Central Nervous System Tumors With Ependymal Features: A Broadened Spectrum of Primarily Ependymal Differentiation?

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Abstract

Ependymomas are well-characterized central nervous system (CNS) tumors that occur most often in children and young adults. Several other CNS tumor entities, including astroblastoma, chordoid glioma, papillary tumor of the pineal region, angiocentric glioma, and pilomyxoid astrocytoma, variably display histopathologic features of ependymal differentiation. The ependymal differentiation in some of these tumors is generally accepted, whereas in others, it is controversial. This article briefly reviews ependymal cell development and conventional ependymomas, the pathologic findings and clinical behavior of tumors with variable ependymal features, and the rationales for their inclusion with ependymomas or exclusion from a larger family of ependymal tumors. These issues are addressed in the context of early morphologic insights of Bailey and Cushing, Friede, and others; contemporary oncologic concepts; and recent relevant molecular and tumor stem cell studies.

Key Words: Developmental, Glia, Neoplasms, Pediatric, Stem cell

EPENDYMAL CELL DEVELOPMENT

Central nervous system (CNS) tumors with ependymal differentiation seem to exhibit cytologic features that recapitulate stages of normal ependymal cell development. The stages range from the most primitive embryonic ependymal precursor cells known as radial glia to the conventional ependymal cells that line the spinal cord central canal and brain ventricles to the highly specialized ependymal cells of the circumventricular organs. In considering ependymal differentiation in glial neoplasms, it is therefore essential to review normal ependymal cell development.

The neuroepithelium of the embryonic neural tube gives rise to multipotent glial and neuronal progenitor cells known as radial glia (1–3). Radial glia are bipolar cells with long slender hairlike (piloid) basal processes that extend to the ventricular surface. The latter may project a single cilium. The oval nuclei of these cells are polar, triangular-shaped cells with long tapering basal processes (Fig. 1C, D). Fetal ependymal tanycytes are polar, triangular-shaped cells with long tapering basal processes (Fig. 1C, D). They comprise the ventricular lining of the fetal brain from 19 to 35 weeks’ gestation (4). By 38 weeks, most of these cells have differentiated into mature ependymocytes: ciliated epithelial-like cells that lack basal processes (4, 6, 7) (Fig. 1E). Fetal ependymal tanycytes strongly express the intermediate filament protein glial fibrillary acidic protein (GFAP) (Fig. 1D). Glial fibrillary acidic protein expression is generally less in mature ependymocytes and in some neoplastic ependymal cells because they may show only weak, focal, or absent GFAP immunoreactivity.

In the adult brain, mature ependymal tanycytes may be found within the hypothalamic region of the third ventricle and the specialized ependyma of the circumventricular organs (SECO) (8, 9). Like fetal ependymal cells, these cells are unipolar (Fig. 1F) or are bipolar and situated immediately below the ependymal lining, extending a short apical process to the ventricular surface (8, 9). Ependymal tanycytes form junctions with subependymal blood vessels, other glia, or neurons. At least 4 subtypes of mature third ventricular tanycytes have been described based on differences in surface protein expression and functional relationships to neuron subpopulations (9).

Specialized Ependymal Differentiation

The ependymal cells of the circumventricular organs (i.e., the pineal gland, choroid plexus, area postrema, subfornical organ, subcommissural organ, median eminence, infundibulum, and organum vasculosum of the lamina terminalis) are similar to ordinary ventricular ependymal cells, with some important exceptions. The SECO have different functional and cytologic characteristics in different anatomic locations (10–12). Most are cuboidal to columnar cells processing numerous apical microvilli and variably few to abundant cilia.
Compared with conventional ependymocytes, SECO generally have greater endocytic and/or secretory capabilities (10, 11). Like ependymal tanycytes, certain SECO contain conspicuous lateral tight junctions (13), allowing them to act as selective molecular sieves between the cerebrospinal fluid and nearby neurons or microvasculature. Some SECO extend basal processes that form gap junctions with neurons or capillaries, blurring the definitions for SECO and tanycytes within the circumventricular organs. The SECO of the subcommissural organ and organum vasculosum of the lamina terminalis are prominent in the fetal brain and are absent or rudimentary in the adult (11, 13).

Choroid plexus cells are even more highly specialized ependymal cells (Fig. 1G). They are packed with mitochondria necessary for generation of the adenosine triphosphate required for cerebrospinal fluid secretion. Unlike other ependymal cells, choroid plexus cells directly rest on a basement membrane. Basement membrane signaling (e.g. via integrins) may result in the more epithelial cell-like phenotype of choroid plexus cells (14, 15). These properties are reflected in their robust expression of cytotkeratins, epithelial cadherin (E-cadherin) and their capacity to form papillomas and carcinomas. Therefore, choroid plexus tumors may be considered as ependymal tumors of very distinct types, if not altogether nonependymal.

