Intraoperative Consultation in the Diagnosis of Pediatric Brain Tumors

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• Context.—The prevalence of brain tumors in the pediatric population differs from that in the adult population. Similarly, the frequency and location of the different histologic types of brain tumors vary significantly between the pediatric and adult populations.

Objective.—To familiarize the pathologist with the pediatric brain tumors encountered during intraoperative consultation and with the appropriate differential diagnoses in this setting.

Intraoperative consultation is an important component in the surgical management of pediatric brain tumors. Critical decisions regarding treatment and the extent of surgical aggression can sometimes depend on an appropriate intraoperative histopathologic diagnosis. Although all tumor types seen in the adult population can be seen in the pediatric population and vice versa, some tumors occur more frequently in the pediatric population. This variation in tumor prevalence necessitates specific differential diagnoses among the pediatric age group during intraoperative consultation. Most brain tumors, including diffuse fibrillary astrocytoma, anaplastic astrocytoma, oligodendroglioma, and glioblastoma multiforme, share similar cytologic and frozen section features in the pediatric and adult populations. Therefore, this article focuses on tumors that occur more commonly in the pediatric population, including primitive neuroectodermal tumor (PNET) (or medulloblastoma [MB]), atypical teratoid rhabdoid tumor (ATRT), ependymoma, choroid plexus carcinoma, juvenile pilocytic astrocytoma (JPA), and pineal region tumors.

PNET OR MB VERSUS ATRT

Developing an appropriate list of differential diagnoses is critical to making a correct intraoperative histopathologic diagnosis. This requires awareness of the clinical history, age of the patient, tumor location, and imaging features. Above all, a knowledge of the clinicopathologic entities that are frequently seen in specific locations is needed for a clinically correlated pathologic diagnosis.1,2

Data Sources.—The medical literature and the author's experience and expertise.

Conclusion.—Compared with adult brain tumors, pediatric brain tumors present different challenges and distinct differential diagnoses that the pathologist should be aware of during intraoperative consultation.

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Figure 1. Cytologic touch imprint of classic medulloblastoma (primitive neuroectodermal tumor) showing a monotonous population of small blue cells with little cytoplasm (hematoxylin-eosin, original magnification ×400).

Figure 2. Cytologic touch imprint showing crush artifact, apoptotic bodies, and a complete lack of fibrillary processes in medulloblastoma (primitive neuroectodermal tumor) (hematoxylin-eosin, original magnification ×400).

Figure 3. Large cells with open chromatin and distinct nucleoli and plasmacytoid cells in atypical teratoid rhabdoid tumor (hematoxylin-eosin, original magnification ×400).

Figure 4. Histologic section showing marked anaplasia in atypical teratoid rhabdoid tumor (hematoxylin-eosin, original magnification ×400).

Figure 5. Increased cytologic atypia in anaplastic medulloblastoma. Characteristic cell wrapping (arrow) can be seen with cytologic touch imprint preparations (hematoxylin-eosin, original magnification ×400).
entiated tumor with a high nuclear-cytoplasmic ratio, nuclear molding, necrosis, frequent apoptosis, and vascular proliferation. An indistinct Homer-Wright rosette is rarely seen with cytologic preparations (Figure 7) but may be seen on frozen section analysis. Similarly, a prominent perivascular pseudorosette suggests the diagnosis of anaplastic ependymoma.

**EPENDYMOMA VERSUS PNET (EPENDYMOMBLASTOMA) OR MEDULLOEPITHELIOMA VERSUS CHOROID PLEXUS CARCINOMA**

Ependymomas, PNETs, and choroid plexus carcinoma represent frequent groups of tumors in the differential diagnoses of supratentorial and infratentorial cerebellar tumors. A common radiologic feature of ependymomas is an intraventricular or periventricular location with contrast enhancement. Well-differentiated ependymoma can be readily diagnosed during intraoperative consultation by the characteristic morphologic features, including a monomorphic population of round cells with salt-and-pepper-like chromatin, perceptible micronucleoli, and arrangement around blood vessels as seen with cytologic preparations (Figure 8). On frozen section analysis, inter-spersed acellular areas that may or may not show an appreciable central blood vessel (ie, the perivascular pseudorosette [Figures 9 and 10]) are helpful in the diagnosis of ependymoma. Cytologic preparations often show glial processes with fibrillary processes and sometimes demonstrate eosinophilic cytoplasm that may be prominent enough to suggest the diagnosis of astrocytoma. Therefore, the findings of acellular perivascular pseudorosette areas and less cytologic pleomorphism than is seen in astrocytoma suggest a tentative diagnosis of ependymoma. Because a frozen section diagnosis of ependymoma would most likely prompt efforts to achieve a gross total resection, the pathologist needs to consider this diagnosis in tumors of ventricular or periventricular origin. Less frequently, ependymomas may occur outside the classic ventricular and periventricular areas.

