Ependymal Tumors

6

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6.1 Overview

- The group of glial tumors exhibiting ependymal differentiation include subependymoma (WHO grade I); myxopapillary ependymoma (WHO grade I); ependymoma (WHO grade II), with variants including cellular, tanycytic, papillary, and clear cell; and anaplastic ependymoma (WHO grade III).
- Most are sporadic; ependymomas may be seen as part of neurofibromatosis type 2, a hereditary cancer predisposition syndrome with germline mutation of the *NF2*/Merlin gene.
- Recent evidence supports radial glia as the candidate cell of origin for ependymomas; subependymomas appear to derive from subependymal glial precursors.

6.2 Clinical Features

- Though much less common overall than infiltrative gliomas, ependymomas are the most common tumor of the spinal cord (particularly in adult patients) and the third most common pediatric central nervous system (CNS) tumor, representing up to 30 % of intracranial tumors in those under 3 years old.
- Infratentorial tumors have their peak age of occurrence in the first decade, while spinal tumors tend to peak in those 30–40 years of age.
- They have an equal gender distribution, but are nearly twice as frequent in Caucasians as in African-Americans.
- Intracranial ependymomas typically result in blockage of cerebrospinal fluid (CSF) pathways, causing signs and symptoms related to hydrocephalus and increased intracranial pressure.
- Anaplastic ependymomas are far more frequent in the pediatric age group, presenting as intracranial tumors, more frequently supratentorial.
  - Clinical signs and symptoms are similar to those for WHO grade II ependymoma, but they tend to develop in an accelerated fashion.
- Spinal ependymomas, including myxopapillary ependymoma, may cause back pain and motor and/or sensory deficits, depending on their specific anatomic involvement.
- Approximately 20 % of myxopapillary ependymomas present in children with a 2:1 male-to-female bias. In this age group, these tumors have a higher rate of occurrence within the extramedullary soft tissue of the sacrococcygeal region, as well as a higher rate of recurrence and dissemination through the CSF pathways.
- Subependymomas are often incidental autopsy findings in the brains of older adults; they are symptomatic when they obstruct CSF flow.
  - They are quite rare in children; when present, they tend to be mixed tumors (with elements of other ependymoma subtypes), involve the infratentorial region, and exhibit shorter progression-free survival than subependymomas arising in older individuals.

6.3 Neuroimaging

- Ninety percent of pediatric ependymomas are intracranial, favoring the fourth ventricle, followed by supratentorial locations.
- Supratentorial tumors (including ependymomas and subependymomas) involve the lateral ventricles more often than the third ventricle.
- Uncommonly, they arise remote from the ventricles, especially in intraparenchymal supratentorial locations in children. Superficial cortical ependymomas have been encountered; these are more frequently anaplastic ependymomas.

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- Rare extraneural sites include the ovaries, mediastinum, and sacrococcygeal locations.
- Ependymomas may arise at any spinal cord level, though certain histologic subtypes have preferred locations:
  - Tanycytic ependymoma: thoracic or cervicothoracic cord
  - Myxopapillary ependymomas: conus medullaris, filum terminale, and cauda equina region
  - Subependymoma: cervical cord
- Myxopapillary ependymomas are the most common intramedullary neoplasms arising in the region of the conus medullaris, cauda equina, and filum terminale; less frequent sites of origin include other cord levels, intracranial sites (both intraventricular and intraparenchymal), and subcutaneous sacrococcygeal areas.
- MRI/CT imaging findings:
  - *Ependymomas and anaplastic ependymomas*
    - Spinal lesions typically involve multiple segments and grow as centrally situated intramedullary tumors that are hyperintense on T2-weighted MR images, with sharp tumor margins; most show uniform contrast enhancement (Fig. 6.1A).
    - Rostral and/or caudal cysts are common, being hypointense on T1- and hyperintense on T2-weighted images.
    - Intracranial tumors are also sharply demarcated, arising within or near the ventricular system. They are at least partially cystic, isointense on T1, isointense to hyperintense on T2, and moderately hyperintense on fluid-attenuated inversion recovery

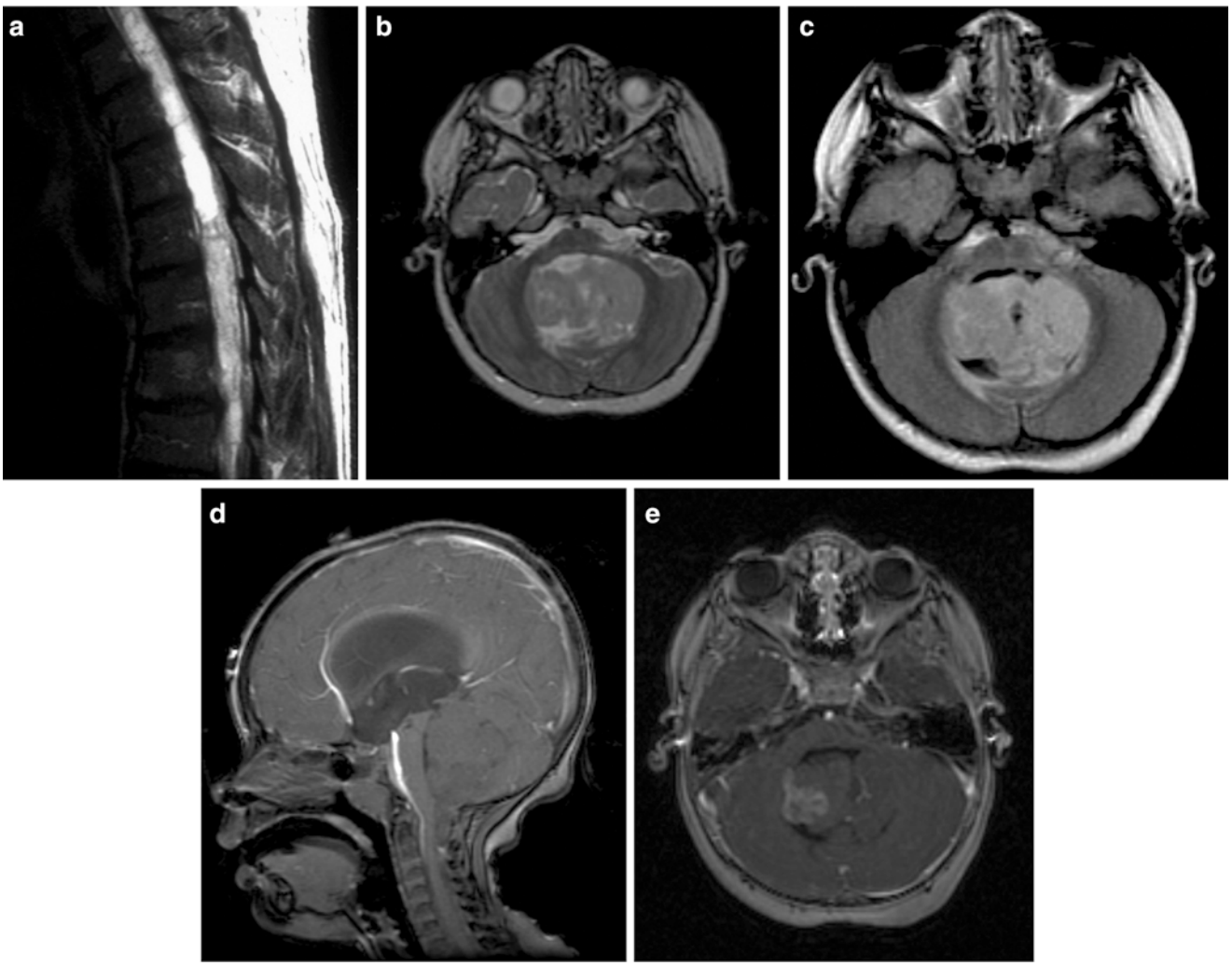


Fig. 6.1 (**A**) Sagittal TI-weighted post-Gd image of a well-demarcated spinal ependymoma with characteristic homogeneous postcontrast enhancement. (**B**) Axial MR images of a fourth ventricular ependymoma show a predominantly solid, well-demarcated tumor that has heterogeneous signal characteristics, being isointense to hyperintense on T2-weighted imaging. (**C**) The same tumor is hyperintense on FLAIR. (**D**, **E**) Sagittal and axial T1-weighted post-Gd imaging shows this same lesion to be isointense, with variable contrast enhancement. Hydrocephalus is prominent in this example. (**A**, C*ourtesy of* Dr. Murat Gokden, University of Arkansas, Little Rock, AR, USA)