**CONVENTIONAL EPENDYMAL TUMORS**

Four types of ependymal tumors are currently recognized by the World Health Organization (WHO) classification system (16). Subependymomas are generally small, slow-growing asymptomatic intraventricular tumors, but they may occasionally cause cerebrospinal fluid obstruction (17).
They are composed of clusters of subependymal glia within a dense glial background (Fig. 2A). Myxopapillary ependymomas most often occur near the filum terminalis or conus medullaris (17) and are composed of predominantly unipolar ependymal cells that form characteristic perivascular pseudorosettes that show apparent retraction of their processes away from the central vessel, leaving an intervening space that contains myxoid material (Fig. 2B). Myxopapillary ependymomas are usually slow-growing WHO Grade I lesions.

The cells of classic ependymomas often resemble normal ependymocytes. They exhibit perivascular pseudorosettes (Fig. 2C) and, less frequently, true ependymal rosettes that mimic the normal ependymal canal (16) (Fig. 2D–F). Their cells have smoothly contoured, round to oval nuclei with evenly dispersed granular chromatin (Fig. 2D, F). The cell body is usually unipolar and variably spindle to polygonal shaped, and contains moderate amounts of finely granular cytoplasm. Anaplastic ependymomas are WHO Grade III tumors that resemble classic ependymomas, except that they may be more poorly differentiated and show higher cellular density focally or throughout (17). They display increased mitotic activity, which is their most important diagnostic criterion (Fig. 2F). Anaplastic ependymomas may also show nuclear pleomorphism, vascular proliferation, and/or necrosis.

Major histologic variants of ependymoma include cellular, papillary, tanyctic, and clear cell types, all of which are well described (16). Rare ependymoma variants include lipomatous, vacuolated, melanotic, and giant cell types, ependymomas with neuropil-like islands, and ependymomas with cartilaginous or osseous differentiation (16–20). Electron microscopy may occasionally be necessary to differentiate ependymoma variants, particularly clear or giant cell types, from other tumors. Histologic features of any of the subtypes or variants can be admixed with those of classical ependymomas.

**Immunohistochemical and Ultrastructural Features of Ependymal Tumors**

Ependymomas are generally GFAP, vimentin, S100, CD99, nestin, and neural cell adhesion molecule (NCAM;...
CD56) immunopositive (16, 17, 21–23). They are also frequently epithelial membrane antigen (EMA) protein immunopositive and varyably positive for cytokeratins such as AE1/AE3 cocktails, CK7, CK18, CK22, and others. Ultrastructurally, like normal ependymocytes, ependymoma cells display well-developed zonula adherens complexes, cytoplasmic glial filaments, microvilli, and cilia. They also frequently exhibit intracellular microlumina containing microvilli, cilia, and proteinaceous material. The latter correspond to the so-called dot-and-ring pattern of EMA

**FIGURE 3.** Ependymal tumors with specialized differentiation. (A–D) Papillary tumors of the pineal region. (A) Mildly, nonhomogeneously enhancing 1.8-cm pineal region tumor in a 51-year-old man. Bizarre giant cells were frequent in this tumor (B). The tumor was neural cell adhesion molecule (NCAM) (C), glial fibrillary acidic protein (GFAP), CK7, p53, and transthyretin immunoreactive, and CK20 and E-cadherin negative. Mitoses were noted, and the Ki-67 labeling index was focally up to 5%. (D) Cystic, enhancing 3.8-cm third ventricular mass in a 62-year-old man. The tumor was strongly NCAM, S100, and CK22 immunopositive, and GFAP, epithelial membrane antigen (EMA), transthyretin, E-cadherin, and Ki-67 immunonegative. These lesions invaded the pineal gland (A), and thalamus (D), respectively. (E–H) Chordoid glioma of the third ventricle in a 24-year-old woman. Low-power (E) and high-power (F) photomicrographs depict chords of polygonal cells in a mucinous background. A GFAP immunostain demonstrated weak diffuse and focal moderate positivity (G). The tumor displayed moderate membrane and cytosolic EMA immunoreactivity (H). It also showed transthyretin cytoplasmic immunopositivity and S100 nuclear and cytoplasmic immunoreactivity. The Ki-67 labeling index was approximately 1%. (I–N) Papillary ependymoma of intermediate differentiation. This recurrent, enhancing tumor initially presented in the thoracic spinal cord of an 8-year-old girl. It was strongly immunopositive for GFAP (J), EMA (K), and transthyretin (L). Note the hobnail appearance of the cells, similar to choroid plexus epithelium. An excisional biopsy of a subsequent subarachnoid brain surface metastasis showed identical histology and was strongly immunopositive for pancytokeratin (CAM 5.2/AE1/AE3), E-cadherin (M), and NCAM (N), which may indicate transitional differentiation between conventional ependymal and specialized ependymal (choroid plexus or SECO) phenotypes. Routine stains are hematoxylin and eosin. Original magnifications: (A, D, E, I) 200×; (B, C, F–H) 600×; (J–N) 400×.
immunopositivity characteristic of many ependymal cells (Fig. 2E) (23) and may appear as intracellular eosinophilic inclusions on hematoxylin and eosin stain (24).