On frozen section analysis, anaplastic ependymoma is less likely to show characteristic perivascular pseudorosettes, and its distinction from ependymoblastoma (PNET with ependymoblastic differentiation) may be difficult (Figures 11 and 12). With a high index of suspicion, clues to a possible diagnosis of ependymoblastoma include high cellularity, undifferentiated “primitive” cytology, a lack of fibrillary processes, and the presence of ependymoblastic rosettes (Figures 13 and 14). Although the presence of the rosette is a prerequisite for the diagnosis of ependymoblastoma, it is not specific for this entity alone. Ependymoblastomatous tissue may represent a major component of medulloepithelioma as well. Medulloepithelioma (a rare tumor) often has a distinct epithelial appearance, with prominent canals and glandlike features that may be accompanied by varying degrees of glioneuronal, epithelial, and mesenchymal (including cartilage, bone, and rhabdomyoblastic) differentiation. The demonstration of epithelial structures lying on a layer of basement membrane as shown by periodic acid–Schiff staining or by immunoreactivity for collagen type IV on permanent section analysis allows for the diagnosis of medulloepithelioma. Significant divergent differentiation, as may be seen in medulloepithelioma on frozen section analysis, may be too readily misinterpreted as indicating mixed germ cell tumor. Availability of adequate tissue for examination and the use of a panel of immunohistochemical stains may be helpful in the definitive diagnosis of each of these entities.

Choroid plexus tumors range from benign well-differentiated papilloma, with uniform epithelial cells and a striking papillary configuration for which the diagnosis is straightforward, to the poorly differentiated, solid, non-papillary tumor with prominent anaplasia. Therefore, high-grade forms of choroid plexus carcinoma should be considered in poorly differentiated tumors with focal epithelial features, cytologic atypia, brisk mitotic activity, and necrosis. In addition, high-grade tumors may not show a papillary configuration (Figure 15), which is the hallmark of low-grade choroid plexus papilloma. Unless the pathologist is aware of the extreme variation in the histologic structure of choroid plexus tumors, these tumors may be misdiagnosed even on permanent section analysis. A definitive diagnosis of high-grade tumors without areas of definite papillary configuration may require immunohistochemical demonstration of positivity for cytokeratin, negativity for epithelial membrane antigen, and clinicopathologic correlation in which the clinical and radiologic features are those of a tumor of possible choroid plexus origin. It may be impractical to expect the pathologist to make a definitive intraoperative diagnosis of these uncommon entities; however, he or she can recognize the high-grade undifferentiated features of these tumors and guide the neurosurgeon in ensuring that adequate diagnostic tissue is obtained for permanent processing and for appropriate immunohistochemical staining.

**POSTERIOR FOSSA LESIONS**

Posterior fossa lesions account for about 70% of tumors in the pediatric population. Most of these tumors occur in the cerebellum and include MB, JPA, and ependymoma. Other less frequently seen tumors include hemangioblastoma and dysembryoplastic neuroepithelial tumor (DNET). Even rarer in the cerebellum are diffuse fibrillary astrocytoma, oligodendroglioma, and glioblastoma multiforme. In the cerebellum, JPA is often cystic with a mural nodule (Figure 16), a radiologic feature that it shares with pleomorphic xanthoastrocytoma, hemangioblastoma, and ganglion cell tumors. Juvenile pilocytic astrocytoma may also occur in the brainstem, where it is often discrete and contrast enhancing with an exophytic component, in contrast to the typically diffusely infiltrating (fibrillary astrocytic) pontine glioma. Juvenile pilocytic astrocytoma is recognized by the fibrillary, piloid (hairlike) appearance of the cells with cytologic preparations, and JPA is frequently associated with variably abundant, often diffusely and randomly distributed, eosinophilic rods and globules of Rosenthal fibers (Figures 17 and 18). Eosinophilic granular bodies can also be of variable abundance. Even when observed in the absence of Rosenthal fibers, a biphasic appearance with alternating microcystic and compact cel-

