Histopathology of Primary Tumors of the Central Nervous System

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Contents

Abstract

Primary central nervous system (CNS) tumors are the second most common cancers among children ages 0–19 years, of which 70% of childhood tumors are infratentorial. Metastatic solid tumors in the brain are frequent in the adult population but are rare in childhood.

The classification of tumors in the CNS is based on the pattern of cell differentiation and assumes that the pattern of differentiation is a reflection of the histogenesis

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of such tumors and is the basis of the World Health Organization (WHO) classification. In spite of its limitation, there is a strong correlation between the degree of cell differentiation and clinical prognosis. However, the clinical outcome is influenced not only by histology (i.e., degree of differentiation) but also by tumor location and extent of surgical resectability, as well as radio- and chemosensitivity. This chapter provides an overview of the pathologic characteristics and salient diagnostic features of brain tumors with special emphasis on the pediatric population.

2.1 Meningeal Tumors

Primary tumors arising in the leptomeninges include meningioma and mesenchymal non-meningothelial tumors such as solitary fibrous tumor (hemangiopericytoma) and melanocytic tumors.

2.1.1 Meningioma

Meningioma is a tumor composed of neoplastic meningothelial cells and accounts for 13–26% of intracranial tumors. Meningiomas are most common in the middle age group and the elderly. The peak incidence is in the sixth and seventh decades and frequently meningioma can occur as an incidental finding at autopsy. When seen in children, meningiomas are often aggressive. Although most tumors are sporadic, multiple meningiomas can be seen as part of the presentation of neurofibromatosis type 2 (NF2), as well as in genetically predisposed non-NF2 individuals.

Histological features allow for the division of meningiomas into three grades which include: (1) benign meningiomas (WHO Grade I) accounting for the bulk of meningiomas, (2) atypical meningiomas (WHO Grade II) which represent 4.7–7.2% of all meningiomas, and (3) anaplastic (malignant) meningiomas (WHO Grade III) representing 1.0–2.8% of all meningiomas.

In general, meningiomas occur more commonly in females, with a female:male ratio of 3:2 for intracranial tumors and a much higher 10:1 ratio for spinal meningiomas. This female predominance, as well as the positivity of about two-thirds of meningiomas for progesterone receptors, is consistent with a putative role for sex hormones in their development. However, for currently unclear reasons, atypical and anaplastic meningiomas predominate in males and in children.

A number of etiologic factors have been proposed for the neoplastic transformation of meningothelial cells. Notable among these is exposure to ionizing radiation. The lag time between exposure to ionizing radiation and clinical diagnosis of meningioma varies from 35 years [as was observed following low dose (800 rads) scalp radiation for tinea capitis] to 19–24 years following higher dose (>2000 rads) radiotherapy for brain tumors. These observations suggest a positive correlation between lag time and the dose of ionizing radiation.

Meningiomas have been referred to by specific names depending on their location, such as the falx, sphenoid ridge, olfactory groove, over the hemispheric

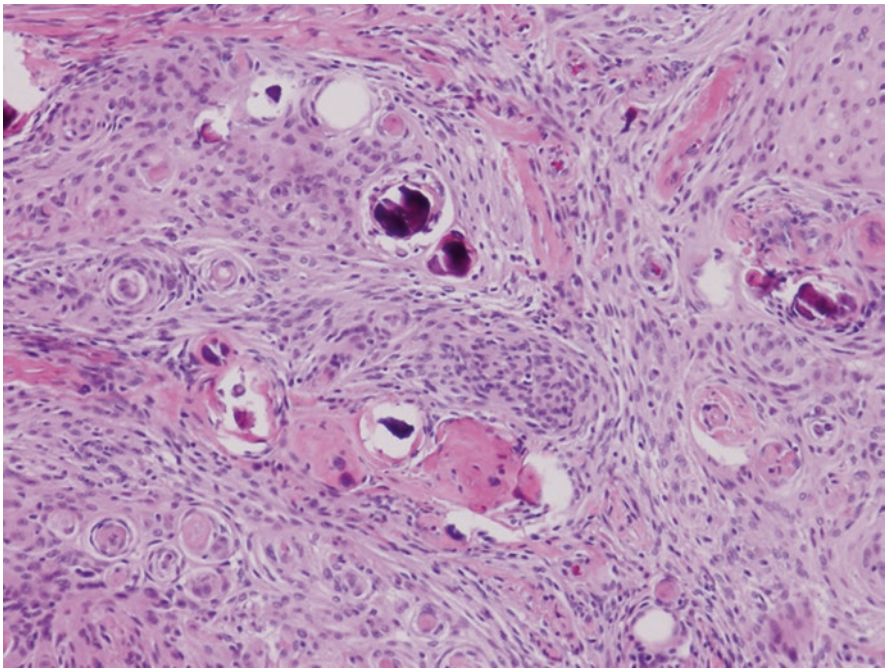

Fig. 2.1 Transitional meningioma showing characteristic concentric whorls and basophilic psammoma bodies. Magnification ×200

convexities, and the foramen magnum with differing clinical presentations related to the functional deficits induced at these specific sites of origin. Meningiomas are usually firm or rubbery, well demarcated, round, and occasionally lobulated masses. They may also grow as flat masses termed "en plaque" meningioma.

The classic meningothelial or syncytial meningioma is composed of epithelioid cells with indistinct cytoplasmic borders, uniform nuclei with frequent intranuclear cytoplasmic pseudoinclusion but no discernible nucleoli. Other subtypes range from the fibroblastic with a predominant benign spindle and fibrous component to the transitional form with a mixture of spindle fibroblastic cells of the fibroblastic meningioma and the epithelioid cells of the meningothelial meningioma arranged in characteristic whorls (Fig. 2.1). Any of the subtypes can have psammoma bodies. A benign vasculature component may be prominent in the angiomatous meningiomas. Prominent microcystic degeneration or pale lipid-containing xanthomatous cells characterize other subsets of meningioma. Gland-like structures with lumina containing eosinophilic periodic acid Schiff (PAS) and epithelial membrane antigen (EMA) positive secretion are seen in the secretory (pseudoglandular) meningioma. Myxomatous or myxoid meningiomas are characterized by the presence of a diffuse myxoid stroma with stellate cells. Identification of such tumors as meningiomas requires the presence of more classic meningothelial components. Such areas can be a minor component requiring generous tissue sampling before identification. In the absence of such a component, the differential diagnosis would include a metastatic

mucin secreting adenocarcinoma. Similarly, the presence of abundant clear cells can raise the differential diagnosis of a metastatic renal cell carcinoma. A diffuse infiltrate of mature, benign lymphocytes and plasma cells is a major component of the lymphoplasmacyte-rich meningioma. There is a need to distinguish these tumors from non-Hodgkin's lymphoma. Metaplastic meningiomas exhibit focal or sometimes florid differentiation into other mature cell types such as osteoid, chondroid, and adipose tissue. Invasion of dura or dural sinuses is common. Skull invasion is usually associated with hyperostosis.

Meningiomas located in the cerebellopontine angle or in relation to cranial/spinal nerve roots raise a differential diagnosis of Schwannoma (neurilemmoma). Histologic differentiation can often be done readily based on light microscopic and immunostaining features. Schwannomas typically show positivity for S-100 protein and negative staining for epithelial membrane antigen. In contrast, meningothelial cells are positive for epithelial membrane antigen and claudin-1 among others and are rarely positive for S-100 protein. Furthermore, electron microscopy demonstrates desmosome junctions, cytoplasmic interdigitations, and a lack of basal lamina in the tumor cells as is characteristic of meningioma, while the presence of a basal lamina and a lack of true desmosome junctions are consistent with Schwann cell differentiation.

A demonstrable invasion of underlying brain is indicative of an aggressive meningioma and is often accompanied by histological features of an atypical or malignant meningioma.

2.1.1.1 Atypical Meningioma (WHO Grade II)

Atypical meningioma represents subset of meningioma with slightly higher risk of recurrence when compared with benign meningiomas (29–39% vs. 7–20%). Such tumors are characterized by increased mitotic rate (>4/10 hpf in the area of highest mitotic activity) *or* at least three of the following histologic findings: hypercellularity, small cell change, prominent nucleoli, sheet-like growth, or foci of spontaneous or geographic necrosis (i.e., not induced by therapeutic embolization). Proliferation index (MIB-1 index) is usually greater than 5% (mean 2.1% vs. mean for benign meningiomas of 0.7%).

Meningiomas with tongue-like invasion of underlying brain and chordoid or clear cell features are clinically aggressive and classified as atypical meningiomas (WHO grade II).

2.1.1.2 Anaplastic (Malignant) Meningioma

1. *Papillary meningioma*
   Papillary meningiomas are by definition malignant meningiomas and the presence of a distinct papillary pattern is the hallmark of this subset of meningiomas (Fig. 2.2). They represent a WHO grade III. Papillary meningiomas tend to occur more commonly in children. Papillary features in a dural-based lesion should raise the differential diagnosis of a metastatic papillary adenocarcinoma.
2. *Malignant (non-papillary) meningioma*
   The diagnosis of anaplastic or malignant meningioma in a non-papillary tumor requires the presence of overt or frank anaplasia and/or metastases. The more classic lesions are usually characterized by increased cellularity, frequent mitotic

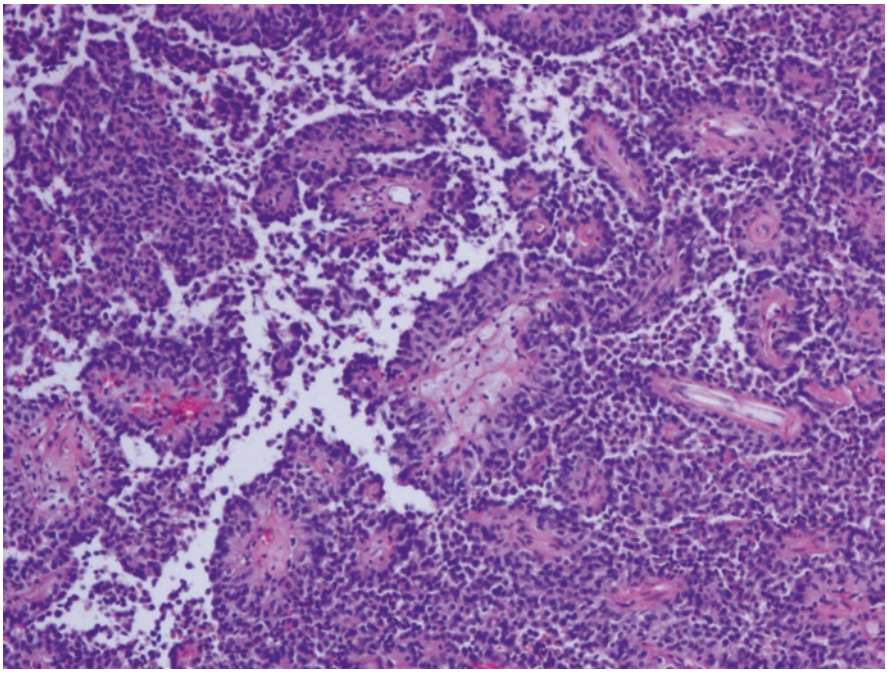

Fig. 2.2 Papillary growth pattern is a characteristic feature of papillary meningioma. Magnification ×100

figures (>20 mitoses/10 hpf), and conspicuous necrosis. The proliferation index (MIB-1 index) is usually greater than 10% (mean = 11%). Rhabdoid meningioma is an aggressive variant of meningioma and is classified also as a WHO Grade III.

Postsurgical recurrence is a common feature of meningiomas and is seen in up to 20% of benign meningiomas after 20 years of follow-up. Indicators of possible recurrence (apart from incomplete resection) are histological subtype and tumor grade. Anaplastic meningiomas have the highest recurrence rate of about 50–78%.