**Ependymal Tumor Genetics and Biologic Behavior**

Common cytogenetic abnormalities observed in ependymomas are complete and partial losses of chromosomes 22, 22q (including the \( \text{NF2} \) gene, particularly in spinal ependymomas), 10q, 3, 6q and 9q (containing the \( \text{PIK3CA} \) gene, particularly in supratentorial ependymomas), and gains of 1q, 12q, 7q, 8, and 9 among others (25). For intracranial ependymomas, aggressive clinical behavior is predicted by proliferative and mitotic indices, that is 10 or more mitoses/10 high-power fields, Ki-67 labeling index greater than 5% to 20.5% depending on method (28). Chordoid meningiomas, aggressive clinical behavior is predicted by proliferative outcome. There is controversy regarding the extent to which patient age younger than 3 years generally predicts poor survival for ependymal tumors (16, 32). Additionally, age younger than 3 years generally predicts poor survival for ependymomas as a group (16, 27, 28). A more recent study by Montange et al (37) reported a 5-year overall survival rate of 73% and progression-free survival rate of 27% for their series of 31 cases of PTPR. These statistics are roughly similar to those for ependymomas as a group (25–27). Montange et al (37) reported a 5-year overall survival rate of 73% and progression-free survival rate of 27% for their series of 31 cases of PTPR. These statistics are roughly similar to those for ependymomas as a group (25–27). Whether they are derived from the embryonic subcommissural organ SECO or from other ependymal progenitor cells, for example, those of the pineal gland or ventricular ependymal layer, these tumors demonstrate so many of the classic features of ependymoma that a strong case can be made for their classification as ependymal tumors. Papillary tumors of the pineal region also express proteins that are highly expressed by the fetal subcommissural organ (43). Thus, the overall protein expression pattern of PTPRs is consistent with SECO differentiation intermediate between conventional ependymomas and chordoid plexus tumors.

The few PTPRs that have been examined by cytogenetics often showed loss of chromosomes 10 and 22q (40), that is, abnormalities that are frequently found in ependymomas (25–27). Whether they are derived from the embryonic subcommissural organ SECO or from other ependymal progenitor cells, for example, those of the pineal gland or ventricular ependymal layer, these tumors demonstrate so many of the classic features of ependymoma that a strong case can be made for their classification as ependymal tumors. Papillary tumors of the pineal region present in older children and young adults and may recur after gross total resection and are, thus, WHO Grade II to III lesions. Chemotherapy currently seems to be relatively nonefficacious.

**TUMORS OF PUTATIVE SPECIALIZED EPENDYMAL DIFFERENTIATION**

**Papillary Tumor of the Pineal Region**

Papillary tumors of the pineal region (PTPRs) are uncommon recently described lesions that bear some resemblance to papillary pineocytomas (36–40). Unlike pineocytomas, however, they are not strongly synaptophysin immunoreactive (37). Some PTPRs were undoubtedly diagnosed as papillary ependymomas due to their strikingly ependymal histologic features. Papillary tumors of the pineal region consist of cuboidal to columnar epithelial-like cells forming papillary structures and pseudorosettes (Fig. 3A, C, D). They may invade the pineal gland and/or periventricular brain structures (38) (Fig. 3A–D). Focal tumor necrosis without associated microvascular proliferation is common. As in other papillary ependymal tumors (Fig. 3I), papillary core vessels in PTPR are frequently hyalinized (Fig. 3A, D).

Electron microscopy reveals abundant microvilli, rare cilia, zonula adherens, and zonula occludens. Perinuclear intermediate filaments and numerous clear and coated vesicles are also found (36). Most PTPRs lack strong GFAP immunoreactivity, variably display weak membrane or rarely dot-and-ring EMA immunoreactivity, and are nestin, NCAM, and CK18 immunopositive (36–38, 40). They tend to also express S100, vimentin, and, often, transthyretin (37, 38). Although PTPRs may be \( \text{CK7} \) immunopositive, as are some ependymomas (21), universal \( \text{CK20} \) negativity suggests that \( \text{CK20} \) may be useful to distinguish PTPRs from metastatic gastrointestinal adenocarcinoma (37). Most chordoid plexus tumors are also \( \text{CK20} \) immunonegative, and many are \( \text{CK7} \) and focally GFAP immunopositive (41). Papillary tumors of the pineal region are reportedly E-cadherin negative (37). The latter, along with NCAM immunopositivity (Fig. 3C), may distinguish PTPRs and other ependymal tumors from chordoid plexus tumors (22). Ki-67 labeling indices of PTPRs vary from less than 5% to greater than 10% (37).