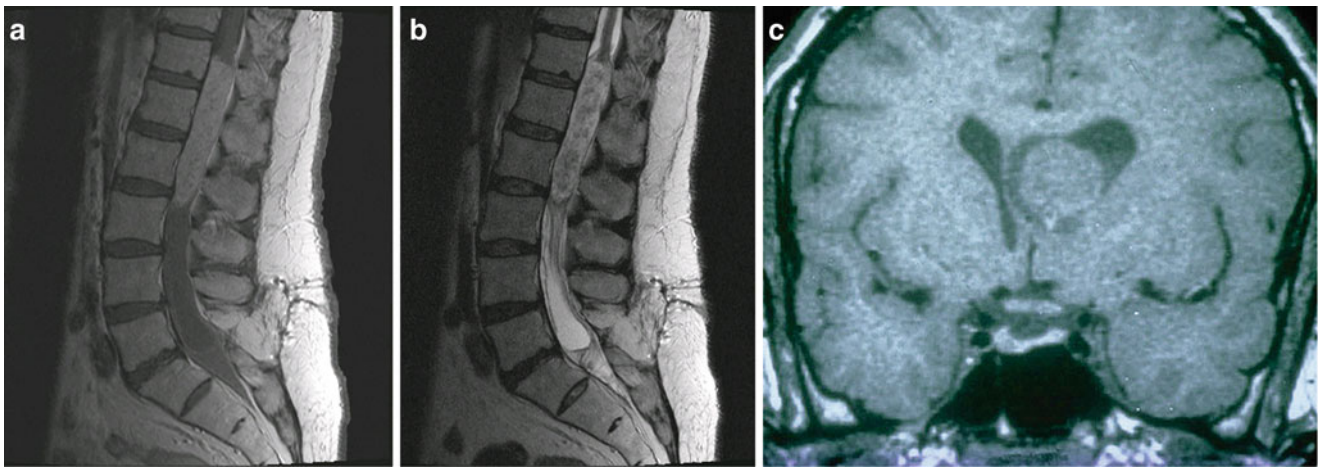


Fig.6.2 (**A**, **B**) Myxopapillary ependymoma. Sagittal T1-weighted and T2-weighted images both show a hyperintense lesion. (**C**) Subependymoma. These lesions tend to be nodular, circumscribed, and intraventricular; this example is isointense on coronal T1-weighted MR imaging

(FLAIR) MR imaging, with variable postcontrast enhancement (Fig. 6.1B–E).
  - Intratumoral hemorrhage and/or calcifications may be seen.
  - Ventricular dilatation is frequently encountered.
  - Occasional tumors show infiltration of surrounding parenchyma, making differentiation from other gliomas difficult.
- *Myxopapillary ependymomas*
  - These tumors are characteristically well-circumscribed, hyperintense on both T1- and T2-weighted MR imaging (Fig. 6.2A and B) (unlike conventional ependymomas, which are typically hypointense on T1), and brightly enhanced with contrast.
  - Cystic change (particularly in intracranial examples) or hemorrhage may be encountered.
- *Subependymomas*
  - These are sharply demarcated, nodular lesions bulging into ventricles or arising eccentrically within the spinal cord.
  - They show variable signal characteristics on MR and CT imaging.
  - They uncommonly enhance, and may contain foci of calcium or hemorrhage (Fig. 6.2C).
- Patterns of metastasis:
  - Ependymomas (grades II and III) and myxopapillary ependymomas (grade I) have been reported to metastasize via subarachnoid spread to seed other spinal and intracranial locations. Metastases to sites outside the CNS have been reported in few instances.

6.4 Pathology

- *Gross pathology*
  - Classic ependymomas are soft tan to grey masses with well-defined borders. They may be partially cystic and/or contain areas of hemorrhage, necrosis, or calcification.
  - Anaplastic examples may show evidence of frank parenchymal invasion.
  - Myxopapillary ependymomas are lobulated, soft, grey to tan, and often encapsulated.
  - Subependymomas are firm, multilobated or nodular intraventricular masses; spinal examples nearly always show an eccentric location.
- *Intraoperative cytologic imprints or smears*
  - Smear preparations of ependymomas contain cohesive clusters of cells with variable cytomorphology, ranging from epithelial-like to bipolar cells with fibrillary processes.
  - Nuclei tend to be round to oval and bland.
  - Perivascular pseudorosettes may be seen (Fig. 6.3A and B).
  - Cytology preparations from the following subtypes may be particularly problematic:
    - Tanycytic: These contain long processes and oval to spindle-shaped nuclei; perivascular pseudorosettes are uncommon, and the smear preparation findings may closely resemble pilocytic astrocytoma.
    - Papillary: These often have a more epithelial consistency and may closely mimic choroid plexus tumors or metastatic carcinomas.

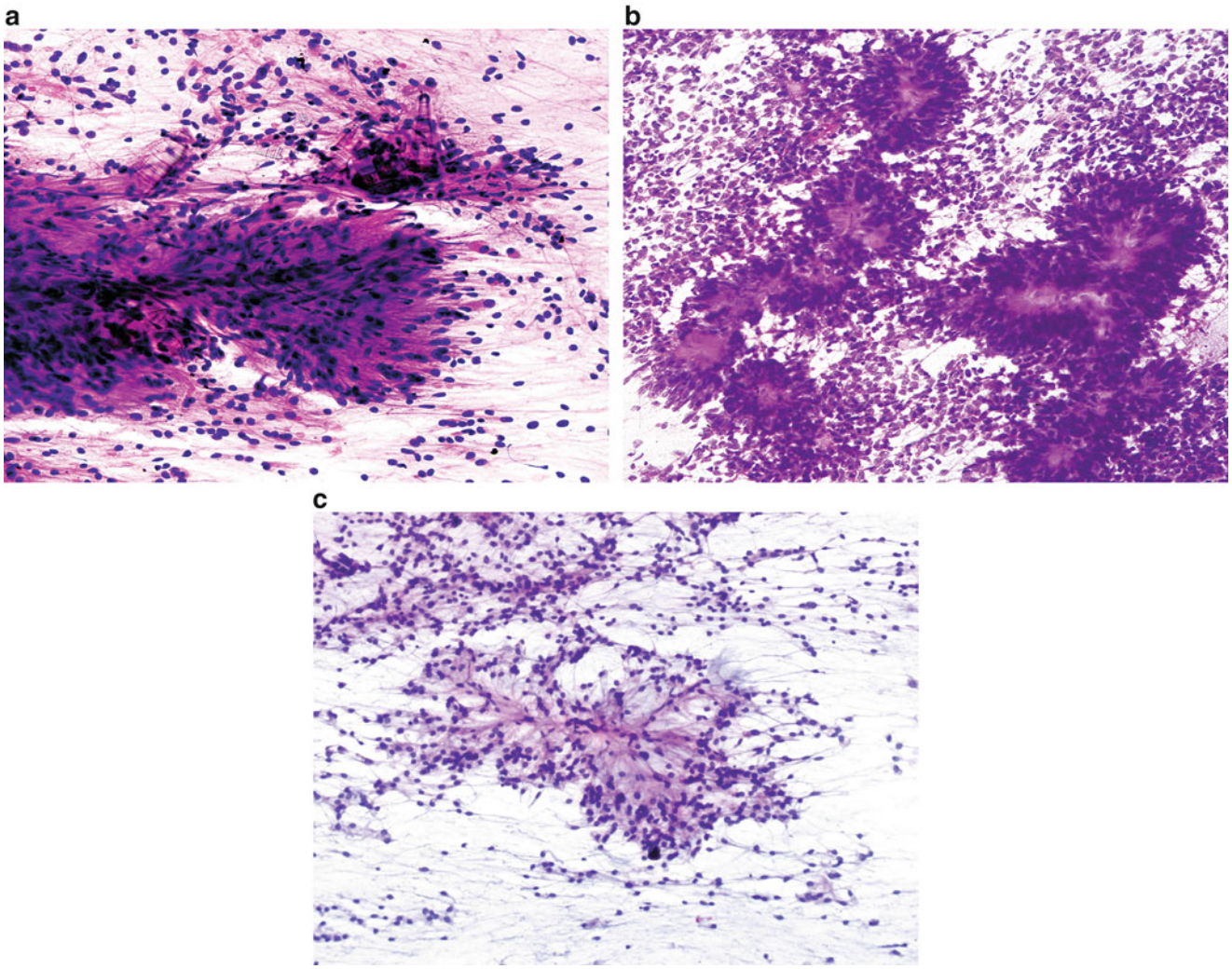


Fig. 6.3 (**A**, **B**) Cytologic preparations of ependymoma often show three-dimensional clusters of cells with elongated, fibrillar glial processes; perivascular pseudorosettes may or may not be obvious. (**C**) Squash preparations of myxopapillary ependymoma are notable for papillary structures with perivascular, radially arranged cell processes and abundant myxoid material