2.1.2 Mesenchymal, Non-meningothelial Tumors

This group of tumors share similar histological features with their counterparts in peripheral soft tissues. They include:

1. Adipose tissue tumors, such as lipomas [fibrolipomatous hamartomas, angiolipomas, and epidural lipomatosis (related to chronic corticosteroid administration)] and intracranial liposarcoma. Lipomas occur most often in the midline, typically located in the corpus callosum, cerebellar vermis, or mammillary bodies. They may also occur as part of a complex malformation. Mature lipocytes

have been described as part of a low-grade cerebellar tumor called liponeurocytoma that is composed of intermixed mature lipocytes and neurocytic cells.
2. Fibrohistiocytic tumors, including benign and malignant fibrous histiocytoma.
3. Fibrous tumors including solitary fibrous tumor, hypertrophic intracranial pachymeningitis, and fibrosarcoma.
4. Muscle forming tumors, such as leiomyoma, intracranial leiomyosarcomas, rhabdomyoma, embryonal rhabdomyosarcoma, and malignant ectomesenchymoma.
5. Osteocartilaginous tumors, including chondroma, osteoma and osteochondroma, mesenchymal chondrosarcoma, and osteosarcoma.
6. Vascular tumors, such as hemangiomas, epithelioid hemangioendotheliomas, angiosarcoma, and Kaposi's sarcoma.
7. Tumors of undefined histogenesis, such as hemangiopericytoma, capillary hemangioblastoma, and meningeal sarcoma/sarcomatosis.
8. Melanocytic tumors.

Since many of these tumors are curiosities in the CNS, only the relatively more frequent tumors will be discussed further. The histological features of the other tumors are similar to those of their soft tissue counterparts and are well discussed in the soft tissue sections of other standard textbooks.

2.1.2.1 Solitary Fibrous Tumor/Hemangiopericytoma

Historically, this tumor has been referred to by various obsolete names such as "angioblastic meningioma" and hemangiopericytic variant of meningioma reflecting a lack of understanding of its true histogenesis. Hemangiopericytoma accounts for only 0.4% of all brain tumors and is a rare tumor in children. It is usually dural based and is rarely intraparenchymal. Clinical presentation is similar to that of meningioma. The cellular variant of solitary fibrous tumor (SFT) shows histologic and immunohistochemical overlap with that of hemangiopericytoma with nuclear immunopositivity for STAT6 and both are regarded as same entities.

Grossly, the tumor is firm, well demarcated, globoid, slightly lobulated, and can bleed profusely during surgical removal. Histologically, it is characterized by monotonous sheets of oval to elongated nuclei, variable degrees of nuclear atypia, and prominent mitotic activity (Fig. 2.3). "Staghorn" vessels of variable prominence are also apparent. Invasion of underlying brain can occur. Since many soft tissue tumors can have hemangiopericytomatous-like areas, immunostaining and electron microscopy, if available, are important aids in ensuring accurate diagnosis. Hemangiopericytomas show an identical immunohistochemical profile as its soft tissue counterpart (now regarded as solitary fibrous tumor) with diffuse positivity for vimentin, CD99, and bcl-2, and more variable positivity for Leu-7, CD34, and factor XIIIa in individual tumor cells. CD34 positivity is generally patchy as opposed to the diffuse positivity typical of solitary fibrous tumor. Unlike the strong diffuse positivity for EMA and claudin-1 displayed by meningiomas, staining is typically patchy and weak for these antibodies in hemangiopericytoma. They are negative for S-100, CD31, and progesterone receptor. Actin, desmin, and cytokeratin (CAM5.2) staining is rare. p53 immunoreactivity may be seen in about one-half of HPC, whereas this is not generally a feature of meningioma or SFT.

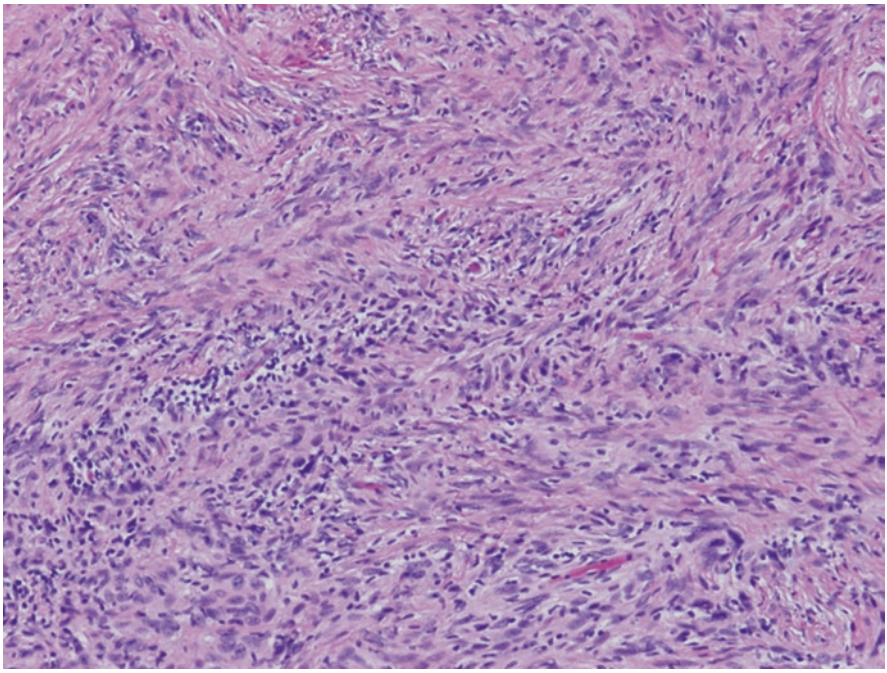

Fig. 2.3 Cellular and fibrosing spindle cell proliferation of a cellular solitary fibrous tumor/hemangiopericytoma. Magnification ×200

The proliferation index (MIB-1 index) varies widely with median values ranging between 5 and 10%. Hemangiopericytomas exhibit a high 15-year local recurrence rate of 85–91% and metastases are also seen in about 65% of cases when followed for over 15 years.

2.1.2.2 Capillary Hemangioblastoma

Capillary hemangioblastoma is a WHO grade I vasoformative tumor of uncertain histogenesis which commonly occurs in the cerebellum. Spinal and brain stem lesions also occur, but less frequently, and supratentorial lesions are very rare. About 25% of cases occur in the setting of Von Hippel–Lindau disease. Von Hippel–Lindau disease-associated tumors occur in younger patients while the non-Von Hippel–Lindau disease-associated tumors occur in adults. Von Hippel–Lindau disease is a neurocutaneous syndrome associated with retinal hemangioblastoma, pheochromocytoma, renal cell carcinoma, and visceral (liver and pancreas) cysts. Hemangioblastomas are slow growing tumors often presenting with features of raised intracranial pressure secondary to the blockage of CSF flow. There is often an accompanying secondary polycythemia due to erythropoietin production by the neoplastic stromal cells.

Grossly, capillary hemangioblastoma consists of well-circumscribed red nodules often in the wall of large cysts. Histologically, the tumors are composed of large vacuolated stromal cells and a rich capillary network. The stromal cells show immunopositivity for vimentin, but the tumors do not show evidence of immunoreactivity for glial fibrillary acidic protein or for endothelial markers such as CD34 or

Von-Willebrand factor. The "clear cell" appearance of the stromal cells can be confused with metastatic renal cell carcinoma. Rosenthal fibers can be seen in the wall of the cysts. The slow growth of capillary hemangioblastoma is consistent with a low proliferation index (MIB-1 index <1%). The stromal cells are consistently positive for vimentin, alpha inhibin, D2-40, and aquaporin, while variably positive for S-100, NCAM, NSE, erythropoietin, EGFR, VEGF, alpha-1-antitrypsin, and antichymotrypsin. Progesterone receptor and Factor XIIIa positivity have also been reported in a high percentage of cases. They may be focally positive for GFAP, keratin, EMA, or desmin, while specific neuronal (neurofilament, synaptophysin, and chromogranin) and endothelial cell (CD31, CD34, and VWF) markers are typically negative.

2.1.2.3 Meningeal Sarcomatosis

Meningeal sarcomatosis is a diffuse leptomeningeal sarcomatous tumor lacking the distinct circumscribed nature that is characteristic of most meningeal tumors. It is composed of poorly differentiated spindle cells characteristic of undifferentiated sarcomas. Apart from immunostaining for vimentin, the tumor cells are negative for all neuroglial markers.

2.1.2.4 Mesenchymal Chondrosarcoma

The most common extraosseous site for mesenchymal chondrosarcoma is the CNS. Mesenchymal chondrosarcoma has a distinct small cell tumor component interrupted by islands of atypical hyaline cartilage (Fig. 2.4). The small cell

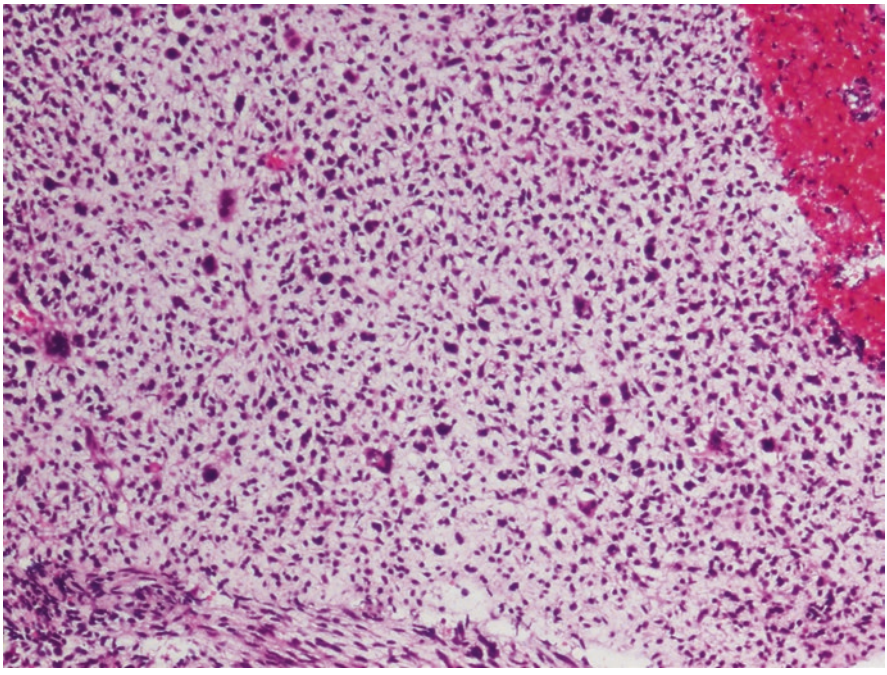

Fig. 2.4 Malignant chondromyxoid proliferation of mesenchymal chondrosarcoma. Note the nuclear pleomorphism. Magnification ×200

component shares histological features with hemangiopericytoma and can be confused with it in small biopsies that lack the characteristic chondroid component.

2.1.2.5 Melanocytic Lesions

Primary melanocytic lesions of the CNS are relatively uncommon, accounting for only 0.06–0.1% of brain tumors. Melanocytic lesions are more common in Caucasians and arise from melanocytes of the leptomeninges. There are three possible forms of CNS melanocytic lesions: (1) diffuse melanocytosis, (2) melanocytoma, and (3) primary leptomeningeal malignant melanoma.