It has been suggested that the immunohistochemical profile, particularly transthyretin positivity, and ultrastructural findings (tight junctions, endocytic/secretory vesicles) of PTPRs support an origin from the subcommissural organ SECO in the posterior third ventricle (36, 38). Like the choroid plexus, the fetal subcommissural organ seems to secrete transthyretin (10). Additionally, approximately 20% to 25% of PTPRs are immunoreactive for the potassium channel Kir7.1 and the calcium-phosphate-regulating polypeptide stanniocalcin-1 (37, 40), which seem to be relatively specific markers of choroid plexus epithelium (42). Papillary tumors of the pineal region also express proteins that are highly expressed by the fetal subcommissural organ (43). Thus, the overall protein expression pattern of PTPRs is consistent with SECO differentiation intermediate between conventional ependymomas and chordoid plexus tumors.

Chordoid Glioma

Chordoid glioma is a relatively recently described, well-circumscribed tumor of the third ventricle (44). Histologically, chordoid gliomas consist of cords of epithelial-like cells within a mucinous background and therefore resemble chordoid meningiomas. Tumor cells show smoothly contoured nuclei and moderately abundant amphophilic to eosinophilic cytoplasm (Fig. 3E, F). Peritumoral Rosenthal fibers and lymphoplasmacytic infiltrates are common. Ki-67 labeling indices are approximately 1% or less. Chordoid...
gliomas tend to be vimentin and GFAP immunopositive (Fig. 3G) and variably positive for S100, CD34, EMA, and cytokeratins (44–49). Epithelial membrane antigen immunoreactivity is usually membranous or cytoplasmic (Fig. 3H). In contrast, meningiomas are usually S100, GFAP, and CD34 immunonegative. Ultrastructurally, chordoid gliomas demonstrate numerous microvilli, adherens and occluden junctions, secretory vesicles, and, less commonly, cilia and intracellular microlamina (45–47). Tumor cells are also frequently associated with basement membrane (47).

Small chordoid gliomas limited to the lamina terminalis of the anterior third ventricle have been described (48, 49). Because all reported cases involve this area, this is reasonable evidence that these tumors arise specifically at that location (49). Instead of the SECO of the lamina terminalis (49), Sato et al (47) favored embryonic tanyctyes as the cell of origin of chordoid gliomas. However, the epithelioid morphology of chordoid glioma cells arguably more closely resembles that of some SECO, rather than tanyctyes. Additionally, some chordoid gliomas show transthyretin and/or E-cadherin immunopositivity, that is, features of specialized differentiation (47).

Arguments favoring the tanyctye as the cell of origin of chordoid gliomas include their generally strong GFAP immunopositivity, and that they have tight junctions, abundant surface microvilli and few cilia, and are associated with basement membrane. The processes of both tanyctyes and SECO, however, can be associated with basement membrane. Furthermore, fetal SECO, like fetal ependymocytes, are likely derived from earlier embryonic radial glia-derived precursors. Because PTPRs and chordoid gliomas most likely do not arise from mature cells, the question of origin from embryonic tanyctyes versus SECO seems moot because both suggest ependymal lineage.

Chordoid gliomas may recur if incompletely excised. They are WHO Grade II lesions, but unresectable examples may be fatal (46, 49). Approximately 3 dozen cases have been reported in patients ranging in age from 12 to 70 years, most often presenting in the third to fifth decade in a 2:1 female predominance (48). Kleinman et al (50) described 2 tumors located in the temporal lobes of adults that were called epithelioid ependymomas. Both were composed of small islands and cords of polygonal ependymal-like cells within a mucoid background. Immunohistochemical and ultrastructural findings were consistent with ependymal differentiation, and histologically, these tumors seem to resemble chordoid gliomas.

CORTICAL TUMORS WITH EPENDYMAL FEATURES

Cortical Ependymoma

Most intracranial ependymomas and recently described ependymal tumors occur within or near the CNS ventricular system. Cortical ependymomas are rare supratentorial ependymomas centered within the cerebral cortex (51–53). They are sometimes referred to as brain surface ependymomas (51). However, this term is less accurate because supratentorial ependymomas arising in the ventricle, periventricular white matter, or cortex may all reach the pial surface (32–34, 51–54). Cortical ependymomas are biologically low grade and most commonly present in patients with histories of poorly controlled seizures beginning in childhood (Fig. 4A–D). They are usually assigned a WHO Grade of II but may behave more like Grade I lesions. Because they are generally well circumscribed and readily accessible surgically, they tend to not recur after gross total resection. The latter may even be true for tumors with high proliferative fractions, in contrast to most intracranial ependymomas in which proliferative fraction generally correlates with prognosis (28, 29). Indeed, Palma et al (33) and Vinchon et al (34) found that extent of resection was the most important factor in predicting outcome in supratentorial ependymomas.