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**Figure 6.** Histologic section of anaplastic medulloblastoma showing marked pleomorphism, cell wrapping (arrows), and apoptotic bodies (hematoxylin-eosin, original magnification ×400).
Figure 7. Cytologic preparation showing a rare Homer-Wright rosette (arrow) (hematoxylin-eosin, original magnification ×400).

Figure 8. Cytologic preparation showing a monotonous cell population with micronucleoli in ependymoma. The presence of few cells with eosinophilic cytoplasm and processes suggests a differential diagnosis of astrocytoma (hematoxylin-eosin, original magnification ×400).

Figure 9. Interspersed acellular areas (arrows) with or without central blood vessels in a frozen section of ependymoma suggest the presence of perivascular pseudorosettes (hematoxylin-eosin, original magnification ×200).

Figure 10. Permanent histologic preparation showing the classic perivascular pseudorosette in ependymoma with clear cell features (hematoxylin-eosin, original magnification ×200).

Figure 11. Anaplastic ependymoma with a less distinct perivascular pseudorosette (hematoxylin-eosin, original magnification ×400).

Figure 12. Perivascular pseudorosette in ependymoblastoma (primitive neuroectodermal tumor). Note the more primitive cytologic features of the tumor cells (hematoxylin-eosin, original magnification ×400).
Figure 13. Ependymoblastic rosettes (arrow) in ependymoblastoma with surrounding primitive cells (hematoxylin-eosin, original magnification ×400).

Figure 14. Ependymal rosettes (canals) in ependymoma. Note the less primitive cytology of the cells, in contrast to the ependymoblastic rosettes in Figure 13 (hematoxylin-eosin, original magnification ×400).

Figure 15. Solid and papillary configuration in choroid plexus carcinoma. Some high-grade tumors may not show a papillary configuration. Anaplastic ependymoma is an important component in the differential diagnoses (hematoxylin-eosin, original magnification ×200).

lular areas and hyalinized vasculature should elicit a differential diagnosis of JPA (Figure 19). When JPA is suspected, the presence of cytologic atypia and vascular proliferation does not have the same ominous implication of aggressive high-grade glioma as in regular diffuse fibrillary astrocytoma. The distinction between gangliogliomas and JPA is straightforward. However, there are gangliogliomas in which the glialomatous component shows unequivocal features of JPA. Verification of an observed ganglionic component in a tumor that otherwise has pilocytic features would need to be deferred until examination of permanent sections.

Dysembryoplastic neuroepithelial tumor presents typically as a superficial cortical mass lesion, a location that is shared with pleomorphic xanthoastrocytoma and ganglion cell tumors. Dysembryoplastic neuroepithelial tumors may also be seen in the cerebellum. These tumors are best recognized on frozen section analysis of lesions that are resected in toto as a single piece. This allows observation of the nodularity of DNET (Figure 20). The nodules are composed of small uniform cells, delicate capillary vasculature, and myxoid microcystic architecture, within which ganglion cells, so-called floating neurons, are present (Figure 21). In the complex variant of DNET, other gliomatous patterns may be present and raise the differential diagnoses of JPA, oligodendroglioma, or ganglion cell tumor (Figure 22).

Brainstem gliomas are a group of low-grade and high-grade astrocytic tumors that occur commonly in children (Figure 23). Except when an exophytic component is present, these tumors are not routinely biopsied but are treated based on the clinicoradiologic appearance of the lesions.

PINEAL REGION TUMORS

Tumors occurring in the pineal region represent some of the most surgically inaccessible lesions in the central nervous system. Tumors in this location are therefore biopsied through ventriculoscopic or stereotactic approaches to obtain tissue for diagnosis, which is an important prerequisite for treatment planning. The list of differential diagnoses of tumors in this location includes (1) pineal
parenchymal tumors such as pineocytoma, pineal parenchymal neoplasm of intermediate differentiation, and pineoblastoma; (2) germ cell tumors; (3) a broad spectrum of tumors that includes meningioma, hemangiopericytoma, juvenile pilocytic astrocytoma, granular cell astrocytoma, ganglioglioma, and melanotic progonoma; and (4) pineal cyst.