1. *Diffuse melanocytosis* usually presents in childhood with seizures, behavioral disturbances, and hydrocephalus. Histologically, the lesion shows a diffuse proliferation of uniform nevoid polygonal cells within the leptomeninges.
2. *Melanocytomas* present as mass lesions composed of a monomorphic population of spindle, fusiform, epithelioid, or polyhedral cells arranged in whorls, sheets, nests, or interlacing bundles of storiform configuration with infrequent mitotic figures. Melanin can be present. The tumors are S-100 protein positive and in our experience are usually negative for the melanoma antigen markers, HMB-45, and Melan A.
3. *Primary meningeal malignant melanomas* also present as mass lesions. They occur classically in the setting of neurocutaneous melanosis, such as in the autosomal dominant Touraine syndrome and in patients with the congenital nevus of Ota. The tumors have similar aggressive behavior as seen in cutaneous melanoma and are characterized histologically by marked pleomorphism, high mitotic activity, necrosis, hemorrhage, and invasion of underlying brain. The diagnosis of a primary CNS melanoma can only be made after a metastatic melanoma has been excluded. As in cutaneous melanoma, the tumor cells are S-100 protein, HMB-45 and Melan A positive while being negative for glial fibrillary acidic protein (GFAP), neurofilament protein (NFP), epithelial membrane antigen (EMA), and cytokeratin. Electron microscopy shows the presence of melanosomes.

2.2 Astrocytic Tumors

Pilocytic astrocytoma (PA) represents a slow growing, often circumscribed fibrillary astrocytoma with a distinctly good prognosis warranting its designation as a WHO grade I. It accounts for 20–25% of all childhood brain tumors occurring frequently as a cystic cerebellar tumor with a mural nodule. Similar tumors may involve the optic nerve, presenting as optic nerve glioma in children and frequently in individuals with neurofibromatosis type 1 (NF1). Supratentorial intra-axial tumors are common in the temporal lobe and may also involve the hypothalamus or thalamus. The characteristic cells are the glial fibrillary acidic protein-positive piloid (elongated or "hair-like") astrocytes which are arranged in a biphasic pattern of cellular fibrillary astrocytes with intervening loose microcystic areas (Fig. 2.5). Rosenthal fibers and eosinophilic granular bodies (EGBs) are frequently present and the abundance of Rosenthal fibers is a helpful diagnostic feature in frozen

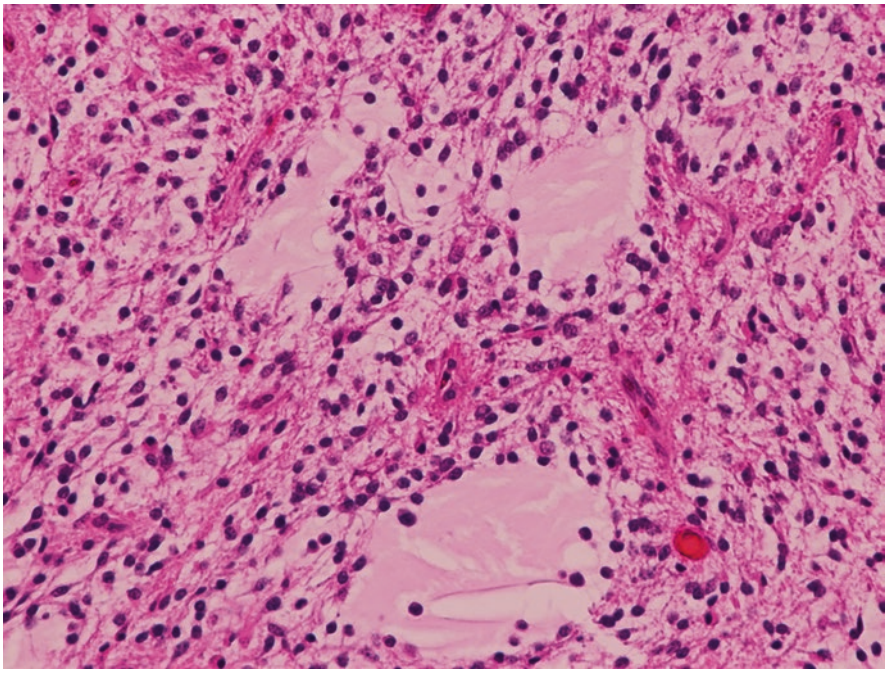

Fig. 2.5 Pilocytic astrocytoma with biphenotypic microcystic and compact cellular components. Eosinophilic Rosenthal fiber is present. Magnification ×200

sections or crush preps made during intraoperative consultation. Unlike the classic diffuse infiltrating astrocytoma, the presence of vascular proliferation and slight pleomorphism does not imply an aggressive high histologic grade. However, in the rare case, the presence of frequent mitotic figures, a significantly increased cellularity, and necrosis justifies the diagnosis of a pilocytic astrocytoma with anaplastic features. Tandem duplication at 7q34 with BRAF-KIAA1549 duplication/fusion rearrangement is seen in 70% of PA. BRAFV600E mutation is seen in 10% of extracerebellar PA, particularly diencephalic tumors. Rare co-occurrence of both events has been seen.

The *pilomyxoid astrocytoma* (PMA), WHO grade II, shares histologic features with the PA. It shows additional features including a monomorphous population of bipolar cells with delicate elongated "piloid" processes in an abundant myxoid matrix. The cell processes frequently radiate from vessels with a pseudorosette pattern. In its pure form, Rosenthal fibers and EGBs are absent. Mitoses may be seen. Maturing PMAs show intermediate histologic features of both PA and PMA.

BRAF-KIAA1549 duplication/fusion rearrangement is seen in 60% of PMA.

Pleomorphic xanthoastrocytoma (PXA), WHO Grade II, is a tumor with distinct radiopathologic features including a superficial meningocerebral location, common location in the temporal lobe, and frequent association with a long-standing history of seizures. Pleomorphic xanthoastrocytoma accounts for <1% of all astrocytic

neoplasms but 2/3 of cases occur in individuals below the age of 18 years. Histologically, it exhibits significant pleomorphism with many atypical giant cells and astrocytic cells with slightly prominent nucleoli. Mitotic activity and necrosis are conspicuously absent in the typical pleomorphic xanthoastrocytoma. There is a variably discernible population of foamy (xanthomatous) cells and focal lymphocytic and plasma cell infiltrate in a background of reticulin-positive desmoplasia. The astrocytic origin of this tumor has come into question because of the demonstration of neuronal markers in subpopulations of tumor cells. In addition, the morphologic pattern seen in pleomorphic xanthoastrocytoma may form the glioma component of a ganglioglioma. BRAFV600E mutation is a frequent event seen in 75% of PXA.

Pleomorphic xanthoastrocytoma with anaplastic features is a variant which may represent WHO Grade III. These are often seen as part of tumor progression in recurrent lesions. They show features indicative of aggressive behavior such as increased mitotic activity [> 5 mitosis per 10 high power fields], necrosis, and endothelial proliferation.

Diffuse astrocytomas are infiltrating fibrillary neoplasms with varying degrees of differentiation and tumor grade. They account for 50% of primary brain tumors. Astrocytic tumors characteristically have infiltrative margins and range from the low grade diffuse astrocytoma which is WHO grade II (peak age of 30–39 years) to the anaplastic (malignant) astrocytoma which is WHO grade III (peak age of 40–49 years), and the most aggressive glioblastoma which is WHO grade IV (peak age of 50–69 years). Approximately 10% of all glioblastomas occur within the first two decades of life. Infiltrative astrocytomas are second to pilocytic astrocytoma in frequency in the pediatric age group.

Diffuse infiltrating astrocytoma, WHO grade II, or well-differentiated (low grade) astrocytoma is most common in the cerebral white matter and accounts for 20% of primary brain tumors. Low grade astrocytomas are composed of a relatively uniform population of proliferating astrocytes in a fibrillary matrix (Fig. 2.6). Mitotic figures are rare. In contrast to reactive gliosis, diffuse astrocytomas have infiltrative poorly defined margins and can have microcystic degeneration. The tumor cells show slight atypia, an important criterion for distinguishing them from reactive gliosis. The tumor cells can have plump eosinophilic cytoplasm (gemistocytes) and are often a minor component of most diffuse astrocytomas. Tumors composed of greater than 20% of gemistocytic tumor cells are called gemistocytic astrocytoma. The astrocytic tumor cells show cytoplasmic positivity for glial fibrillary acidic protein.

2.2.1 Anaplastic (Malignant) Astrocytoma

Anaplastic astrocytoma represents a high grade diffuse fibrillary astrocytoma classified as WHO grade III. It has a similar distribution to low grade astrocytoma but is characterized by a greater degree of cellularity and pleomorphism. Mitotic figures are readily discernible (Fig. 2.15).

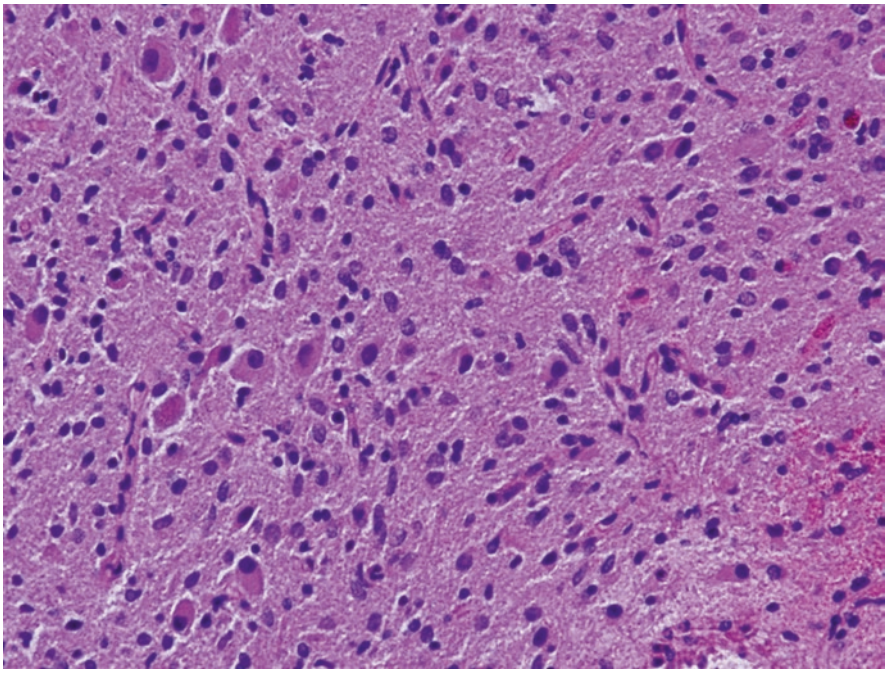

Fig. 2.6 Low grade diffuse infiltrating astrocytoma with mild increase in cellularity, astrocytic differentiation, and rare mitotic figures. Magnification ×200

2.2.2 Glioblastoma

Glioblastoma is the most common glioma, accounting for 50% of all gliomas. It is clinically the most aggressive glioma and represents an extreme expression of astrocytic anaplasia. Glioblastoma occurs frequently as a white matter lesion, is diffusely infiltrative, and can cross the midline by involving the corpus callosum to produce the radiologic "butterfly pattern." Glioblastoma is characteristically grossly hemorrhagic and necrotic. Histologically, it shows marked cellular pleomorphism, frequent mitotic figures, tumor giant cells, endothelial proliferation, and necrosis with or without pseudo-palisading (Fig. 2.7). A high proliferation index and immunopositivity for p53 protein is a common feature of glioblastoma.