Angiocentric Glioma

Two recently described tumors, monomorphic angiocentric glioma (55) and angiocentric neuroepithelial tumor (56), are closely related if not identical entities and have been termed angiocentric gliomas in the 2007 WHO classification (57). These tumors display many clinical and histologic similarities to cortical ependymomas. Angiocentric gliomas occur in children and young adults with a history of seizure onset from 2 to 23 years of age. They are characterized anatomically by cortical centricity and histologically by small spindle- to polygonal-shaped tumor cells with ependymal nuclear and ultrastructural features. Several reported examples displayed dot-and-ring pattern EMA immunopositivity, formed perivascular pseudorosettes, true ependymal rosettes, and subpial clear cell mounds similar to cortical ependymomas (52, 53, 55, 56) (Fig. 4B).

The distinguishing features of angiocentric gliomas are that they are locally infiltrative within the neuropil and display “nonradial” circumferential or longitudinal angiocentric growth patterns (55, 56). Similar nonrosetting angiocentric growth can occasionally be seen at the interface of supratentorial ependymomas and neighboring brain tissue (Fig. 4A).

Astroblastoma

Astroblastomas were first described by Bailey and Cushing (58) in 1926. These rare tumors share many histologic and clinical features with conventional ependymomas (58–64). Astroblastomas occur most commonly in the cerebral hemispheres, often involving the cortex, and like many supratentorial ependymomas (33, 52, 54), are frequently cystic and enhancing on imaging (62–65). Like ependymomas, it has also been hypothesized that astroblastomas may be derived from radial glia-like tanyctyes (5, 60, 62). Astroblastomas form perivascular pseudorosettes and are generally strongly GFAP, vimentin, and S100 immunopositive, and variably EMA immunopositive (59). Compared with ependymomas, tumor cell processes forming astroblastoma perivascular pseudorosettes are generally thicker, less tapered, and more distinct (Fig. 4E, F, H, J, L). These processes often widen or flare where they contact the blood vessel similar to tanyctye endfeet and were termed the “sucker foot” by Bailey and Cushing (58) (Fig. 4H, J, L). The nuclei of astroblastomas may more closely resemble
those of astrocytomas with more vesicular, less evenly dispersed chromatin and a more prominent nucleolus than typically seen in ependymomas (Fig. 4E, F, H–J). As in some supratentorial ependymomas (18, 19, 52–54), clear, signet ring, vacuolated, or lipomatous-like cells can be seen in low-grade astroblastomas (64) (compare Figs. 4D and H).

Ultrastructurally, astroblastomas exhibit microvilli, cilia, and adherens junctions. Compared with ependymomas, their cilia tend to be rarer, and their junctional complexes are both rarer and less well developed (60). Despite many overlapping histologic, immunophenotypic, and ultrastructural features with ependymomas, astroblastomas

FIGURE 4. Cortical ependymal tumors with mixed astrocytic and ependymal features. (A–D) Previously reported cortical ependymoma in a 10-year-old boy (52). (A) Nonrosetting angiocentric growth (arrows) at the periphery of the tumor. (B) Subpial epithelioid clear cell mounds. (C) Occasional perivascular pseudorosettes resembled those of astroblastomas. (D) Signet ring cells were also present. (E–I) Low-grade astroblastoma in a 10-year-old girl presenting with partial complex seizures. Neuroimaging showed a large enhancing left parietal mass. The tumor recurred after initial resection but has not recurred after a second gross total resection, now 5 years from presentation. The tumor was glial fibrillary acidic protein (GFAP) and S100 immunopositive and epithelial membrane antigen negative. The Ki-67 labeling index was less than 2%. (E) Astroblastoma perivascular pseudorosette. Occasional clear cells were present. (F) Elongated tumor cells. (G) Low-power photomicrograph showing occasional hyalinized pseudorosette vessels. (H) Signet ring or lipomatous type cells near pseudorosette-forming cells. Note the distinct basement membrane adjacent to wide astroblastoma perivascular foot process. (I) Intraoperative cytologic preparation showing more astrocyte-like appearance of smeared tumor cells. (J–L) High-grade astroblastoma in a 40-year-old man with seizures. This parietal tumor was treated with gross total resection and radiotherapy. The patient has survived 8 years without recurrence. (J) Note occasional flaring of endfoot processes. (K) Numerous mitotic figures, perivascular pseudorosettes (the arrow indicates the pseudorosette shown in [J]), vascular proliferation (arrowhead), and pseudopalisading necrosis were present. (L) Glial fibrillary acidic protein immunoperoxidase stain highlighting long astroblastoma processes and endfeet. Hematoxylin and eosin stains, except (L). Original magnifications: (A, G) 200×; (B, D, F, H–J, L) 600×; (C–E) 400×; (K) 100×.
may more closely resemble astrocytomas on smear preparations due to their nuclear characteristics and thicker, generally more eosinophilic cytoplasmic processes (Fig. 4I).