- Myxopapillary ependymoma can appear as papillary structures with perivascular, radially arranged cells with delicate glial processes within abundant myxoid material (Fig. 6.3C).
- Subependymomas present bland nuclei in a fibrillary background, sometimes with discernable microcysts.
- *Histology*
- *Ependymoma* (WHO grade II)
  - Ependymomas classically present as well-demarcated, moderately cellular tumors with bland round to oval nuclei and a fine chromatin pattern (Fig. 6.4A).
  - Several key architectural features may be seen:
- Perivascular pseudorosettes (anuclear zones formed by the elongated glial-like processes of tumor cells in their radial arrangement around blood vessels) are seen in most cases (Fig. 6.4B), but they may be poorly formed in hypocellular areas (Fig. 6.4C).
- True ependymal rosettes and canals (cuboidal to columnar epithelial-like tumor cells surrounding a true central lumen) are seen in a minority of cases (Fig. 6.4D).
- Conversely, ependymal-type lining seen at the periphery of tissue fragments from an ependymoma sampling is not uncommon, and is a helpful diagnostic aid (Fig. 6.4E).
- On occasion, epithelial-type elements predominate, imparting a "tubular adenoma-like" appearance (Fig. 6.4F) or an organoid appearance (Fig. 6.4G).
  - Mitotic figures are uncommon; foci of necrosis may be present, though pseudopalisading necrosis and endothelial proliferation are absent.
- Degenerative changes are common and include myxoid degeneration, vascular hyalinization, hemorrhage, and calcification (Fig. 6.4G).

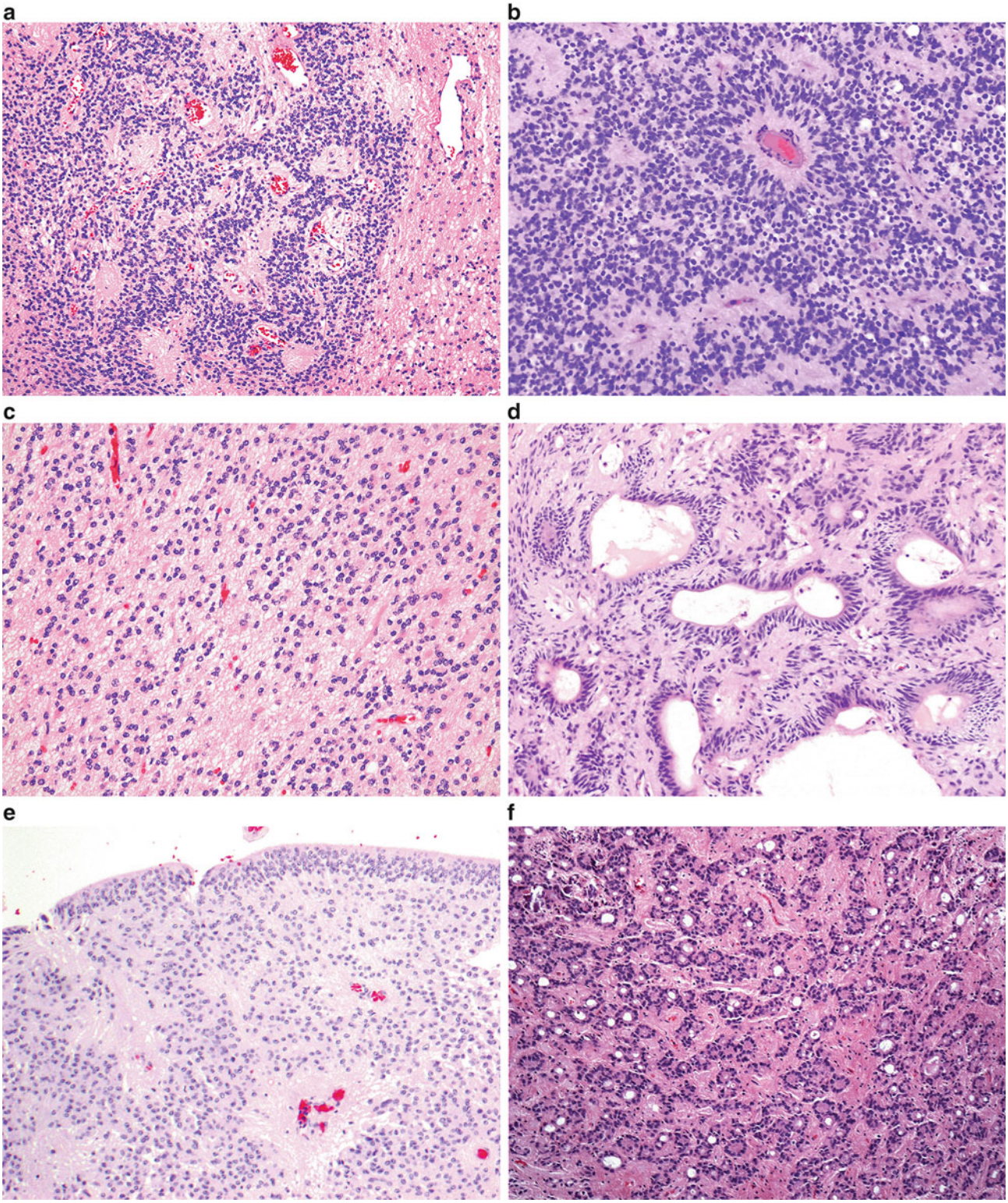


Fig. 6.4 (**A**) Conventional ependymomas exhibit a solid growth pattern with circumscription from surrounding parenchyma. (**B**) Perivascular pseudorosettes are a nearly universal finding. (**C**) The pseudorosettes may be inconspicuous in hypocellular areas. (**D**) Ependymal canals and true rosettes are seen less frequently. (**E**) Identifying ependymal-type lining at the periphery of individual biopsy or resection tissue fragments is a helpful and not-infrequent diagnostic finding indicative of ependymal neoplasm; it may be encountered even in the absence of canals or ependymal rosettes elsewhere in the sample. (**F**) Rarely, epithelial-type differentiation may predominate, as in this "tubular adenoma-like" pattern. (**G**) Epithelial-type differentiation also predominates in this example of an organoid growth pattern, which also shows focal calcification. (**H**) Signet ring–like cells are an uncommon finding

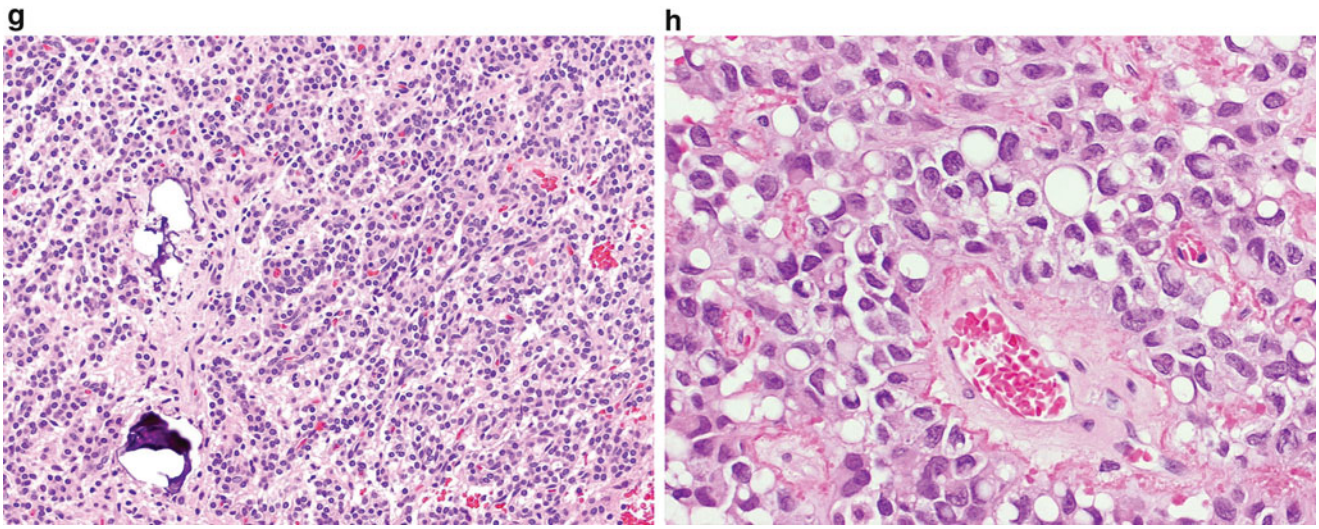


Fig. 6.4 (continued)