A predominant population of highly proliferative small cells can be seen in the variant form called small cell glioblastoma. The predominance of such cells often raises a differential diagnosis of "small blue cell tumors." Although cellular pleomorphism is an inherent histologic feature of glioblastoma, an extremely pleomorphic variant with florid multinucleated giant cells constitutes the giant cell glioblastoma. A spindle mesenchymal sarcomatous transformation can also be seen in a variant referred to as the gliosarcoma which must be differentiated from the secondary diffuse spindle (fibroblastic) cell proliferation that can accompany the invasion of the leptomeninges by glioblastoma cells. The giant cell glioblastoma has

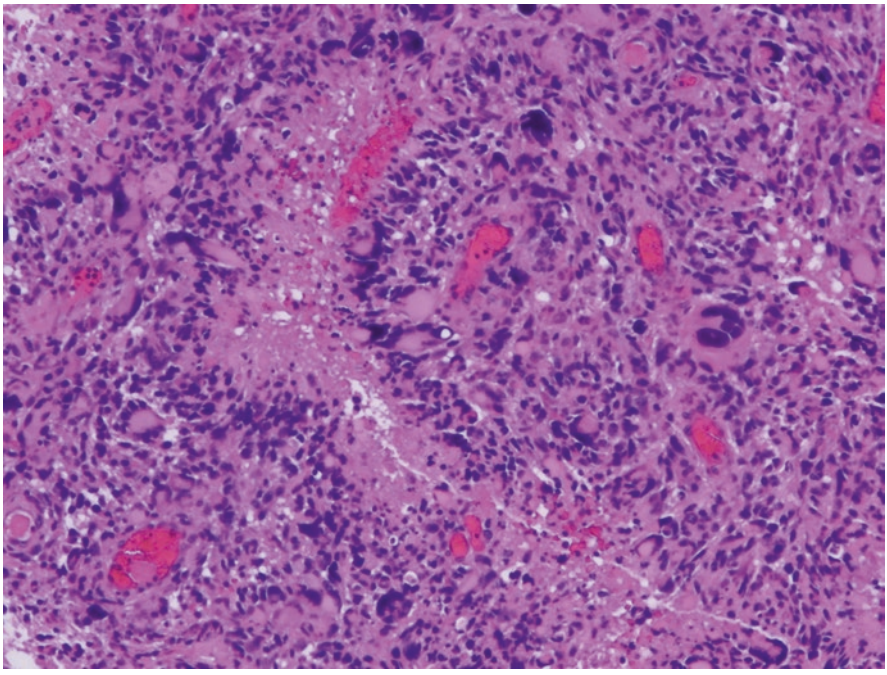

Fig. 2.7 Glioblastoma with increased cellularity, marked pleomorphism and pseudo-palisaded necrosis. Vascular endothelial proliferation is also present (not shown). Magnification ×200

a slightly better prognosis than the classic glioblastoma while the gliosarcoma has no significantly different outcome from the classic glioblastoma.

Mutation of the p53 gene has been shown to be especially common in the evolution of low grade astrocytoma and in the progression from low grade astrocytoma to high grade astrocytoma. Amplification of mdm2 gene which provides an alternative pathway for p53 inactivation only occurs in a minor subset of glioblastomas. The subset of glioblastomas arising secondary to p53 mutation or inactivation has been designated as secondary glioblastoma. In contrast, de novo or primary glioblastomas are less likely to have mutations of the p53 gene and are more likely to have amplification of the epidermal growth factor receptor gene. Therefore, there seem to be at least two largely separate operant pathways in the biologic evolution of the classic types of glioblastoma.

Additional genetic events in the development of high grade gliomas include epidermal growth factor (EGF) and transforming growth factor-α (TGF-α) expression providing a loop for autocrine stimulation. Fibroblast growth factor and vascular endothelial growth factor overexpression probably plays a major role in the development of angiogenesis, a critical element in the transformation of low grade astrocytoma to glioblastoma multiforme. Other reported genetic events in astrocytoma progression include loss of the deleted in colon carcinoma (DCC) gene, loss of heterozygosity (LOH) for chromosome 10q23.3 (PTEN gene locus) which is

mutated in 30–49% of high grade gliomas, total loss of chromosome 10, loss at chromosome 19q13.3, and loss of chromosome 22q. The giant cell glioblastoma does not appear to share these molecular pathways thus suggesting that it is a distinctly different biologic entity, a feature consistent with its differing clinical aggressiveness.

Based on a combination of studies including determination of epigenetic/methylation status as well as gene copy number and expression profiles, glioblastomas can be divided into distinct molecular and prognostic subgroups:

1. H3F3a K27M and G34R mutated subgroups which represent a predominant group among pediatric glioblastomas. These are usually negative for IDH1 mutations, frequently show TP53 mutations, and generally display widespread genomic hypomethylation.

   The K27M subgroup is more frequent in children and is associated with midline tumors (DIPG and GBM of thalamus and spinal cord). The G34R subgroup is most frequent in adolescents with tumors of cerebral hemispheric location.
2. IDH1 mutated tumors represent a minor proportion of pediatric glioblastomas, display global genomic hypermethylation, and frequently harbor TP53 mutations. This group includes older children/young adults with tumors of cerebral hemispheric location.
3. PDGFRA amplified tumors are associated with a proneural gene expression profile. This group has a wide age distribution, with a proportion occurring in pediatric tumors with cerebral hemispheric location.
4. Mesenchymal subgroup tumors exhibiting a mesenchymal gene expression signature and no defining gene copy number alterations or point mutations. This group also has a wide age distribution, with a proportion occurring in pediatric tumors of cerebral hemispheric location.
5. “Classic” subgroup is limited to GBM arising in older adults, and this group shows high frequency of chromosome 10 loss, homozygous deletion of CDKN2A, and EGFR amplification.

Diffuse infiltrating pontine glioma (DIPG) represents a diffusely infiltrative glioma involving the basis pontis which may histologically be low grade or high grade. It accounts for 10% of childhood brain tumors and is composed of fibrillary astrocytes. The diagnosis is often based on its classic neuroradiologic presentation with no attempts at resection or biopsy. Treatment usually involves radiotherapy, but there is an attendant high propensity of surviving tumor cells to dedifferentiate to a more anaplastic histology including glioblastoma.

A number of genetic events have been reported in DIPGs including: (1) K27M mutations in H3F3A (H3.3) or HIST1H3B (H3.1) which are extremely common and present in nearly 80% of DIPG. (2) Gain of function ACVR1 mutations found exclusively in DIPG (up to 30% of cases), whereas FGFR1 mutations or fusions are seen in thalamic HGAs. (3) Global DNA hypomethylation is an epigenetic alteration frequently encountered in DIPG, and may be detectable as decreased tumor staining by H3K27me3-specific immunohistochemistry. (4) TP53 (75%) and ATRX

(10%) mutations may be encountered in subpopulations of DIPG, with ATRX mutations being more frequent in tumors arising in older children. PIL3CA mutations and PDGF-a gains/amplifications have been reported. Subgroups with frequent loss of 17p and 14q and others with lack of IDH1/2 mutations or CDKN2a/CDKN2B deletions have also been reported.

2.3 Ependymal Tumors

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 at age 30–40. Ependymal tumors are subdivided into the low grade ependymoma (WHO grade II) and the higher grade anaplastic ependymoma (WHO grade III). Variants include the very low grade, WHO grade I myxopapillary ependymoma which occurs exclusively in the conus medullaris-cauda equina-filum terminale region, as well as the subependymoma usually found in the floor of the fourth ventricle which is also low grade and is often an incidental finding at autopsy in the elderly. Subependymomas can rarely undergo spontaneous intratumoral hemorrhage with associated intraventricular hemorrhage. Recent evidence supports radial glia as the candidate cell of origin for ependymomas while subependymomas appear to derive from subependymal glial precursors.

Ependymoma, WHO grade II, is classically a ventricular tumor. It may also arise in extraventricular sites, as well as the spinal cord, and the filum terminale. It is most frequent in the fourth ventricle, often presenting with obstructive hydrocephalus. Ependymoma is most common in childhood, accounting for 20% of childhood brain tumors but only 5% of adult brain tumors.

The characteristic feature of ependymoma is the gland-like ependymal rosette with blepharoplasts. However, the perivascular pseudorosette with the central blood vessel and the radiating a cellular glial fibrillary acidic protein-positive processes is more commonly seen (Fig. 2.8). The tumor cells are round, relatively uniform with only slight hyperchromasia. Prominent gemistocyte-like cells with fibrillary processes can occasionally be evident especially in frozen sections, creating a diagnostic dilemma during intraoperative consultation. Infrequently, CSF dissemination can occur. A prominent papillary pattern, a predominance of clear cells evidence of tanycytic (bipolar spindle) cells, lipomatous differentiation, signet ring cell features, or the presence of melanin define some of the histologic subsets of ependymoma. Increased cellularity without significant increase in mitotic activity constitutes the cellular ependymoma, an entity without any additional adverse prognostic implication. Although most ependymomas have well-demarcated borders, infiltrative tumors can occur in the cerebral hemispheres and spinal cord. Electron microscopic features of ependymal differentiation include formation of cilia, blepharoplasts, luminal microvilli, junctional complexes, and cell processes with intermediate filaments.

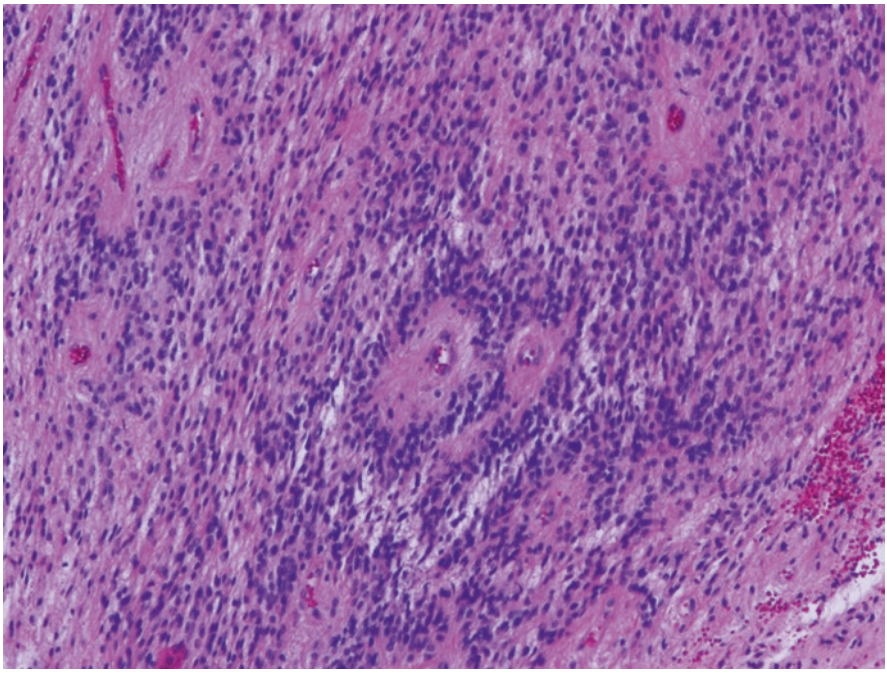

Fig. 2.8 Ependymoma with variable cellularity and characteristic perivascular pseudorosettes. Magnification ×100

The anaplastic ependymoma shows a significantly increased cellularity with anaplasia, frequent mitotic figures, endothelial proliferation, and necrosis. This tumor has a propensity for CSF dissemination. The presence of necrosis alone without the other cytologic changes and mitotic activity does not imply aggressive behavior since necrosis can be seen even in the low grade ependymoma. Predictors of poor prognosis in ependymomas include age below 3 years, anaplastic features (high cell density and frequent mitotic figures), incomplete tumor resection, and CSF dissemination. Molecular genetic studies of ependymomas have not identified any of the genetic events associated with astrocytomas. Mutations involving the NF2 have only been found in spinal cord ependymomas, raising the possibility that ependymal tumors of the spinal cord represent a distinct molecular subset.

Ependymomas are positive for S100, GFAP, and vimentin. Epithelial membrane antigen (EMA) often shows a characteristic punctuate, dot-like positivity and membranous staining. Stains for neuronal markers are generally negative except for NeuN which may show nuclear positivity in some anaplastic ependymomas.

Transcriptional profiling studies suggest that ependymomas can be divided into two clinically and molecularly distinct subgroups of posterior fossa ependymomas.