Comparative genomic hybridization data reported for 7 cases of astroblastoma revealed gains of chromosomes 20q and/or 19 in approximately half of the cases (59). Losses of chromosomes 9q, 10, and X were also found. These specific gains and losses have also been reported in ependymomas (25–27).

Astroblastomas have not been assigned a WHO grade, but most behave like Grade II to III lesions (59). Low-grade astroblastomas generally present in younger patients (first and second decades), whereas high-grade tumors present in older patients (third to fourth decades). Cases exhibiting high-grade features (i.e. mitotic activity, vascular proliferation, or necrosis) have been referred to as malignant or anaplastic (59, 61) (Fig. 4J–L). Yet, because like Grade III ependymomas, astroblastomas tend not to be diffusely infiltrative across large anatomic distances (65), anaplastic astroblastomas are generally associated with a better prognosis than are Grade III astrocytomas or oligodendrogliomas. Like anaplastic ependymomas, anaplastic astroblastomas often do not recur if completely excised (61, 63) (Fig. 4J–L).

**TANCYTIC EPENDYMAL TUMORS AND PILOID ASTROCYTOMAS**

**Tanycytic Ependymoma**

Tanycytic ependymomas are composed of bipolar cells with long slender processes thought to be analogous to those of radial glia (tanycytes) (66) (Fig. 5A–C). These cells may be indistinguishable from those of pilocytic astrocytomas on smear preparations (67). Pseudorosettes may be indistinct, and true rosettes are usually absent (16, 66) (Fig. 5A). Occasionally, however, perivascular pseudorosettes are distinct (Fig. 5B, C). Tanycytic ependymomas occur most often in the cervical, followed by the thoracic spinal cord of young adults, and rarely within the brain (66, 68). They have been designated WHO Grade II lesions but are generally slow growing, noninvasive, and often behave like Grade I lesions.

**FIGURE 5.** Tumors with radial glia-like tanycytic features. (A) Tanycytic ependymoma. (B) Distinct perivascular pseudorosettes in the same tumor as in (A). (C) Similar perivascular pseudorosettes in a different tanycytic ependymoma. (D–F) Pilocytic astrocytoma with pilomyxoid features. (D) Most of the tumor showed loose architecture consisting of piloid cells in a mucinous background with areas of microcyst formation. (E) Numerous perivascular pseudorosettes reminiscent of those sometimes seen in tanycytic ependymomas were also present. (F) The pseudorosettes were strongly glial fibrillary acidic protein (GFAP) immunopositive. Hematoxylin and eosin stains, except (F). Original magnifications: (A–C, E) 200×; (D, F) 600×.
Clinical outcome is usually limited only by the potential for resection without damaging the spinal cord.

**Pilocytic Astrocytoma**

Pilocytic astrocytoma is a recently described variant of pilocytic astrocytoma composed of bipolar piloid cells within a myxoid background (69). They otherwise closely resemble conventional pilocytic astrocytomas but generally lack alternating loose and dense regional architecture, prominent microcysts, eosinophilic granular bodies, and Rosenthal fibers (69–73). They affect young children and rarely adults and, like conventional pilocytic astrocytomas, may involve the optic chiasm, hypothalamus, cerebellum, spinal cord, and, more rarely, the cerebral cortex. Pilocytic astrocytomas recur more frequently after resection and spread within the subarachnoid space more often than do pilocytic astrocytomas and are thus WHO Grade II neoplasms.

Perivascular pseudorosettes occasionally seen in pilocytic (74) and more often in pilomyxoid (69) astrocytomas may closely resemble those sometimes found in tanyctic ependymomas (compare Figs. 5B and C to E). Both Fuller et al (70) and Lieberman et al (71) reported finding microvilli, rare cilia, and synaptoid complexes in supratentorial pilomyxoid astrocytomas ultrastructurally, consistent with a possible derivation from tanyocytes. Lieberman et al (71) therefore proposed the term *tanycytoma* to describe these tumors. However, earlier electron microscopy studies of pilocytic astrocytomas found that they display primarily astrocytic ultrastructural features (75).

**CURRENT PERSPECTIVES ON THE HISTOGENESIS OF EPENDYMAL TUMORS**

Most cancer biologists have adapted the cancer stem cell theory of tumorigenesis (76). This theory states that tumors develop from tissue-specific stem or progenitor cells of the fetus, child, or adult that proliferate, differentiate, and undergo neoplastic transformation. Furthermore, many neoplasms, including glial tumors, contain a tumor stem cell component that is necessary and sufficient for cellular proliferation and tumor formation in vitro or in experimental animals, respectively (77, 78).