Pineocytoma, pineal parenchymal neoplasm of intermediate differentiation, and pineoblastoma represent a spectrum of tumors, ranging from the well-differentiated pineocytoma, composed of large cells with open chromatin, rare mitosis, and pineocytomatous rosettes, to pineoblastoma, with poorly differentiated small blue cells, brisk mitosis, necrosis, and apoptosis, similar to features seen in other PNETs (Figure 2). Homer-Wright rosettes or Flexner-Wintersteiner (retinoblastomatous) rosettes may also be seen in pineoblastoma.10 Pineal parenchymal neoplasm of intermediate differentiation is difficult to diagnose on frozen section analysis, and its definitive recognition requires permanent section analysis. However, a pineal-based tumor without pineocytomatous rosettes or overt features of PNET, in which the cells have appreciable cytoplasm and some mitotic activity but lack necrosis, is compatible with a diagnosis of parenchymal neoplasm of intermediate differentiation.

Germ cell tumors represent an important group of tumors that occur in the pineal and suprasellar regions. Therefore, they are primary entities in the differential diagnoses of midline or pineal-based tumors. Germinomas are the easiest to recognize with cytologic touch imprint preparations and frozen section analysis. They are identified with cytologic preparations as a population of large cells with distinct borders, prominent nucleoli with or without cytoplasmic vacuolation, and small benign lymphocytes (Figure 24).11 Frozen section analysis shows the same mixed population, which may be accompanied by significant crush artifact (Figure 25). The presence of large multinucleated giant cells is consistent with a population of sycytiotrophoblasts, some of which may be present as mononuclear cells. Nongerminomatous germ cell tumors constitute a mixed group of tumors that may vary in the preponderance of individual elements in a given tumor. Therefore, what is seen on intraoperative consultation will depend on the sample provided. The spectrum may include cytologic features showing mature differentiation of ectodermal, endodermal, or mesenchymal patterns, as seen in mature teratomas. An immature, fetal, or embryonic appearance suggests an immature teratoma. More aggressive cytologic features, including anaplastic epithelial sheets or cords of large cells having prominent nucleoli and accompanying necrotic debris, suggest the presence of an embryonal carcinoma component. Recognizing the anastomosing thin core of cells and the microcystic features of yolk sac tumor can be challenging because of fixation artifact associated with frozen sections. Even on permanent sections, these lesions are diagnostically challenging, and the pathologist must ensure that the surgeon obtains adequate tissue to allow for a definitive diagnosis on permanent section analysis.

CONCLUSIONS

Accurate intraoperative diagnosis of pediatric brain tumors requires familiarity with the spectrum of tumors that commonly occur in this age group, as well as with the
Figure 18. Frozen section from the same tumor as in Figure 16, showing the fibrillary stroma and abundant Rosenthal fibers (hematoxylin-eosin, original magnification ×400).

Figure 19. Juvenile pilocytic astrocytoma microcystic pattern, which is a common architectural pattern in this cerebellar tumor (hematoxylin-eosin, original magnification ×400).

Figure 20. Nodule illustrating the nodular microcystic feature of dysembryoplastic neuroepithelial tumor (hematoxylin-eosin, original magnification ×100).

Figure 21. Mixed population of small oligo-like neurocytes and ganglion cells in dysembryoplastic neuroepithelial tumor (hematoxylin-eosin, original magnification ×400).

Figure 22. Juvenile pilocytic astrocytoma-like areas in dysembryoplastic neuroepithelial tumor. Note the eosinophilic Rosenthal fibers (hematoxylin-eosin, original magnification ×400).
clinical and radiologic features of these lesions. Although a specific pathologic diagnosis is desirable, even after careful examination, the best information that a pathologist can sometimes provide during an intraoperative consultation is assurance that lesional tissue has been obtained. In such situations, tissue should be submitted for ancillary studies, such as electron microscopy, flow cytometry, and cytogenetics, and should be properly processed for immunohistochemistry.

References