Group A (Group 1) tumors are seen in younger patients, occur in lateral location, have balanced genome with increased frequency of chromosome 1q gain, and with more biologically aggressive behavior having shortened PFS and OS. Immunostaining for Laminin alpha-2 (LAMA2) detection may serve as a marker for this group of tumors.

Group B (Group 2) tumors are seen in older patients, occur in midline, have numerous cytogenetic abnormalities involving whole chromosomes or chromosomal arms, with frequent chromosome 6q and 22q loss and 9p, 15q, and 18q gain. Neural Epidermal Growth Factor Like-2 (NELL2) detection by immunohistochemistry may serve as a marker for these tumors.

On the other hand, supratentorial ependymomas show significant overexpression of neuronal markers in comparison to their infratentorial counterparts; in particular, neurofilament light polypeptide 70 (NEFL) is overexpressed in supratentorial tumors. Nestin and VEGF are both expressed more frequently in supratentorial ependymomas, and are associated with a poor PFS.

Greater than 2/3 of supratentorial ependymomas contain oncogenic fusions between RELA (involved in canonical NF-κB signaling) and C11orf95.

2.4 Oligodendroglioma

Oligodendroglioma is a low grade, slow growing glial tumor with oligodendroglial differentiation and has a predominant proportion involving the frontal and parietal lobes. Oligodendrogliomas are uncommon in pediatric age group. Frequently, there is a long history of poorly controlled seizures. The tumors are composed of uniform round cells with the characteristic delicate capillary vasculature (so-called "chicken wire" vasculature) (Fig. 2.9). Formalin fixation of the tumor produces an artifactual

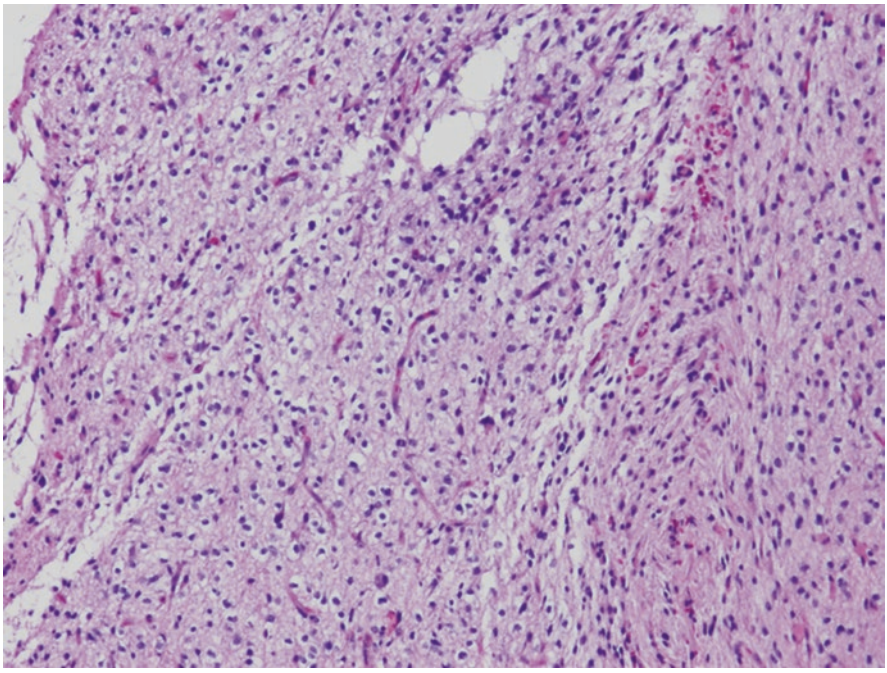

Fig. 2.9 Oligodendroglioma with infiltrating uniform round cells showing perinuclear halo (fried egg pattern) and delicate "chicken wire" capillary network. Magnification ×200

perinuclear halo giving the so-called "fried egg" appearance to the cells of an oligodendroglioma. Calcification is also frequent. A striking pattern of nuclear palisades is sometimes seen. An uncommon variant of oligodendroglioma can have a significant component of minigemistocytes. The gliofibrillary oligodendrocyte and minigemistocytes represent transitional forms that express glial fibrillary acidic protein. Differential diagnosis of the classic oligodendroglioma includes: (1) central neurocytoma which can be distinguished by the presence of acellular neuropil islands and positive immunostaining for neuronal antigens such as synaptophysin and (2) clear cell ependymoma which can be readily recognized by the presence of focal areas with the more classic ependymal rosettes and positive immunostaining for epithelial membrane antigen (EMA) and/or cytokeratin.

Anaplastic oligodendroglioma is characterized by a significantly increased cellularity with nuclear overlap, necrosis, increased mitotic activity, and endothelial proliferation. Increased cellularity and mitotic activity are helpful indicators of anaplastic progression in otherwise classic oligodendrogliomas.

Occasional familial clustering of oligodendroglioma cases has been reported. However, hereditary cancer syndromes involving oligodendrogliomas are rare. Loss of heterozygosity at chromosome 1p36 and 19q13 represents the most common genetic alterations in low grade oligodendrogliomas (Kros et al. 1999 and Reifenberger et al. 1996). Mutations of IDH1 (R132H) are also frequent in these tumors occurring concomitant with codeletion of 1p/19q. In pediatric oligodendroglial tumors, these genetic events are uncommon and are seen in tumors in children >10 years old. Anaplastic oligodendroglioma while showing chromosome 19q and 1p alterations also shows epidermal growth factor receptor overexpression often without gene amplification. Cdk4 amplification has been reported in a small subset of anaplastic oligodendroglioma. Chromosome 1p and/or 19q deletions in anaplastic oligodendrogliomas are positive predictors of prolonged survival and response to combination chemotherapy with procarbazine, cyclophosphamide, and vincristine (PCV).

Disseminated oligodendroglial-like leptomeningeal neoplasm (*DOLN*) is a recently described entity showing typical cytomorphologic features of low grade (WHO grade II) oligodendroglioma diffusely involving the leptomeninges. No associated intra-axial mass is seen in these patients. Significant desmoplasia is prominent in the involved leptomeninges. Rare cases show ganglion/ganglioid cells or anaplastic features. DOLN has been reported to show isolated 1p deletions with concurrent BRAF-KIAA1549 gene fusion. Occasional 1p/19q codeletion has been reported as well. Unlike oligodendroglioma, IDH1R132H mutations are infrequent in DOLN.

2.4.1 Mixed Glioma

Mixed gliomas are being increasingly recognized. Histologically, they are composed of two or more distinct populations of glial elements which can be diffusely mixed or have predominant cell types in varying proportions in different areas of the tumors. The more common mixed glioma is the oligoastrocytoma which can present

as a WHO grade II tumor or as an anaplastic oligoastrocytoma which is WHO grade III. The recognition of mixed gliomas and, in particular, the presence of an oligodendroglial component can have therapeutic implications.

2.4.2 Choroid Plexus Tumors

Choroid plexus tumors are intraventricular papillary tumors ranging from the benign choroid plexus papilloma (WHO grade I) to the malignant choroid plexus carcinoma (WHO grade III). Choroid plexus papillomas (CPPs) occur more commonly in children with about 10–20% presenting within the first year of life.

The majority of these tumors are sporadic with a minority arising in the context of hereditary cancer predisposition syndromes, including the Li–Fraumeni syndrome (germline TP53 mutation), Rhabdoid Predisposition Syndromes (germline mutation of SNF5/INI1/SMARCB1), Aicardi syndrome and rarely in von Hippel–Lindau disease. Congenital tumors can also occur. Most lateral ventricle tumors are seen in individuals below the age of 20 years. Grossly, choroid plexus papillomas present as well-circumscribed cauliflower-like masses. Histological features include a distinct papillary pattern with fibrovascular core and a single layer of cuboidal to columnar epithelium reminiscent of the normal choroid plexus (Fig. 2.10).

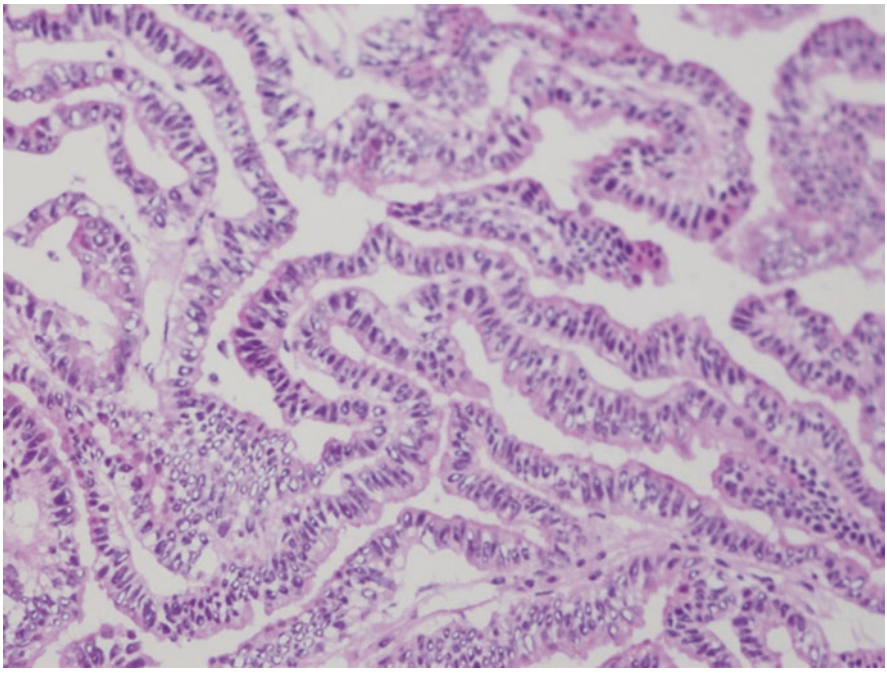

Fig. 2.10 Well-differentiated papillary configuration of choroid plexus papilloma. Magnification ×200

Atypical choroid plexus papillomas (WHO grade II) are CPPs with elevated mitotic activity (>2 mitoses per 10 high power fields). Notable histologic features in atypical CPPs include hypercellularity, nuclear pleomorphism, focal loss of papillary architecture/solid growth pattern, and necrosis. Complex growth with formation of cribriform and anastomosing papillary architecture may be seen.

In contrast, the choroid plexus carcinoma is an invasive tumor which can appear solid, hemorrhagic, and necrotic. Histologic features are those of a poorly differentiated anaplastic epithelial-like invasive tumor with significant increase in cellularity, brisk mitotic activity, and necrosis. Expression of cytokeratin, vimentin, S-100 protein, and synaptophysin are helpful in distinguishing choroid plexus carcinoma from a metastatic adenocarcinoma, since the latter should be negative for S-100 protein and synaptophysin. Nuclear immunopositivity for INI1 allows a distinction between a CPC with a rhabdoid phenotype and a true AT/RT lacking nuclear INI1 positivity.

2.5 Embryonal Tumors

Embryonal neuroepithelial tumors represent a significant group of brain tumors that occur predominantly in the pediatric population and less frequently in the adult population. They are characterized by "small blue cells" and exhibit a distinct pattern of divergent differentiation and have been referred to as primitive neuroectodermal tumors (PNETs). Other distinctive histologic features, though uncommon, can be seen in subsets of PNETs. These include characteristic ependymoblastic rosettes (multilayered rosettes which merge with surrounding tumor cells) in ependymoblastoma, fleurettes or Flexner–Wintersteiner rosettes in pineoblastomas, and florid desmoplasia (mesenchymal component) in supratentorial PNETs. A subset including medulloepithelioma, ependymoblastoma, some PNETs without rosettes, and embryonal tumor with abundant neuropil and true rosettes (ETANTR)] share a common genetic signature of C19MC (at chr19q13.41-42) amplification and together represent a subset of supratentorial PNETs now referred to as embryonal tumors with multilayered rosettes. Medulloblastoma represents a subset of "small blue cell" tumors that occur specifically in the cerebellum, accounts for 25% of childhood intracranial tumors, and is the second most common malignant tumors in childhood. This leaves a vanishing small subset of supratentorial PNETs designated as embryonal neuroepithelial tumors, not otherwise specified (NOS).