Although modern techniques were required to fully develop the stem cell theory of tumorigenesis, it is a theory with roots in the classic literature of neuropathology. Particularly for ependymomas, there are insightful historic precedents. In 1926, Bailey and Cushing wrote “...clusters of cells resembling lymphocytes may occasionally be found near the ependymal lining of the ventricles and in the vicinity of blood vessels. These appear to represent undifferentiated cells, for some reason arrested in their development, and it is reasonable to suppose that certain types of brain tumors may arise from them.” (58). Other authors had theorized that supratentorial and ectopic ependymomas were derived from neoplastic transformation of embryonic ependymal rests left over from fetal development. Inasmuch as these rests were thought to be composed of embryonic precursor cells, this was essentially an early stem cell hypothesis of ependymoma tumorigenesis.

Historically, radial glia, once called primitive spongiosblasts, were thought to give rise to both astrocytic and ependymal lineages (5, 58). More contemporarily, emphasis was placed on their function as scaffolds for migrating neuronal and glia precursor cells. Radial glia are now again believed to represent pluripotent neural stem cells capable of giving rise to not only ependymal cells and astrocytes but also oligodendrocytes, neurons, and adult neural stem cells (1–5).

Recent findings defining the molecular profiles of ependymomas have shed light onto their ontogenesis. In a microarray study, Taylor et al (78) provide evidence that human supratentorial and spinal ependymomas share similar molecular profiles with the radial glia of their corresponding locations in the embryonic mouse brain lateral ventricle and spinal cord central canal regions, respectively. They found approximately 80% overlap of the expression of genes highly expressed in tumors in the radial glia of the CNS compartment in which they arose. Notably, upregulation of components of the EphB-ephrin and Notch signaling pathways were found in supratentorial ependymomas, and upregulation of Hox family patterning transcription factors were found in spinal ependymomas (78). Gene expression patterns of posterior fossa ependymomas correlated with gene expression patterns of cells surrounding the fourth ventricle but also overlapped with expression patterns of the lateral ventricle and spinal central canal regions. Furthermore, in all cases, tumor stem cells isolated from ependymomas showed an immunophenotype consistent with radial glia. Taylor et al (78) therefore suggested that radial glia of specific regions of the brain are candidate precursor cells for ependymomas. Local environmental cues or stages of differentiation of radial glia subtypes may further dictate specific phenotypes (e.g. unipolar or bipolar vs polygonal clear cell cytology) or a tendency to mostly form solid or infiltrating tumors.

In another recent microarray study, Sharma et al (79) found distinct gene expression patterns for infratentorial versus supratentorial pilocytic astrocytomas. These human tumor region-specific gene expression patterns correlated with region-specific gene expression patterns in primary astrocyte cultures and neural stem cells isolated from corresponding mouse cerebellum or neocortex. These authors compared their microarray data to the region-specific ependymoma microarray data discussed in the previous sentences (78) and, remarkably, found region-specific patterns of overlap among 7 genes between supratentorial pilocytic astrocytomas and supratentorial ependymomas, and posterior fossa pilocytic astrocytomas and posterior fossa ependymomas. These region-specific patterns were verified at the protein level by immunohistochemistry for 2 genes. Pax3 homeotic protein expression, characteristic of posterior fossa pilocytic astrocytomas, was detected exclusively in posterior fossa ependymomas: 28 of 30 were immunopositive, and 7 of 7 supratentorial ependymomas were immunonegative. Lhx2 homeobox protein, highly expressed in supratentorial pilocytic astrocytomas, was detected in all 8 supratentorial ependymomas and in only 3 of 31 posterior fossa ependymomas examined.
These studies suggest that pilocytic astrocytomas and ependymomas may share a similar lineage- and anatomic region-specific histogenesis from common radial glia populations. Consistent with this hypothesis, Komotar et al (72) reported a pilomyxoid astrocytoma in the amygdala of an adult, and Maruyama et al (80) reported bilateral temporal pilocytic astrocytomas with focal ependymal differentiation in a 7-year-old boy. These are anatomic locations where cortical ependymal lesions have also been documented (53, 55, 56).

Because most of the ependymal tumors discussed in this review present in childhood to young adulthood, it is possible that the neoplastic process for this group of generally slow-growing tumors begins in utero or in early childhood from radial glia-derived precursor cells. Ependymomas only more rarely present in older adults. Such tumors may represent progression of exceedingly slow-growing lesions or tumors that arise de novo from adult periventricular neural stem cells, as theorized for some CNS tumors. The latter possibility might explain why supratentorial ependymal tumors in older adults are often more aggressive lesions.