  - Cartilage, bone, lipomatous elements, neuropil-like islands, and cells with melanin, signet-ring appearance (Fig. 6.4H) or giant cell morphology, or eosinophilic intracytoplasmic inclusions have all been described.
  - Well-characterized histopathologic variants of ependymoma include the following:
- *Cellular ependymomas*: Variant with notable hypercellularity yet lacking an elevated mitotic rate, vascular proliferation, or pseudopalisading necrosis. Perivascular pseudorosettes may be inconspicuous, and true rosettes and canals are generally lacking (Fig. 6.5A).
- *Tanycytic ependymoma*: Typified by elongated, often thin, eosinophilic cell processes and inconspicuous perivascular pseudorosettes within an otherwise fascicular architecture; true ependymal rosettes are not seen. Nuclear pleomorphism may be prominent in some cases, mimicking the "ancient change" one can encounter in nerve sheath tumors (Fig. 6.5B and C).
- *Papillary ependymomas*: Rare subtype in which single or multiple layers of cuboidal to columnar cells rest upon central fingerlike projections of fibrillary glial "stroma." Fibrovascular cores are not a feature, and the epithelial-like surfaces tend to be smooth in contour (Fig. 6.5D).
- *Clear cell ependymomas*: These contain sheets of cells with rounded nuclei and abundant surrounding clear cytoplasm; perivascular pseudorosettes are invariably present, though true rosettes are absent. Branching thin-walled vessels may be present, and many cases show anaplastic features (including vascular proliferation, hypercellularity, and frequent mitoses), warranting a grade III designation (Fig. 6.5E and F).
- Both clear cell and papillary areas may be intermixed components with otherwise typical, cellular, or anaplastic ependymoma.

  - *Myxopapillary ependymoma* (WHO grade I)
    - Characteristically shows a papillary architecture with cuboidal to elongated glial cells radially arranged around Alcian blue–positive myxoid stroma with central vascular structure. Occasional examples harbor more epithelioid-appearing cells (Fig. 6.6A–C).
    - Some lesions are not particularly papillary at all, instead taking on a reticular or microcystic pattern with intermixed mucin-rich microcysts and occasional perivascular pseudorosettes (Fig. 6.6D and E).
    - Collagen balls or "balloons" may be seen in some cases (Fig. 6.6F); these may be highlighted by trichrome or periodic acid–Schiff (PAS) stains.
    - The mitotic rate is low, and necrosis and vascular proliferation are usually absent.
    - Degenerative changes, including vascular hyalinization or fibrosis, are occasionally prominent (Fig. 6.6G and H).
    - Rare anaplastic and giant cell variants have been described.
  - *Subependymoma* (WHO grade I)
    - Often having a nodular appearance at low power (Fig. 6.7A), subependymomas are composed of hypocellular collections of monotonously bland cells with round to oval nuclei set within a delicate glial matrix. The cells tend to cluster, and microcysts are commonly present (Fig. 6.7B–D).

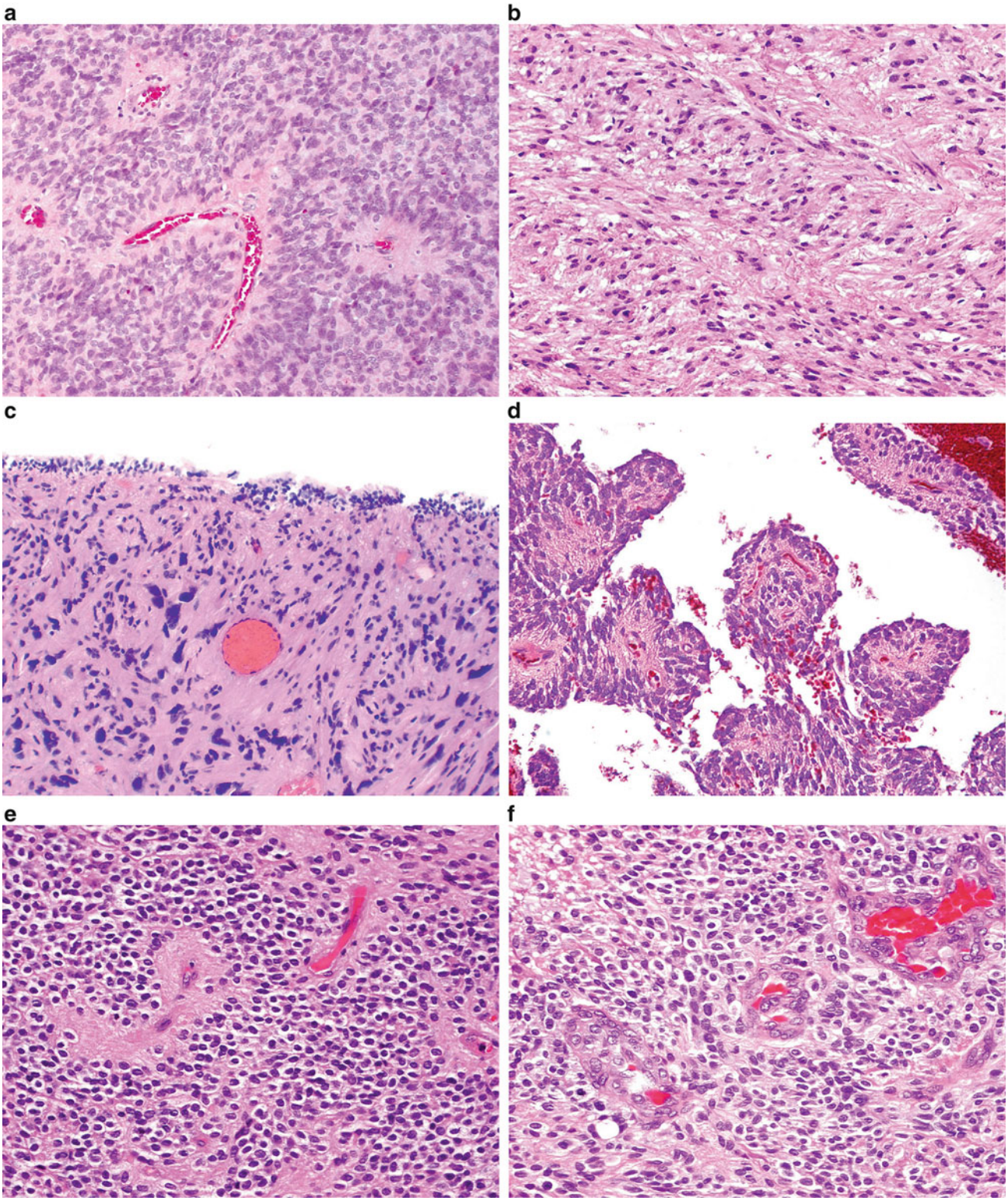


Fig. 6.5 (**A**) Cellular ependymomas are quite hypercellular, though they lack other histologic features of anaplastic ependymomas, including vascular proliferation and increased mitoses. (**B**) The fascicular architecture of the tanycytic ependymoma renders perivascular pseudorosettes inconspicuous. (**C**) Striking nuclear pleomorphism may be encountered in some cases of tanycytic ependymoma. (**D**) Papillary ependymomas exhibit one or more layers of bland neoplastic ependymal cells resting upon papillary fingerlike projections of fibrillary glial processes with central blood vessels. (**E**) Perivascular pseudorosettes are a helpful feature in differentiating clear cell ependymoma from other lesions with clear cell morphology. (**F**) Many clear cell ependymomas display high-grade features including vascular proliferation