The most primitive of the embryonal tumors is the medulloepithelioma which corresponds to WHO grade IV. It occurs characteristically in young children below the age of 5 years. Medulloepithelioma can arise in any part of the neuraxis but the most frequent site is a periventricular location within the cerebral hemispheres. Intraorbital medulloepitheliomas can also occur. The medulloepithelioma is a primitive neoplastic neuroepithelium mimicking the primitive neural tube and can be papillary, tubular, or trabecular, and represents a distinctive and diagnostic histologic pattern. Aggressive histologic features such as mitotic figures, necrosis, and a population of undifferentiated cells can be present. The tumor cells are positive for

nestin and vimentin. Divergent differentiation along neuronal, glial, or mesenchymal elements can also occur.

Bailey and Cushing proposed the name medulloblastoma for a specific group of highly aggressive childhood tumors that they presumed arose from the putative stem cell "medulloblast" in the cerebellum. Although this name has been widely used for these tumors over the years, the "medulloblast" has remained undefined and has no counterpart in neurogenesis.

The morphologic spectrum of medulloblastoma and related PNETs is varied. It often includes a predominant population of sheets of round to oval (carrot-shaped) undifferentiated highly proliferative [proliferation index (MIB-I Index) is usually >30%] small blue cells (Fig. 2.11). These cells constitute the characteristic histology of the classic medulloblastoma. Anaplasia may vary from slight to moderate to severe. Regions with monomorphic discohesive large round cells with prominent nucleoli are suggestive of the presence of a large cell component. Predominance of large cells or severe anaplasia represents the *large cell/anaplastic* (Fig. 2.12) subtype and accounts for about 4% of medulloblastoma. Severe anaplasia is often associated with increased apoptosis, increased frequency of mitotic activity, and "cell wrapping" or cannibalism. Other histologic variants include the *nodular (desmoplastic) medulloblastoma* (Fig. 2.13) which is characterized by the presence of multiple reticulin-free pale nodules of neurocytic cells within a neuropil-like background, rarely mitotic with increased apoptosis; the

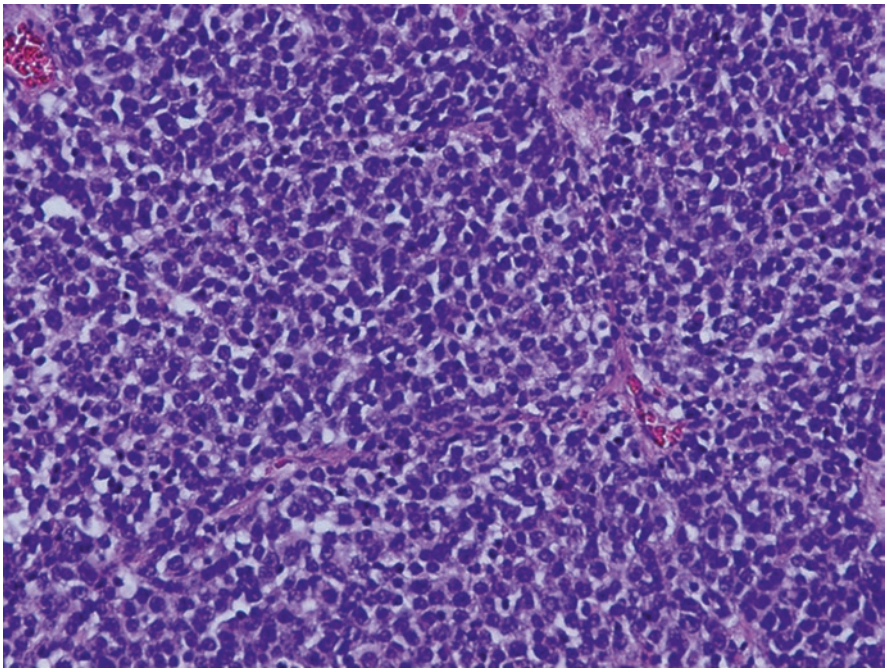

Fig. 2.11 Classic medulloblastoma with diffuse sheets of undifferentiated "small blue cells." Magnification ×200

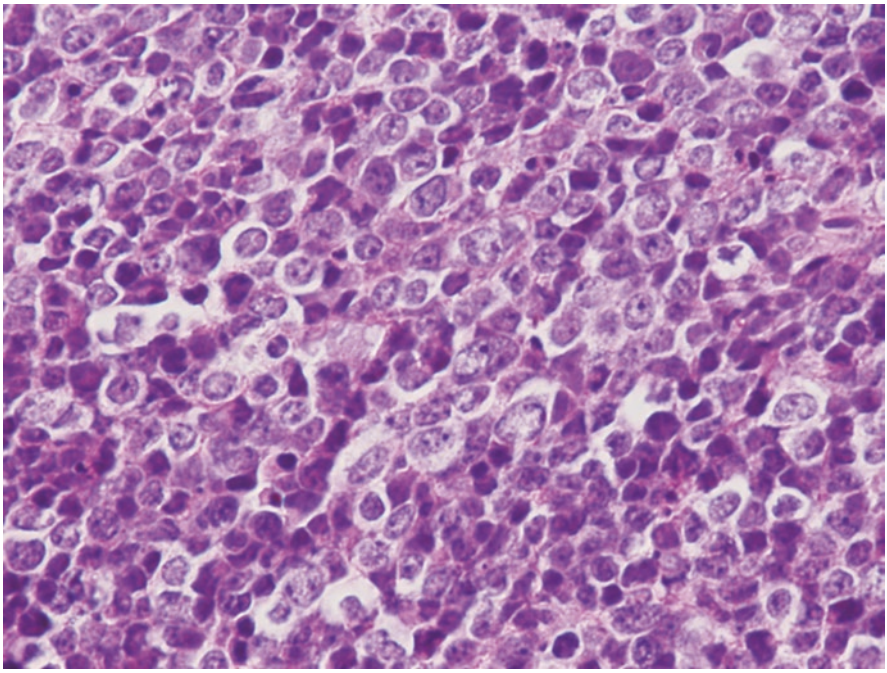

Fig. 2.12 Anaplastic/large cell medulloblastoma. Note enlarged cells with vesicular nuclei and prominent nucleoli as well as cellular pleomorphism. Magnification ×200

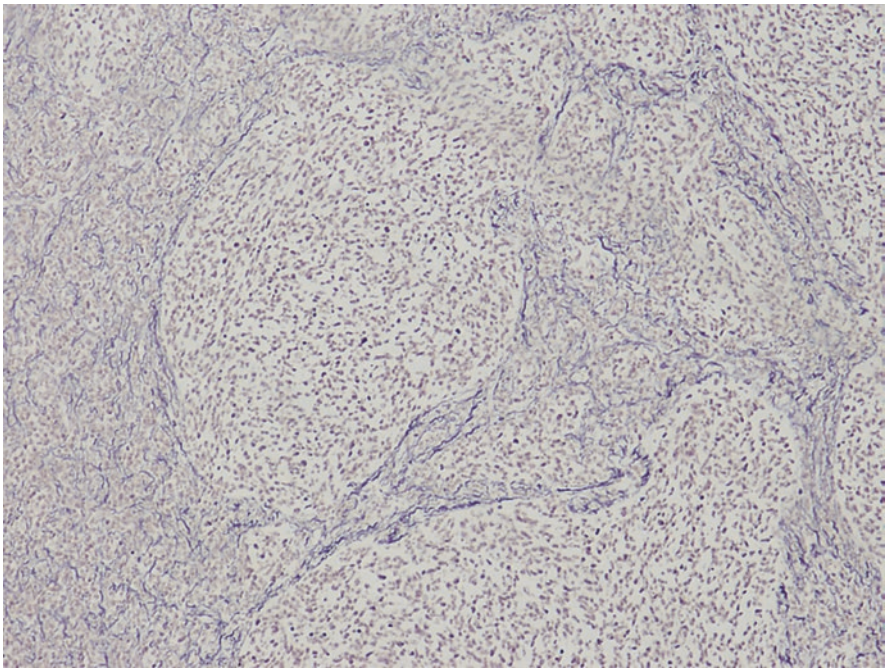

Fig. 2.13 Reticulin stain showing reticulin-free nodules of desmoplastic medulloblastoma. Magnification ×200

extensively nodular medulloblastoma (previously termed cerebellar neuroblastoma) showing florid nodularity and neurocytic differentiation with absent or minimal undifferentiated internodular component; and *biphasic medulloblastoma* which represents a tumor with mixed classic and nodular components in which the nodular component is not surrounded by desmoplasia, i.e., the internodular areas are reticulin free. This represents an important distinction from the nodular/desmoplastic medulloblastoma. In a minority of these tumors, neuroblastic differentiation is demonstrated by formation of Homer-Wright rosettes. Focal areas of astrocytic differentiation can be seen. Divergent differentiation with rhabdomyosarcomatous (medullomyoblastoma) and melanocytic differentiation can also be seen. Neuroblastic and astrocytic differentiation when present are accompanied by immunopositivity for synaptophysin or other neuronal antigens and glial fibrillary acidic protein, respectively.

Further molecular profiling studies of medulloblastomas have emphasized tumor heterogeneity and association of developmental signaling pathways with the establishment of four molecular subgroups. Groups A and B are associated with activation of the Wnt and Sonic hedgehog pathways, respectively. Subgroups C and D are non-wnt, non-SHH and are biologically more aggressive and may overexpress *MYCN* (group C) and/or *OTX2* and *FOXG1*. They are more likely to show i17q as well. Deregulation of p53 expression confers a poor prognosis. Molecular subgrouping can be done immunohistochemically by using a combination of antibodies to beta catenin for *wnt* pathway activation detection and *GAB1, YAP1, filamin 1,* and *Gli2* for *SHH* pathway activation detection.

Clinical determinants of poor outcome in medulloblastomas include age <3 years, dissemination at time of presentation, and partial surgical resection. The desmoplastic subtype appears to be associated with favorable outcome while the anaplastic/large cell variant is associated with shortened survival.

The *atypical teratoid/rhabdoid tumor* is a CNS embryonal tumor with histological features similar to those of the malignant rhabdoid tumor of the kidney. Even within the same tumor, histologic features can be extremely variable, including rhabdoid, primitive neuroepithelial, epithelial, and mesenchymal components. Irrespective of the spectrum of histologic features, the typical rhabdoid cells with eccentric nuclei and prominent nucleoli represent a constant feature. The cytoplasm is notably dense pink containing whorled bundles of intermediate filaments on electron microscopy (Fig. 2.14). Mitotic activity is very brisk with areas of necrosis often noted. A germ cell component is notably lacking. The cells show variable immunostaining for vimentin, epithelial membrane antigen, glial fibrillary acidic protein, smooth muscle actin, and sometimes neurofilaments; keratin and desmin can be focally positive. Germ cell tumor markers are usually negative. Molecular studies confirm that this tumor is biologically distinct from the PNETs, with 90% of tumors demonstrating monosomy and/or loss of heterozygosity for chromosome 22. Mutations/deletions in the hSNF/INI1/SMARCB1 is the hallmark of this subset of CNS tumors and related renal rhabdoid tumors with lack of detectable nuclear INI1 protein expression (Fig. 2.15).