**Considerations for a Broader Family of Ependymal Tumors**

The unique third ventricular ependymal tumors chordoid glioma and PTPR share some phenotypic features with the SECO of that region. The cells of these tumors generally do not produce large numbers of cilia and are more epithelial-like and secretory than are conventional ependymomas. These characteristics are exemplified by their greater tendency toward cytokeratin and transthyretin immunopositivity, and membranous and/or cytoplasmic, rather than dot-and-ring pattern EMA immunopositivity. In addition, some tumors within this group may also express the SECO markers E-cadherin, Kir7.1, or stanniocalcin 1 (37, 40, 43, 47) (Fig. 3M). Tumors of this more specialized ependymal region of dogs as comprising a spectrum (70, 71, 73).

Chordoid gliomas are more convincing; angiocentric gliomas are biologic similarities between angiocentric gliomas and ependymomas can be logically grouped based on their SECO-like properties. However, the ependymal lineage of chordoid glioma is much less certain than that of PTPRs particularly because they do not closely resemble ependymomas cytologically and do not form pseudorosettes or true rosettes. The latter are considered by many to be key features of ependymal differentiation. Additionally, chordoid gliomas display overlapping features with chordoid meningiomas and express CD34, which is generally not expressed by ependymomas. Despite these dissimilarities, 1 author suggested that, based on immunohistochemical and ultrastructural features, chordoid gliomas should be called chordoid ependymoma (of the lamina terminalis area) (46).

In contrast to chordoid gliomas, the histopathologic and biologic similarities between angiocentric gliomas and ependymal tumors are more convincing; angiocentric gliomas are now recognized to be of ependymal differentiation (57). It may therefore be appropriate to consider angiocentric gliomas to be angiocentric cortical ependymal tumors. They may thus represent manifestations within a spectrum of cortical ependymal tumors. This would emphasize the possible similar derivation of angiocentric gliomas and cortical ependymomas from radial glia-derived precursor cells, their common anatomic locations, and their nearly identical clinical behavior.

Astroblastomas share some histologic and clinical features with supratentorial ependymomas and share some cytologic features with astrocytomas. Their biologic behavior is perhaps also intermediate between ependymal tumors and astrocytomas (59, 61); therefore, they may be derived from an intermediated differentiated stage of radial glia-derived cell. Uncommon locations of astroblastomas include the posterior fossa and cauda equina, suggesting an ontologic relationship to ependymomas (17). Many astroblastomas are low-grade tumors, and even resected anaplastic astroblastomas often have a relatively good prognosis. It thus seems unfortunate to continue the use of the suffix -blastoma for these tumors because this usually connotes highly malignant behavior. More phenotypically accurate names for these tumors might be astroependymoma and anaplastic astroependymoma.

Less clear, but nonetheless compelling, is the possibility that pilocytic astrocytomas, like tanycytic ependymomas, may be differentiated more closely toward primitive radial glia-like tanycytes, rather than astrocytes. Although a definite ontologic tree cannot yet be drawn for these tumors, contemporary molecular and stem cell research suggest that ependymomas and pilocytic astrocytomas are derived from radial glia (tanyctyes). This seems to have at least partially confirmed previous hypotheses based on comparative histomorphology alone. Indeed, more than 30 years ago, Blakemore and Jolly (81) described cells populating the subependymal region of dogs as comprising “…an ependymal (normal and ectopic), tanycytic, astrocytic (ETA) series”. Approximately the same time, Friede and Pollak (5) proposed “…a spectrum of ependymoglia-tanyctye-pilooid astrocyte-differentiation…” in reference to ependymomas, astroblastomas, and pilocytic astrocytomas (polar spongioblastomas).

Tanycytic ependymomas show some overlapping cytomorphologic and clinical features with pilocytic and pilomyxoid astrocytomas. They both show piloid morphology, both can form similar perivascular pseudorosettes, are intensely GFAP immunopositive, and are usually clinically low grade. These observations support the genetic evidence for a possible common histogenesis from radial glia tanycytes for these lesions (79). Nevertheless, significant differences in the histopathologic and clinical features of these tumors exist. Pilocytic astrocytomas form eosinophilic granular bodies and Rosenthal fibers and display distinct histologic architectural features, all of which tanycytic and other ependymomas lack. Furthermore, their respective putative derivations from radial glia may be so divergent and/or so early in development to be of much significance to their tumor biology.

**SUMMARY**

Clinical, histologic, immunohistochemical, ultrastructural, and genetic evidence suggests, with variable degrees of evidential strength, that some or many of the glial lesions...
reviewed herein may be phenotypically and ontologically related to ependymal tumors. Although many neuropathologists recognize the specialized ependymal differentiation of PTPRs (37, 38) and the ependymal differentiation of angiogenic gliomas (57), questions regarding the significance of putative ependymal features remain in chordoid gliomas, astroblastomas, and pilocytic/pilocytic astrocytomas. Future developmental, genetic, and clinical studies will be needed to more definitively establish the ontology of all of the above-discussed putative ependymal tumors and, perhaps, the appropriateness of their inclusion in or exclusion from the family of ependymal tumors.

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