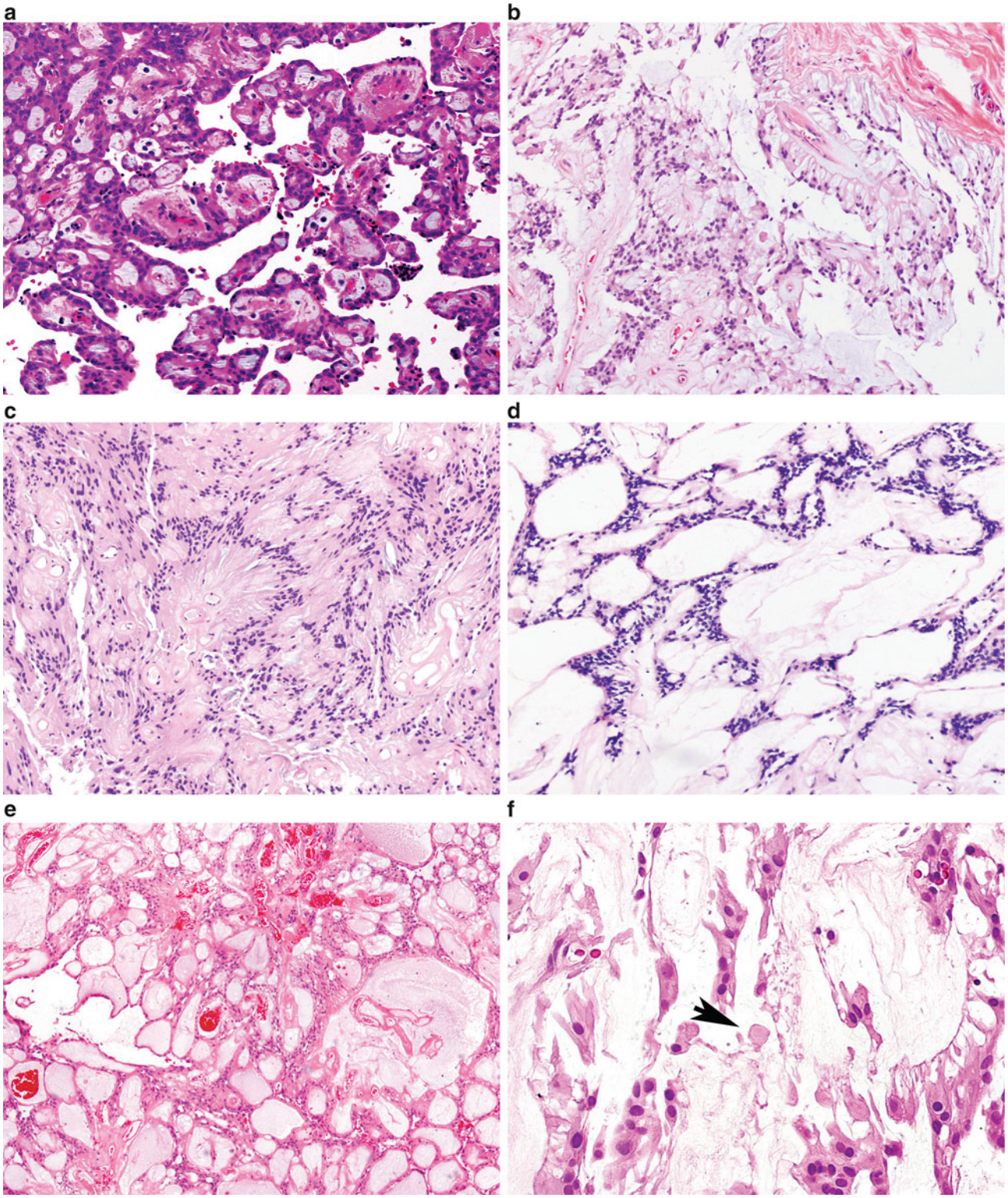
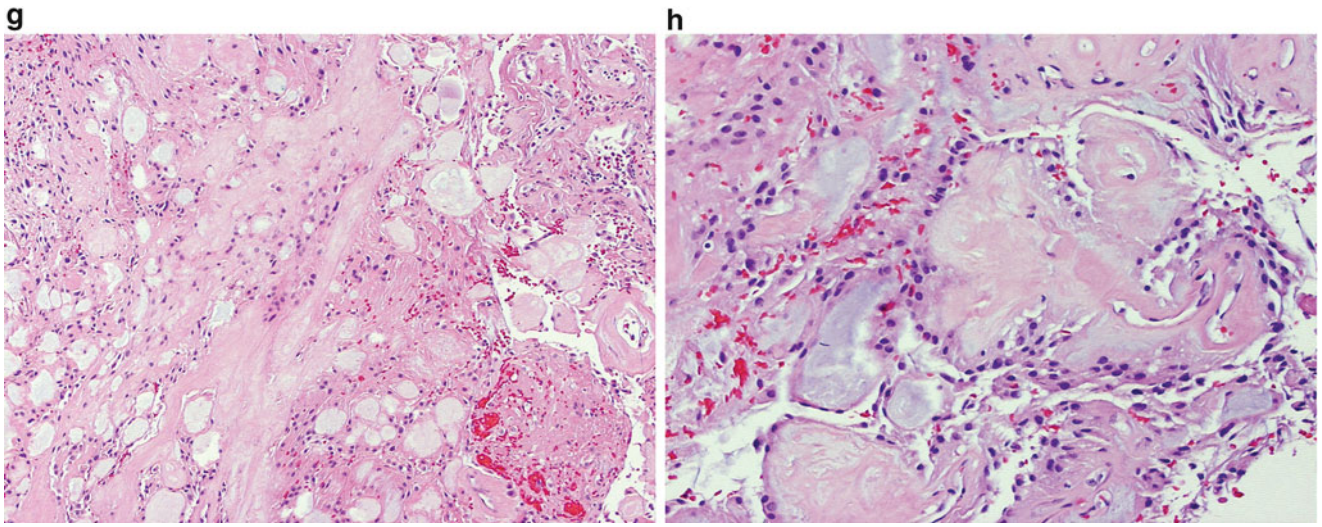


Fig. 6.6 Myxopapillary ependymomas, similar to other ependymal tumors, contain ependymal cells with variable epithelial (**A**) to glial morphology with elongated eosinophilic processes (**B**, **C**), but in this context, the perivascular pseudorosettes take the form of myxoid stroma-rich papillary structures. This papillary architecture may be inconspicuous in some cases, replaced instead by a more solid (**C**), reticular (**D**), or microcystic (**E**) pattern, again with characteristic myxoid material and scattered perivascular pseudorosettes. Collagen "balloons" (**F**, *arrow*) and tumoral (**G**) or vascular (**H**) hyalinization may be encountered