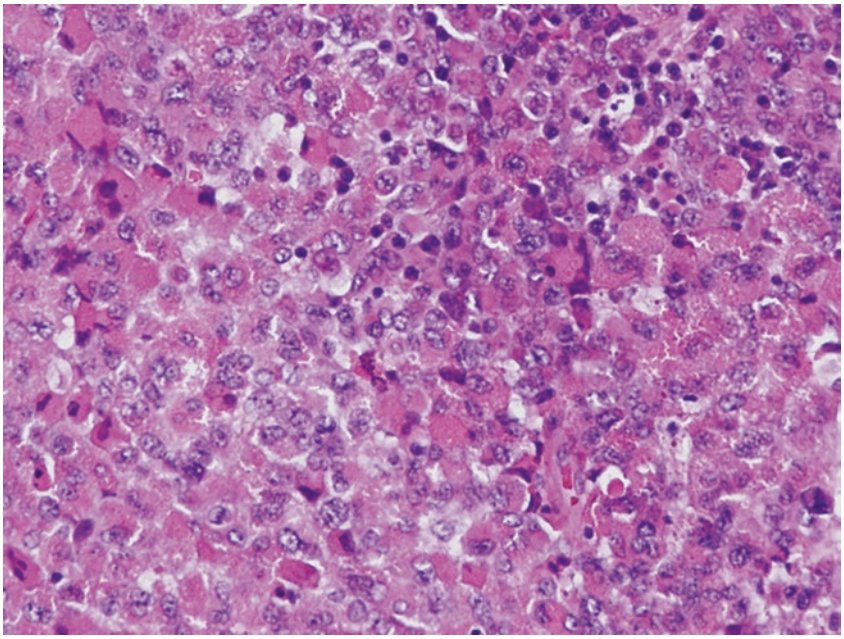

Fig. 2.14 Rhabdoid cells with eosinophilic cytoplasmic globules and eccentric nuclei are characteristic of the atypical teratoid rhabdoid tumor. Magnification ×200

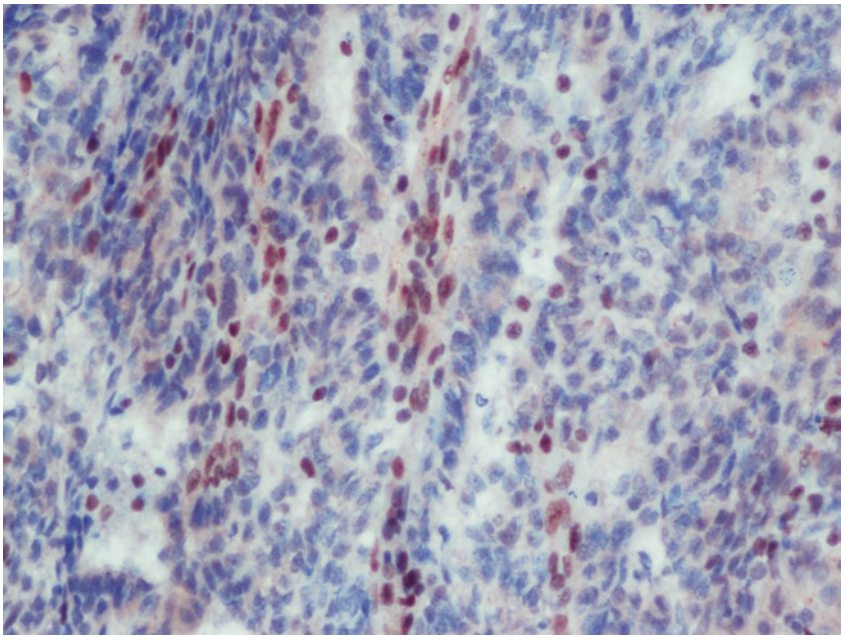

Fig. 2.15 Immunostain showing loss of nuclear expression of INI1 in tumor cells. Endothelial cells with immunopositivity (*brown*) serve as positive internal control. Magnification ×200

2.6 Neuronal and Mixed Neuronal-Glial Tumors

Gangliocytoma (WHO grade I) and ganglioglioma (WHO grade II) are uncommon tumors accounting for only 0.4–1.3% of all brain tumors with a median age of 8.5–25 years. Although these tumors can occur anywhere in the neuraxis, the majority are supratentorial. They are commonly associated with seizures and most tumors arise in the temporal lobe as a cystic lesion with a mural nodule.

The hallmark of these tumors is the presence of large, multipolar dysplastic neurons (Fig. 2.16). In the gangliocytoma, a stroma of nonneoplastic glia cells and reticulin fibers is present, while in the ganglioglioma, there is a neoplastic gliomatous (often pilocytic) component. Perivascular lymphocytic infiltration is a frequent feature of this tumor. Eosinophilic granular bodies (similar to those in pilocytic astrocytomas), microcysts, and calcification can be seen. The gliomatous component can sometimes show anaplastic features warranting a diagnosis of anaplastic ganglioglioma (WHO Grade III). BRAF V600E mutations are seen in approximately 45% of pediatric gangliogliomas while KIAA1549-BRAF fusion gene is rare and has only been reported in infratentorial gangliogliomas with prominent pilocytic glial components.

Recently described variants of glioneuronal tumors include the papillary glioneuronal tumor characterized by a pseudopapillary histology, and rosette forming glioneuronal tumor of the fourth ventricle.

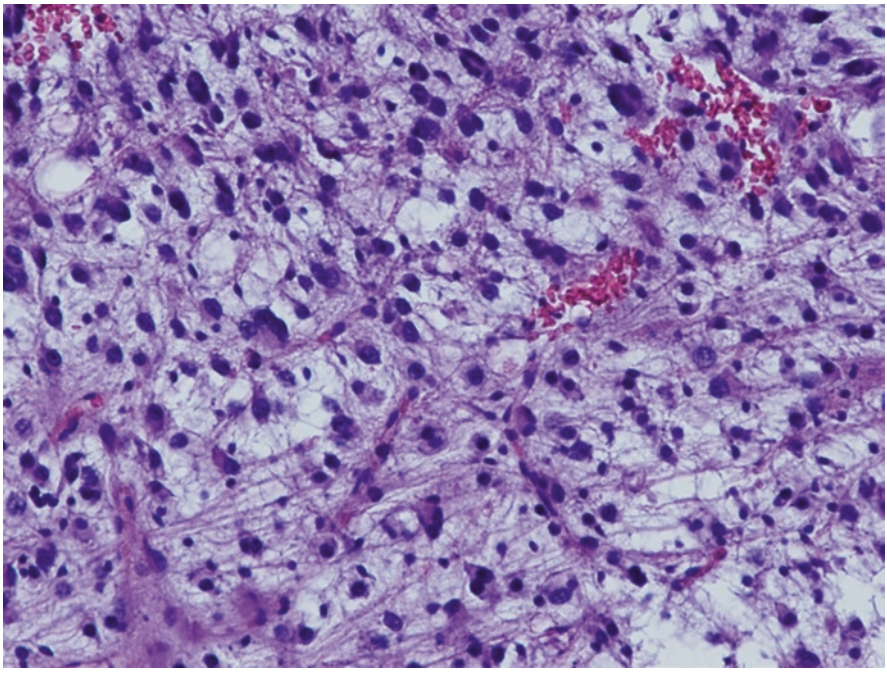

Fig. 2.16 Ganglioglioma showing pleomorphic ganglion/ganglioid cell differentiation. Magnification ×200

Desmoplastic infantile astrocytoma (DIA) represents a distinct low grade (WHO grade I) meningocerebral astrocytoma with a prominent desmoplasia characteristically occurring in children below the age of 2 years, although cases occurring in older children have now been reported. When a neuronal component is demonstrable, the lesion is referred to as desmoplastic infantile ganglioglioma (DIG). An immature population of neuroepithelial cells can be present. Notable is the frequent attachment of this tumor to dura. Tumors can have a uniloculated or a multiloculated cystic component and a solid (often superficial) component. The desmoplastic component can have a prominent storiform pattern and florid reticulin fibers, mimicking a mesenchymal tumor. Immunostaining shows only glial fibrillary acidic protein and vimentin positivity in the desmoplastic infantile astrocytoma, or a neuronal component with positivity for synaptophysin and other neuronal antigen markers in the desmoplastic infantile ganglioglioma.

2.6.1 Central Neurocytoma

The central neurocytoma is a neuronal tumor that is typically supratentorial, arising in relation to the lateral and third ventricles, but origin from intraparenchymal sites and the spinal cord has also been described. Peak incidence of the tumor is from 20 to 29 years and central neurocytoma corresponds to WHO grade II. It is composed of oligodendroglioma-like cells with intervening nucleus free neuropil. Central neurocytomas show immunopositivity for synaptophysin and other neuronal antigens. Ganglionic/ganglioid differentiation may be seen. Astrocytic differentiation, though rare, has been observed.

Anaplastic variants characterized by increased cellularity and increased mitotic activity can occur. The anaplastic central neurocytomas often have a proliferation index (Ki-67 index) greater than 2% and demonstrable parenchymal invasion.

Dysembryoplastic neuroepithelial tumor is a benign WHO grade I tumor arising predominantly in the superficial cortex. This tumor bridges the border land between hamartoma and neoplasia. Dysembryoplastic neuroepithelial tumor occurs predominantly in children and young adults who often have a long history of poorly controlled partial seizures. The classic complex dysembryoplastic neuroepithelial tumors are multinodular and are characterized by "specific glioneuronal elements" arranged in columns perpendicular to the cortical surface. The columns are formed by bundles of axons with intimately associated oligodendroglia-like (occasionally synaptophysin-positive) cells. Microcystic basophilic areas with floating neurons are also present (Daumas-Duport et al. 1988 and Daumas-Duport 1993). Cortical dysplasias are often present in adjoining cerebral tissue. In the simple form, the histology is less dramatic, can be patchy, and consists of the unique glioneuronal elements only. Deep-seated basal ganglia origin/localization though reported is extremely rare. It cannot be overemphasized that combined clinical, radiologic, and pathologic correlation is critical in the accurate diagnosis of dysembryoplastic neuroepithelial tumor (Fig. 2.17).

Subependymal giant cell astrocytoma (WHO grade I) is an intraventricular mass seen in the setting of tuberous sclerosis complex. It appears to evolve from the enlargement of subependymal hamartomatous nodules. It is composed of large eosinophilic astrocyte-like cells with prominent neuron-like nucleoli (Fig. 2.18). The cells typically immunostain for glial fibrillary acidic protein have also been reported to be positive for neuronal antigen markers such as synaptophysin.

