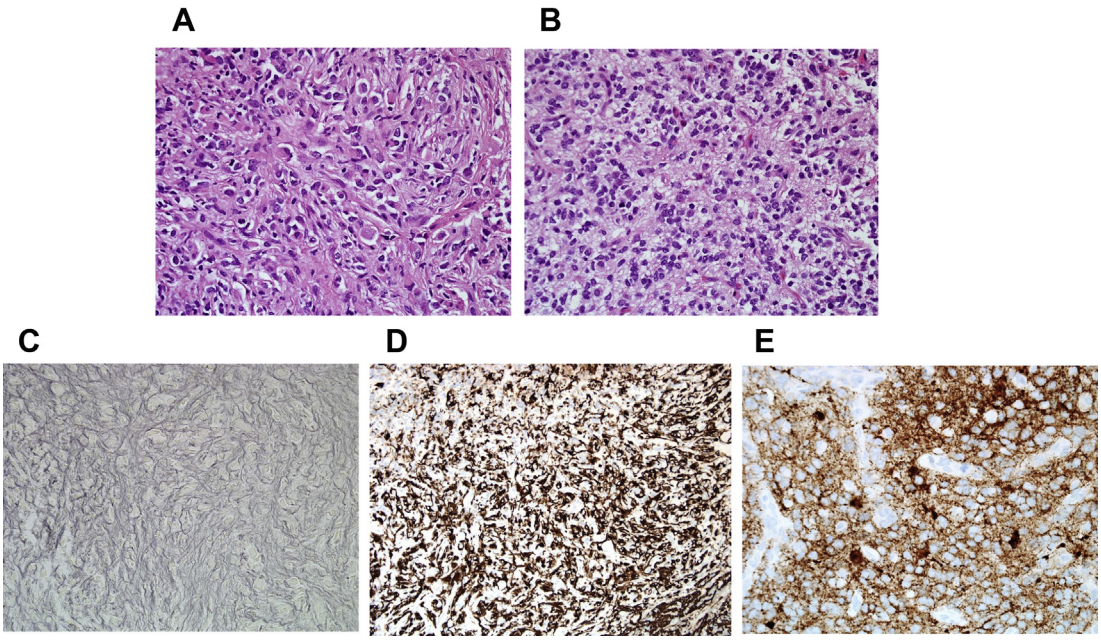

Fig. 22. DIG. Glial and dysmorphic neuronal elements are present in a fibrotic appearing stroma (*A*). Cellular appearing areas with high nuclear cytoplasmic ratio (somewhat blue cells) can be appreciated in some examples (*B*). Rich reticulin meshwork (*C*) with widespread expression of GFAP (*D*) and neuronal marker, synaptophysin (*E*).

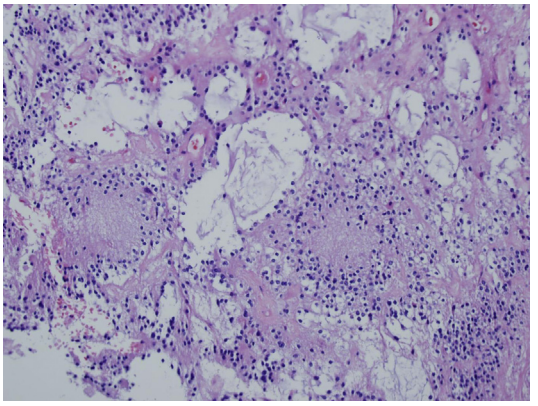

Fig. 23. RGNT with conspicuous rosetted architecture characterized by central neuropil which is surrounded by relatively uniform-appearing neurocytic cells. Also appreciated are microcysts that can characterize some cases.

ROSETTE-FORMING GLIONEURONAL TUMOR

Rosette-forming glioneuronal tumor (RGNT) is a circumscribed, slow-growing tumor that typically arises in the fourth ventricle of young adults (median age, 22.5 years[55]). Histologically, it is a biphasic tumor with distinct neuronal and glial components. The neuronal component consists of small round bland neurocytes forming rosettes or perivascular pseudorosettes in a fibrillary background with or without microcysts (**Figs. 23** and **24A**). The glial component is usually composed of spindled cells that resemble those of pilocytic astrocytoma and can be highlighted by glial marker such as GFAP. In contrast, the neurocytic cells immediately surrounding the central neuropil are generally strongly reactive for synaptophysin (**Fig. 24**B). They may also have oligodendroglioma-like or DNET-like areas. Although morphologically similar, RGNTs are distinct from pilocytic astrocytomas because they do not harbor *BRAF-KIAA1549* fusion or *BRAF V600E* mutation. Instead, a recent study has identified *FGFR1* mutation in 100%, *PIK3CA* mutation in 63%, and *NF1* mutation in 33% of RGNTs. This means RGNTs are characterized by combined genetic alterations affecting both mitogen-activated protein kinase and PI3K pathways.[56] RGNT is a WHO grade I tumor with a good prognosis.[55]

Key Features
ROSETTE-FORMING GLIONEURONAL TUMOR (RGNT)

- Corresponds to WHO grade I
- Composed of glial and neuronal (neurocytic) components
- Fourth ventricle is preferred site but can occur in third ventricle
- Rosettes are formed by central neuropil with surrounding neurocytic cells
- *FGFR1* alterations are common
- Differential diagnoses includes pilocytic astrocytoma (lacks the neuropil-rich rosettes and often has *BRAF* alteration)

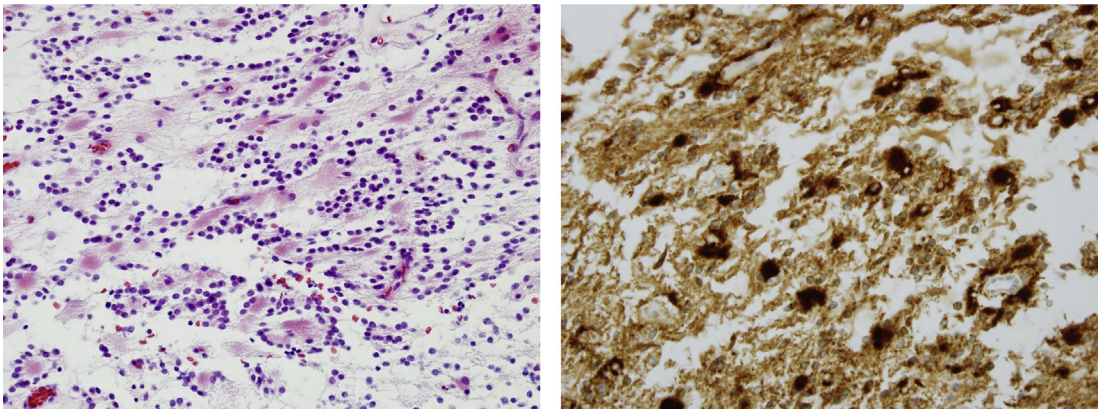

Fig. 24. RGNT. High-power showing neurocytic cells arranged in a rosetted arrangement (*A*). The central neuropil of rosettes is highlighted by its strong reactivity with synaptophysin (*B*).

DISCLOSURE

The authors have nothing to disclose.

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