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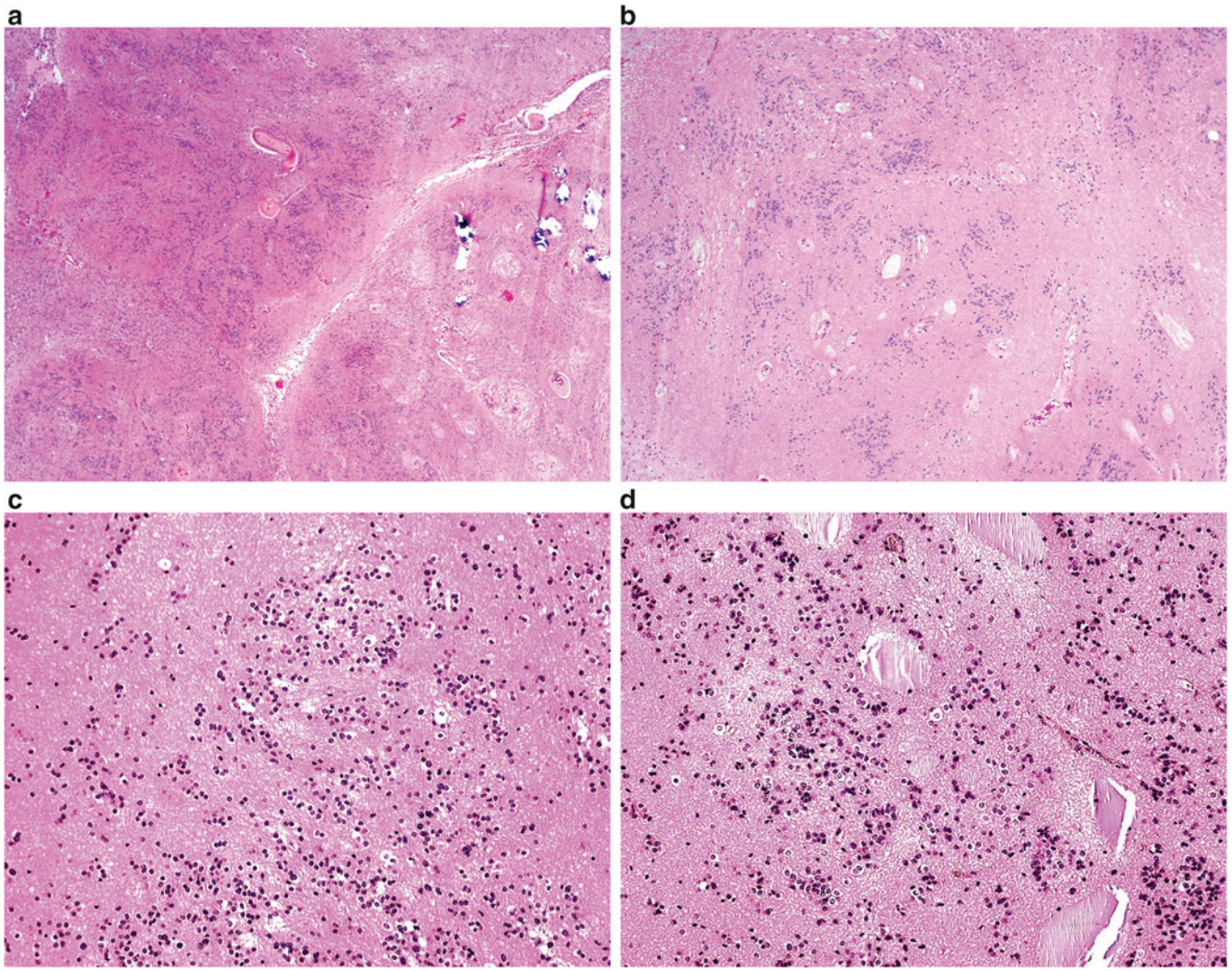

Fig. 6.7 (**A**) Subependymomas tend to be nodular on low-power microscopy and may show calcification. (**B**) These hypocellular lesions contain abundant glial matrix interspersed with monotonously bland cells with rounded to oval nuclei. (**C**) The tumor cells tend to cluster. (**D**) Microcysts are not infrequent

  - Perivascular pseudorosettes are quite uncommon, and true rosettes are not encountered.
  - Hemorrhage and/or hemosiderin-laden macrophages, calcification (*see* Fig. 6.7A), sclerotic vessels, and focal nuclear pleomorphism have all been described.
  - About 20 % of subependymomas harbor areas of classic or even anaplastic ependymoma; in these instances, the lesions should be graded according to the highest-grade component.
- *Anaplastic ependymoma* (WHO grade III)
  - Grading of ependymomas has historically been a contentious issue. Studies aimed at identifying histopathologic parameters that can distinguish different prognostic groups of ependymomas found that ependymomas harboring two or more of the following features were strongly correlated with shortened event-free survival and were indicative of a WHO grade III designation:
    - Elevated or brisk mitotic index (>5 per 10 high-power fields, seen throughout the tumor, not just focally) (Fig. 6.8A)
    - Hypercellularity with nuclear hyperchromasia and/or pleomorphism with marked atypia (Fig. 6.8B and C)
    - Vascular proliferation
    - Pseudopalisading necrosis (Fig. 6.8D).
  - They retain many features of conventional ependymoma, including perivascular pseudorosettes, which may contain normal vessels or proliferating vasculature (Fig. 6.8E).
  - Unfortunately, there is a subset of ependymomas containing only small areas of "focal anaplasia," the significance of which is unclear; they may suggest a more aggressive biologic potential than that of WHO grade II ependymoma (Fig. 6.8F). Such findings should be mentioned in the pathology report, to alert the treating clinicians of this possibility.

6.5 Immunohistochemistry

- Ependymomas and anaplastic ependymomas are positive for S100, glial fibrillary acidic protein (GFAP) (Fig. 6.9A), and vimentin. Epithelial membrane antigen (EMA) staining often shows a characteristic punctate, dot-like positivity (Fig. 6.9B); ring-like EMA staining is less frequently encountered but more specific. CD99 is often positive, with varying membranous or dot-like staining. Stains for neural markers are generally negative except for NeuN, which may show nuclear positivity in some anaplastic ependymomas.
- Myxopapillary ependymomas are positive for GFAP, S100, vimentin, and CD99. Occasional examples are immunopositive for p53. They are negative for cytokeratin and have a low Ki67 labeling index. Unlike other ependymomas, these are generally EMA negative.
- Subependymomas are positive for GFAP (Fig. 6.9C) and S100; they are also often weakly positive for low-specificity neuronal markers such as neural cell adhesion molecule (NCAM) and neuron-specific enolase (NSE). The Ki67 labeling index is lower than for all other types of ependymoma.
- Mib-1/Ki67 may be helpful in confirming brisk proliferation in areas of anaplasia, including examples of focal anaplasia (Fig. 6.9D).

6.6 Electron Microscopy

- Ependymomas and anaplastic ependymomas, including all of the variants listed above, share similar ultrastructural characteristics of ependymal differentiation, including intracellular intermediate filaments, intercellular junctional complexes (including desmosomes), occasional cilia, and microvilli, which are present both on the cell surface and within microlumina (Fig. 6.10).
- Myxopapillary ependymomas exhibit interdigitating cell processes and microtubular aggregates bound by rough endoplasmic reticulum, as well as the features typical for ependymal differentiation (intermediate filaments, microvilli, cilia).
- Subependymomas show ultrastructural features typically associated with ependymal differentiation, including intermediate filaments, lumen-like structures, microvilli, and cilia.

6.7 Molecular Pathology

- Transcriptional profiling by a number of independent groups has delineated two clinically and molecularly distinct subgroups of posterior fossa ependymomas:
  - *Group A (Group 1)* tumors occur in younger patients, with lateral location, balanced genome with increased occurrence of chromosome 1q gain, and with more biologically aggressive behavior (shortened progression-free survival [PFS] and overall survival [OS]). Laminin alpha-2 (LAMA2) detection by immunohistochemistry may serve as a marker for this group of tumors.
  - *Group B (Group 2)* tumors occur in older patients, with midline location, and numerous cytogenetic abnormalities involving whole chromosomes or chromosomal arms, with frequent chromosome 6q and 22q loss and 9p, 15q, and 18q gain. Detection of neural epidermal growth factor like-2 (NELL2) by immunohistochemistry may serve as a marker for these tumors.

