Medulloblastoma, Primitive Neuroectodermal Tumors, and Pineal Tumors

Summary
Chapter 8 addresses three different tumors: medulloblastoma, primitive neuroectodermal tumors, and pineal tumors. The genetic and molecular studies in medulloblastoma are legion; yet, the basic changes responsible for the development of these tumors have remained evasive. Nevertheless, cytogenetically about one third of the medulloblastomas contain loss of 1p or i(17q), and less common anomalies of chromosomes 1 and 7, loss of chromosome 7, and loss of chromosome 22 (-22) and other changes. Of interest is the presence of double minutes in some medulloblastomas (approx 7%). The aforementioned changes have been supplemented with those obtained by spectral karyotyping, fluorescence in situ hybridization, comparative genomic hybridization (CGH), and loss of heterozygosity (LOH) results. Possible candidate genes playing a role in medulloblastoma development may reside at 10q or 8p. The changes of MYCN (amplification) in approximately 10% of medulloblastomas are of interest. Other genes investigated in these tumors include TP53 and ARF, IGF, epidermal growth factor receptor (EGFR)-ErbB, PDFGFα, RAS/MAPK, and PAX and ENI. The sonic hedgehog (SHH) and Wingless signaling pathways may play a role in medulloblastoma biology, and also neurotrophins and other factors (related to apoptosis), such as somatostatin receptors, Notch signaling, epigenetic events, the HIC gene, caspase8 gene, RASSF1A gene, and telomerase activity. The hereditary and genetic susceptibilities to medulloblastoma development are discussed. Chapter 8 also addresses primitive neuroectodermal tumors (PNET) cytogenetically; the changes in PNET show a variable pattern, as do the changes obtained with CGH and LOH. Molecular studies of PNET have included p53, Notch signaling, and the SHH pathway. Approaches similar to those used for the study of PNET have been applied to pineal tumors with the results being variable and not specific for any of the tumors.

Keywords medulloblastoma · PNET · pineal tumors · genetics · molecular biology.

Introduction
Chapter 8 has been divided into three main sections: medulloblastoma (posterior fossa or infratentorial tumors), primitive neuroectodermal tumors (PNET) (anterior fossa or supratentorial tumors or cerebral neuroblastomas) and pineal tumors (primarily pineoblastoma). Although there is biologic and histologic overlap among these tumors (1, 2), we have followed “a rule of thumb” in which we treat all infratentorial (posterior fossa) tumors, essentially those of the cerebellum, as medulloblastomas, and those of supratentorial (anterior fossa) location as PNET, including cerebral neuroblastomas. Although problems arose in occasional cases with this approach, in the preponderant number of tumors the correlations seemed to be valid and informative. Generally, the genetic changes (particularly cytogenetic) in these tumors complemented their anatomic location, histology and behavior, lending the approach not only practicality but also a correlative meaning.

Medulloblastoma
Clinical Aspects and Pathology of Medulloblastoma
Medulloblastoma is a malignant, poorly differentiated, highly aggressive, invasive embryonal tumor of the cerebellum primarily affecting children, showing predominantly neuronal differentiation, and an inherent tendency to disseminate via the cerebral spinal fluid (CSF) pathways (3–5,5A). Adult cases, although rare, have been reported, and their manifestations summarized (5B). Information regarding the incidence, epidemiology, and histoclinical aspects of medulloblastoma is given in Table 8.1.
Medulloblastoma is not simple tumors histologically. The World Health Organization (WHO) classification (6) lists four variants in addition to the classic type (i.e., desmoplastic, large-cell, medulomyoblastic, and melanotic). Other types have been described and reviewed previously (1). The WHO classification of brain tumors (6, 7) has been generally accepted, with some sobering but mostly approving commentaries regarding the WHO classification (8–10).

Chapter 8 provides the genetic information for those medulloblastoma types for which such information is available. Not infrequently, there is no clear-cut dividing line existing in the histologic features of medulloblastomas, particularly between classic and large-cell types, and this may account for some of the variability of results for these tumors presented in the literature.

The salient histologic features of the various types of medulloblastoma applicable to the interpretation of the genetic and molecular data presented here summarized in Figures 8.1 and 8.2. Concise descriptions of the histologic aspects of medulloblastoma are presented in Table 8.2.

### Classic medulloblastomas

Classic medulloblastomas account for about 80% of all medulloblastomas (1), and they grow as sheets of cells with a high nuclear:cytoplasmic ratio and a capacity to invade adjacent brain and leptomeninges. Classic medulloblastomas are composed of densely packed cells with round-to-oval or carrot-shaped highly hyperchromatic nuclei surrounded by scanty cytoplasm. Neuroblastic rosettes are a typical but not a constant feature (observed in <40% of tumors) (4). Round