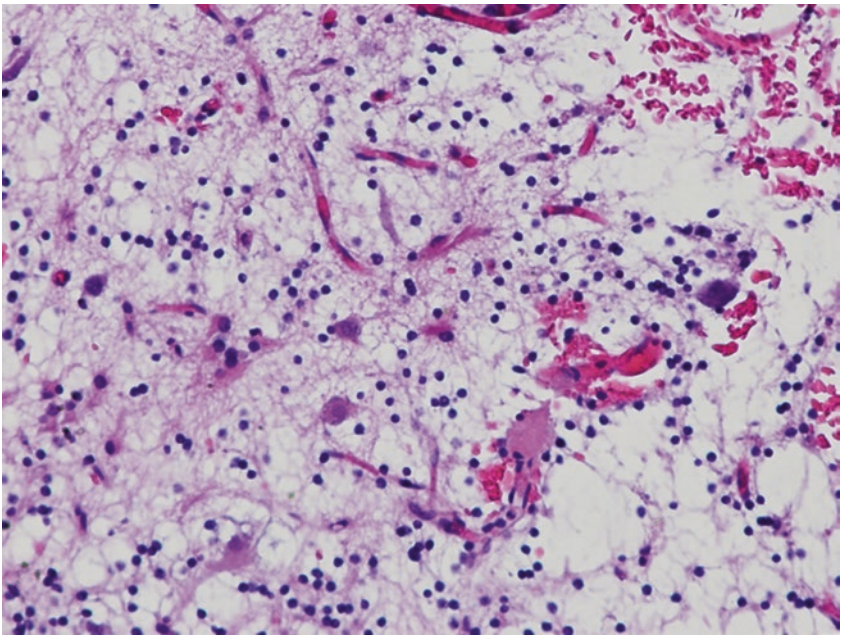

Fig. 2.17 The specific glioneuronal element of DNET with myxoid microcystic pattern and "floating neurons." Magnification ×200

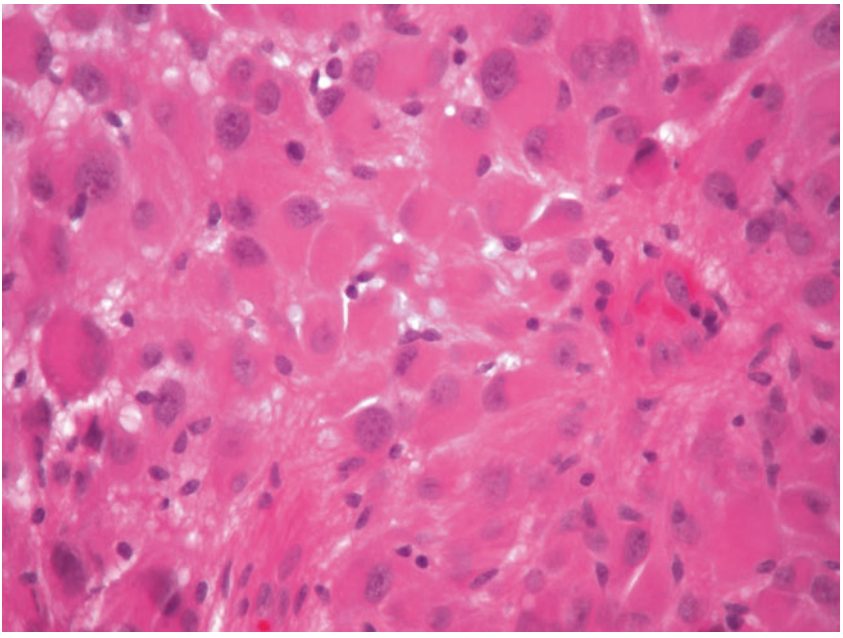

Fig. 2.18 Subependymal giant cell astrocytoma with uniform cells having plump eosinophilic cytoplasm. Magnification ×200

2.7 Miscellaneous Tumors

2.7.1 Schwannoma (Neurilemmoma)

Schwannoma is a benign tumor of the peripheral nerve sheath with predilection for sensory nerves. It most commonly affects the vestibular portion of the eighth cranial nerve producing the cerebellopontine angle mass lesion commonly referred to as the acoustic schwannoma. Bilateral acoustic schwannoma is a feature of neurofibromatosis type 2 (NF2). Although seen less frequently, schwannoma can also involve the fifth cranial nerve, but other cranial nerves are only rarely involved. The classic histologic features include the cellular Antoni A areas, Verocay bodies, and loose myxoid Antoni B area (Fig. 2.19). The presence of thick walled hyalinized vessels is a histologic hallmark of schwannomas. Immunostains show positive staining for S-100 protein and vimentin and negative staining for epithelial membrane antigen. Malignant transformation is rare in these tumors.

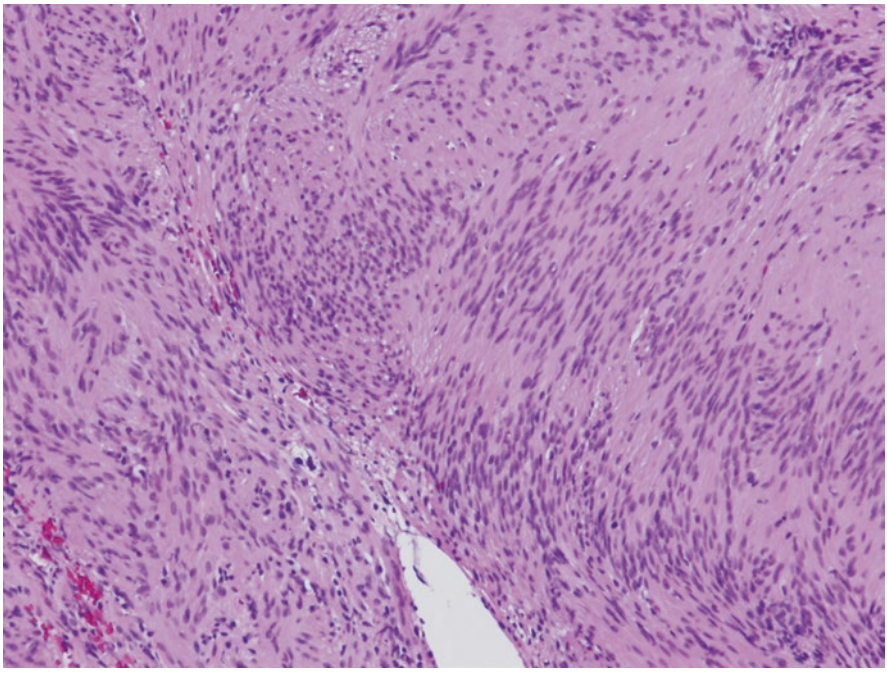

Fig. 2.19 Benign spindle cell proliferation with nuclear palisades having intervening acellular stroma to form Verocay bodies characteristic of Schwannoma. Magnification ×100

2.7.2 Germ Cell Tumors

Germ cell tumors are uncommon in the CNS accounting for 0.3–0.5% of all primary intracranial tumors. They present as midline tumors often in the region of the pineal gland and the suprasellar region in children and adolescents below the age of 20 years. Other sites of tumor occurrence include the basal ganglia, thalamus, intraventricular, bulbar, and intramedullary spinal cord locations. Histologically, the dysgerminoma is similar to gonadal seminoma with a uniform population of cells having large vesicular nuclei, prominent nucleoli, and a clear glycogen-rich cytoplasm (Fig. 2.20). Lymphocytic infiltrate and syncytiotrophoblastic giant cells can be seen. Immunostaining for placental alkaline phosphatase (PLAP) and c-kit (CD107) is usually positive. OCT3/4 and SALL4 immunostains are often positive as well. The identification of a cytotrophoblastic component is aided by immunostaining for beta-human chorionic gonadotropin (β-HCG) and human placental lactogen (HPL). Other germ cell tumors can also occur showing either a pure histologic subtype or a mixed germ cell tumor composed of any combination of embryonal carcinoma, yolk sac carcinoma, choriocarcinoma, and immature or mature teratomatous components.

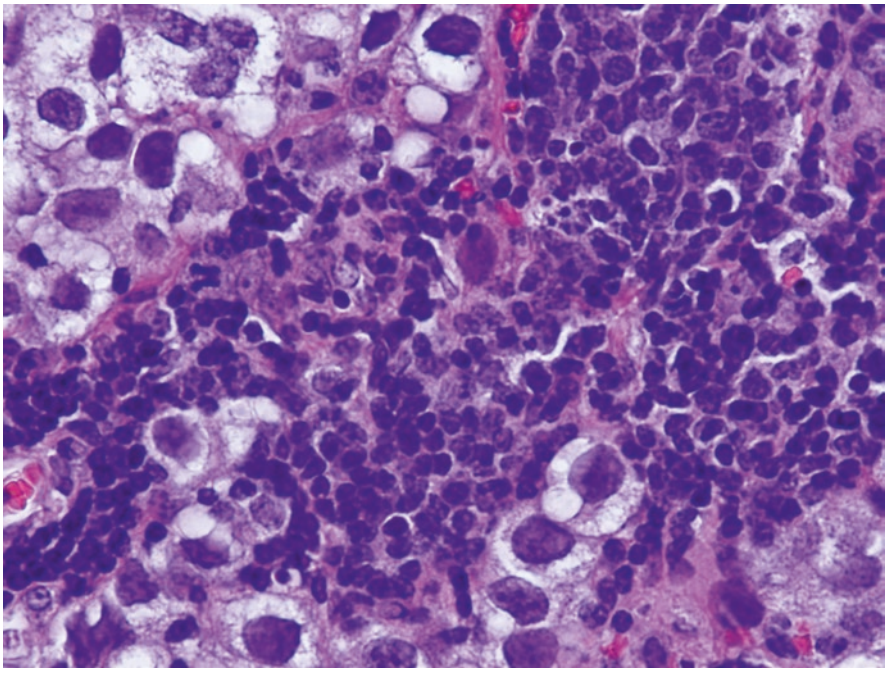

Fig. 2.20 Germinoma with mixed mature lymphocytes and neoplastic vacuolated epithelioid germ cells. Magnification ×400

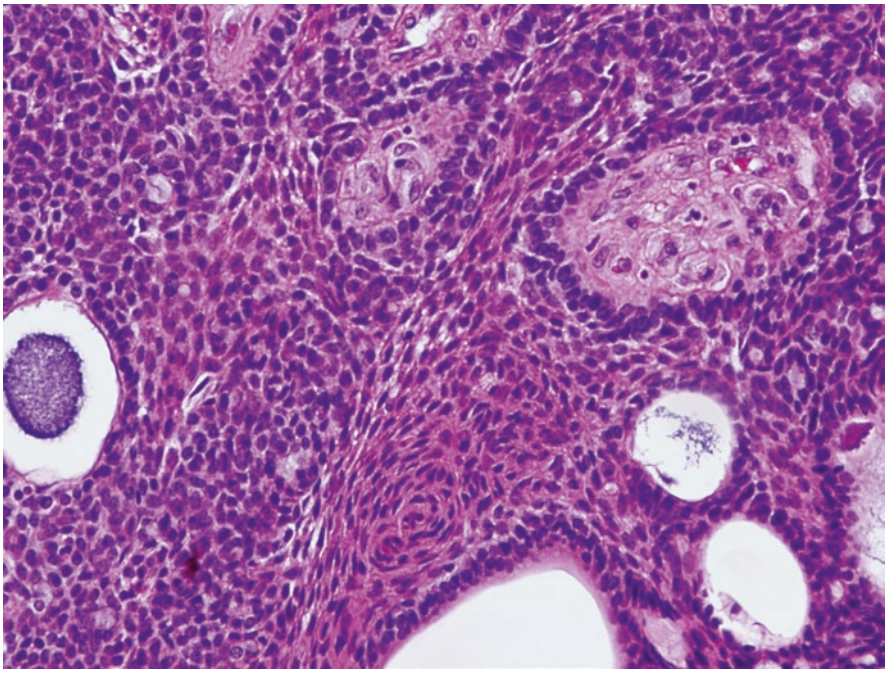

Fig. 2.21 Adamantinomatous craniopharyngioma with mixed microcystic epithelial elements and cellular reticular stroma. Magnification ×200

Craniopharyngiomas are derived from Rathke's pouch cell rests and present as intrasellar or suprasellar mass lesions with compressive effect on the optic chiasm, third ventricle, hypothalamus, and pituitary. They are usually partly cystic with prominent calcification. The epithelial component is characterized by keratinizing squamous epithelium with peripheral palisading, sometimes having a close histologic resemblance to adamantinoma (Fig. 2.21). A pseudopapillary pattern is another histologic subtype. A xanthogranulomatous component can also be seen. The cysts often contain oily material, (so-called "machinery oil"), and spillage of this material into CSF causes chemical meningitis. Tumor recurrence is frequent when incompletely resected. Beta catenin mutation is a frequent event in craniopharyngiomas.

Chordomas are formed from remnants of the notochord in the clivus or in the vertebral column, most frequently the sacrum. Chordomas are slow growing, lobulated with variable cellularity arranged in rows or cords in a myxoid matrix. The typical cell is the vacuolated physaliphorous ("bubble bearing") cell. Chordomas show positive immunostaining for vimentin, cytokeratin, epithelial membrane antigen (EMA), brachyury, and S-100 protein. A histologic subtype with a distinct chondroid component has been referred to as the chondroid chordoma.

Suggested Reading

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