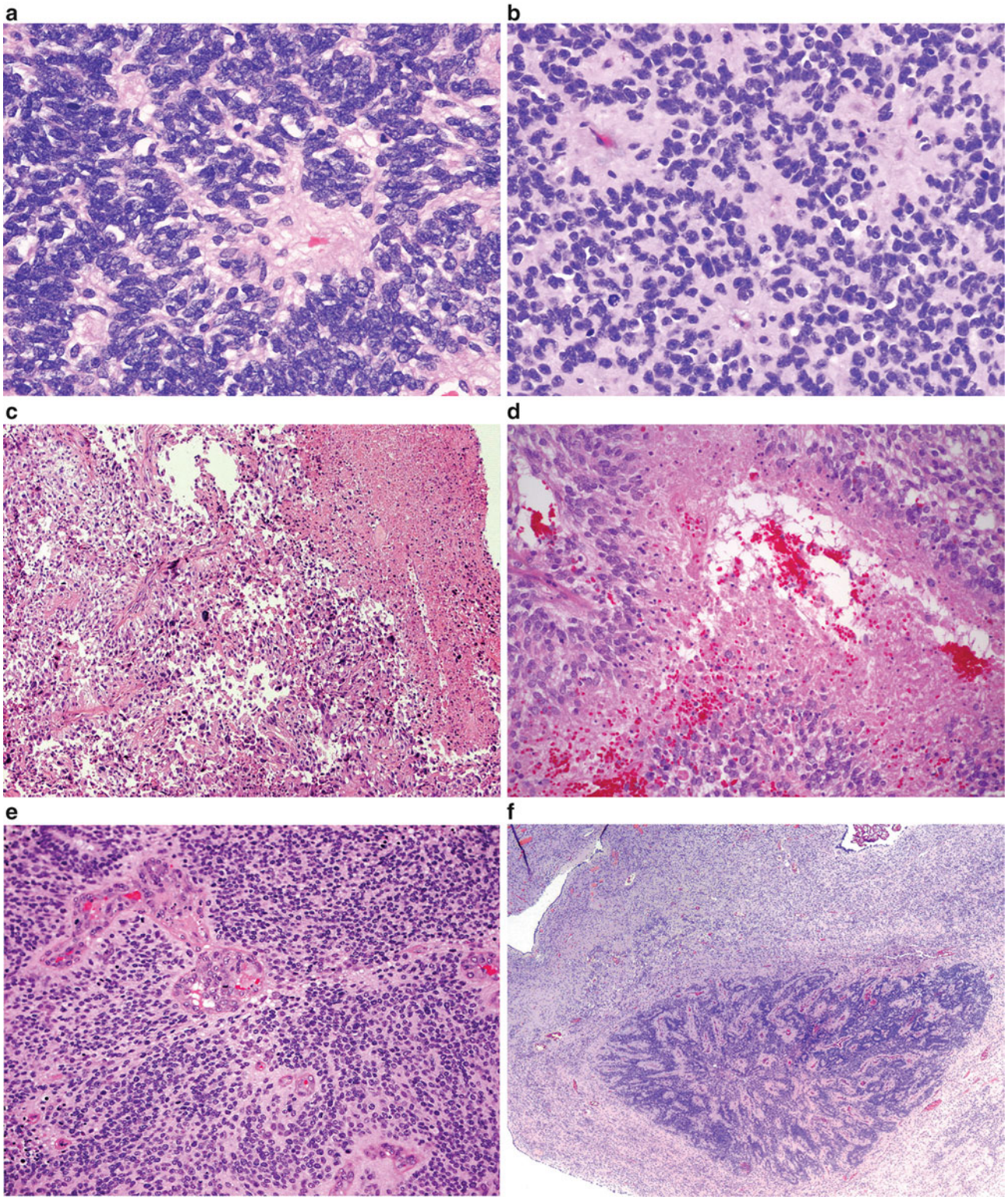

Fig. 6.8 Anaplastic ependymomas are notably hypercellular, with elevated mitotic activity (**A**) with moderate (**B**) to significant (**C**) nuclear pleomorphism. Extensive necrosis is common, often showing surrounding pseudopalisading of tumor cells (**D**). Vascular proliferation often residing within perivascular pseudorosettes (**E**) is another typical feature. Discrete foci of "focal anaplasia" (**F**), replete with any or all of the features noted above, may be encountered in otherwise lower-grade ependymoma variants; their significance is yet unclear

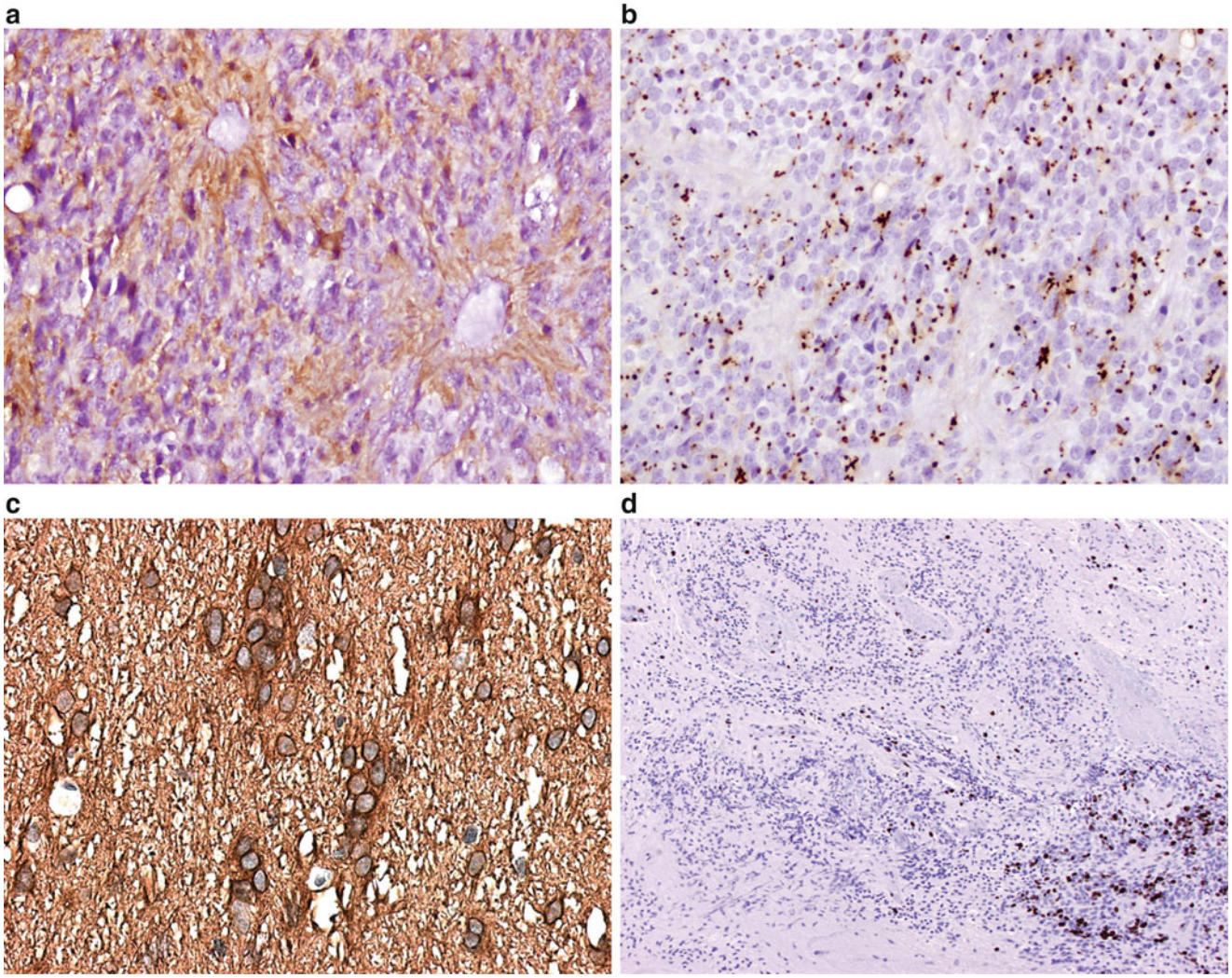

Fig. 6.9 Immunohistochemical stain for glial fibrillary acidic protein (GFAP) (**A**) highlights the elongated, fine perivascular processes in ependymomas. EMA staining (**B**) tends to present in a punctate, dot-like pattern. Subependymomas are similarly diffusely positive for GFAP (**C**). Ki67 labeling is markedly elevated within this focus of focal anaplasia (**D**)

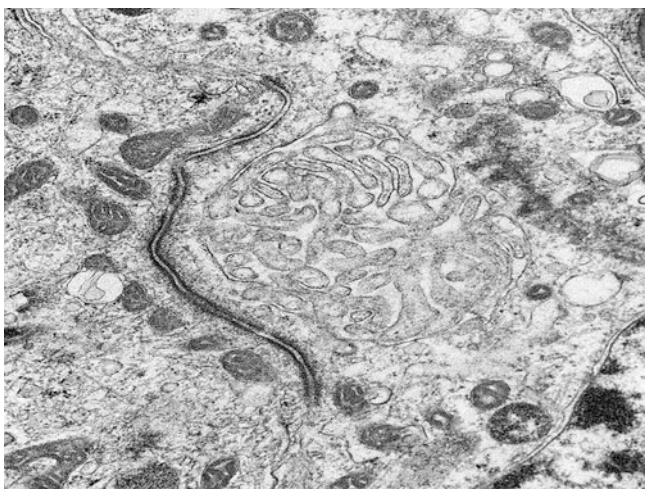

Fig. 6.10 Junctional complexes and microlumina bearing numerous microvilli are ultrastructural features indicative of ependymal differentiation

- A prognostic 10-gene expression signature has been proposed by one group, correlating well with the separation of group A and group B posterior fossa ependymomas.

