activating mutation in the *BRAF* gene (V600E), and are associated with a shorter recurrence-free survival.

Gangliogliomas are most commonly found in the temporal lobe and often have a cystic component. The neoplastic ganglion cells are irregularly clustered and have apparently random orientation of neurites. Binucleate forms are found. The glial component of these lesions usually resembles a low-grade astrocytoma, lacking mitotic activity and necrosis.

- *Dysembryoplastic neuroepithelial tumor* is a rare, low-grade (WHO Grade I) tumor of childhood that often presents as a seizure disorder. It has a good prognosis following surgical resection, with both low recurrence rates and favorable seizure control. These lesions are typically located in the superficial temporal lobe, although other cortical sites are seen. There is often attenuation of the overlying skull, suggesting that the lesion has been present for some time.

  These lesions typically form multiple discrete intracortical nodules of small, round cells, arranged in columns around central cores of processes, and are associated with a myxoid background. There are well-differentiated "floating neurons" that sit in the pools of mucopolysaccharide-rich fluid of the myxoid background. The larger neurons and the small, round cells of the specific element express neuronal markers. Surrounding the nodules, there may be focal cortical dysplasia; lesions that show both the specific element and a glial component are termed complex.
- *Central neurocytoma* typically is a low-grade (WHO Grade II) neuronal neoplasm found within the ventricular system (most commonly the lateral or third ventricles), characterized by evenly spaced, round, uniform nuclei and often islands of neuropil. Although in pattern and shape the cells resemble oligodendroglioma, ultrastructural and immunohistochemical studies reveal the neuronal lineage of the tumor cells.

Poorly Differentiated Neoplasms

Some tumors, though of neuroectodermal origin, express few if any markers of mature neural cells and are described as poorly differentiated or embryonal, meaning that they retain cellular features of primitive, undifferentiated cells. The most common is the *medulloblastoma*, which accounts for 20% of brain tumors in children.

Medulloblastoma

This malignant embryonal tumor occurs predominantly in children and exclusively in the cerebellum (by definition). Neuronal and glial markers may be expressed, but the tumor is often largely undifferentiated and corresponds to WHO grade IV.

Molecular Genetics. Molecular subtypes of medulloblastoma have been identified through genomic studies, revealing alterations of signaling pathways involved in normal cerebellar development, such as the sonic hedgehog-patched (SHH) pathway involved in control of normal proliferation of cerebellar granule cells, and the WNT/β-catenin signaling pathway. On the basis of molecular alterations, medulloblastoma can be divided into four groups:

- The *WNT type*, characterized by mutations in the WNT signaling pathway, tends to occur in older children, has a classic medulloblastoma histology, and shows monosomy of chromosome 6 and nuclear expression of β-catenin. The prognosis is best in this subtype with 90% 5-year survival.
- The *SHH type,* characterized by mutations involving the sonic hedgehog signaling pathway, tends to occur in infants or young adults, tends to have a nodular desmoplastic histology and may have *MYCN* amplification. The prognosis is intermediate between the WNT subtype and groups 3 and 4.
- *Group 3 medulloblastoma*, often with *MYC* amplification and isochromosome 17 (i17q), tends to occur in infants and children, with a classic or large cell histology and the worst prognosis.
- *Group 4* is characterized by an i17q cytogenetic alteration, classic or large cell histology, without *MYC* amplification, but sometimes with *MYCN* amplification. The prognosis in group 4 is intermediate. In general, isochromosome 17q signals a poor prognosis, and is restricted to groups 3 and 4.

MORPHOLOGY

In children, medulloblastomas are located in the midline of the cerebellum, but lateral locations are more often found in adults. Rapid growth may occlude the flow of CSF, leading to hydrocephalus. The tumor is often well circumscribed, gray, and friable, and may be seen extending to the surface of the cerebellar folia and involving the leptomeninges (Fig. 28-52*A*). On microscopic examination, medulloblastoma is very densely cellular, with sheets of anaplastic cells (Fig. 28-52*B*). Individual tumor cells are small, with scant cytoplasm and hyperchromatic nuclei that are frequently elongated or crescent shaped. Mitoses are abundant, and markers of cellular proliferation, such as Ki-67, are detected in a high percentage of the cells. The tumor may express neuronal (neurosecretory) granules, form Homer-Wright rosettes, as occur in neuroblastoma Chapter 10), and express glial markers (e.g., GFAP). The **nodular desmoplastic variant** is characterized by areas of stromal response, marked by collagen and reticulin deposition and nodules of cells forming "pale islands" that have more neuropil and show greater expression of neuronal markers. The **large cell variant** is characterized by large irregular vesicular nuclei, prominent nucleoli, and frequent mitoses and apoptotic cells.

At the edges of the main tumor mass, medulloblastoma cells have a propensity to form linear chains of cells infiltrating through cerebellar cortex and penetrating the pia, spreading into the subarachnoid space. Dissemination through the CSF is a common complication, giving rise to nodular masses at some distance from the primary tumor (e.g. as far as the cauda equina); these are sometimes termed "drop metastases."

Clinical Features. The tumor is highly malignant, and the prognosis for untreated patients is dismal; however, it is exquisitely radiosensitive. With total excision and irradiation, the 5-year survival rate may be as high as 75%. How the different molecular subtypes of medulloblastoma respond to therapies is under active investigation; early clinical trials suggest some medulloblastomas may respond to inhibitors of the hedgehog signaling pathway.