- Supratentorial ependymomas
  - Show significant overexpression of neuronal markers in comparison to their infratentorial counterparts; in particular, neurofilament light polypeptide (NEFL) appears overexpressed in supratentorial tumors.
  - Nestin and vascular endothelial growth factor (VEGF) are both expressed more frequently in supratentorial ependymomas, and are associated with a poor PFS.
  - In one study, more than two thirds of supratentorial ependymomas were found to contain oncogenic fusions between *RELA* (involved in canonical NF-kB signaling) and *C11orf95* (a currently uncharacterized gene).

- Array-based comparative genomic hybridization (CGH) analysis has demonstrated a significant increase in genomic imbalances in relapsed ependymomas, particularly gains of 9qter and 1q; gain of 9qter has been associated with tumor recurrence, age greater than 3 years, and posterior fossa location.
- Alterations of the Wnt/beta-catenin signaling pathway appear to play a significant role in anaplastic ependymoma tumorigenesis.
- Activation of tenascin C and the Notch pathway have also been implicated to play a role in ependymoma progression, and both may also represent potential targets for therapy.
- Myxopapillary ependymomas exhibit a unique gene expression pattern with upregulation of homeobox B13 (*HOXB13*), neurofilament light polypeptide (*NEFL*), and *PDGFRα*.

6.8 Differential Diagnosis

- Ependymomas in general may be differentiated from infiltrative gliomas by virtue of their solid growth pattern, lacking significant intratumoral neurofilament-positive processes.
- Highly cellular anaplastic ependymomas may resemble ependymoblastomas and other primitive neuroectodermal tumors (PNETs), though anaplastic ependymoma are more diffusely positive for GFAP and lack ependymoblastic rosettes and neuronal-type markers by immunohistochemistry.
- Ependymomas, especially the tanycytic variant, may closely resemble astrocytoma (particularly pilocytic astrocytoma), schwannoma, or meningioma. Ependymomas in general lack Rosenthal fibers and eosinophilic granular bodies of pilocytic astrocytomas, and are positive for GFAP, unlike schwannomas and meningiomas. In rare cases, however, definitive diagnosis may rely heavily on ultrastructural findings of ependymal differentiation.
- Clear cell ependymoma must be differentiated from other primary CNS lesions containing clear cells (oligodendroglioma, neurocytoma, and hemangioblastoma) and metastatic clear cell carcinomas. Identification of perivascular pseudorosettes is the first clue to the diagnosis of clear cell ependymoma; immunohistochemistry (especially dotlike positivity for EMA), electron microscopy features of ependymal differentiation, and molecular findings (lack of 1p/19q deletion) help confirm the diagnosis.
- Papillary ependymoma may be confused with choroid plexus tumors, papillary meningiomas, or metastatic carcinomas. Strong positivity for GFAP and lack of diffuse cytokeratin staining are characteristic of papillary ependymoma, and electron microscopy confirmation is usually not necessary.
- Myxopapillary ependymoma may be differentiated from potential diagnostic mimics such as chordoma, renal cell carcinoma, myxoid chondrosarcoma and other myxoid soft tissue lesions, and paraganglioma by virtue of its immunohistochemical pattern (positive for vimentin, S100, and GFAP; cytokeratin negative) and characteristic ultrastructural finding of microtubular aggregates.
- Subependymomas may mimic other hypocellular glial tumors, including low-grade astrocytoma or pilocytic astrocytoma. Identification of a lobular architecture, cell clustering, microcysts, and lack of Rosenthal fibers or eosinophilic granular bodies is helpful is separating subependymoma from these potential diagnostic pitfalls.

6.9 Prognosis

- In general, children with ependymomas tend to fare far worse than their adult counterparts, partly because of a much higher incidence of intracranial or posterior fossa location and higher-grade tumors arising in the pediatric age group.
  - Those affected during the first few years of life have particularly poor outcomes, especially because related morbidities make it difficult to administer radiotherapy to these immature brains.
  - Neoadjuvant chemotherapy for ependymomas in infants has been found to be effective in reducing tumor vascularity and facilitating maximal tumor resection.
- Extent of tumor excision has consistently been shown as a key variable predictive of outcome.
  - In most instances, the first recurrence is at the site of the tumor resection bed, and recent evidence indicates that demonstration of tumor microinvasion on the original resection specimen correlates with poor PFS and OS.
- Though most studies have found histologic grading (grade II *vs* grade III) to be significantly predictive of OS and recurrence-free survival, a few observers have shown otherwise.
  - Specific diagnostic criteria for grade III designation have been proposed as outlined above, providing excellent prognostic correlation in those studies. Elevated Ki67 proliferation index correlates well with grade III status and with more aggressive biologic behavior.
- As noted above, pediatric posterior fossa ependymomas can be molecularly classified into two distinct subgroups:
  - Group A tumors are more biologically aggressive and harbor frequent gain of chromosome 1q. LAMA2 is detected by immunohistochemistry.

- Group B tumors are more biologically indolent and harbor frequent chromosome 6q and 22q loss and 9p, 15q, and 18q gain. NELL2 is detected by immunohistochemistry.
- Interestingly, the subgroup designation may change at tumor recurrence. Changing from group A to group B at recurrence does not appear to provide survival benefit, whereas switching from group B to group A at recurrence corresponds with poor prognosis.

- In addition, a number of other potential biologic predictors of outcome have been proposed in independent studies:
  - Low nucleolin expression is associated with prolonged PFS.
  - Gain of chromosome 1q and homozygous deletion of *CDKN2A* (*p16*) is associated with shortened PFS and OS; gains of chromosomes 9, 15q, and 18 or loss on chromosome 6 may be associated with better prognosis.
  - Strong expression of NEFL in supratentorial ependymomas has been correlated with better PFS.
  - Overexpression of transcription factor EVI1 has been correlated with shorter PFS and OS in infratentorial ependymomas.
  - Human telomerase reverse transcriptase (hTERT) mRNA overexpression has been correlated with shorter OS.
  - Children with telomerase-active ependymomas have poorer PFS and OS; telomerase inhibition may represent an actionable target in these tumors.
  - EZH2 (enhancer of zeste homolog 2) represents a marker of poor prognosis in pediatric intracranial ependymomas, particularly those arising in the posterior fossa.
  - Overexpression of kinetochore proteins (ASPM, KIF11) and downregulation of metallothioneins (MT3) have been found to be associated with ependymoma recurrence; the latter are a potential target of histone deacetylase inhibitors.
- Clear cell ependymomas appear to constitute a more aggressive phenotype, often representing grade III tumors.
  - Local recurrence is quite common, and these tumors may infrequently show transdural invasion into venous sinuses or extracranial metastasis into soft tissue and lymph nodes.
- Myxopapillary ependymomas are generally slow-growing tumors with a 10-year OS rate approximating 95 %.
  - Despite their WHO grade I designation, up to 45 % of patients may experience local recurrence, regardless of adequate excision. Patients who succumb to their disease typically do so following a protracted course with multiple recurrences.
  - Tumor encapsulation (enabling gross excision) portends a lower rate of recurrence, compared with tumors removed piecemeal or subtotally.
  - Adjuvant radiation therapy has been shown to aid in reducing the recurrence rate.
  - Neuraxis metastasis is more frequent in pediatric patients, thus emphasizing the importance of complete neuraxis screening both at the time of diagnosis and during long-term follow-up.
  - One report suggests that epidermal growth factor receptor (EGFR) expression may be a predictive marker of recurrence.
- Subependymomas are typically viewed as benign neoplasms that grow slowly, with a significant proportion remaining clinically silent throughout life and being detected only incidentally at autopsy. When they arise in children, however, they are more commonly mixed lesions (with subependymoma and ependymoma components) that exhibit biologic behavior akin to the higher-grade component.

Suggested Reading

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