PRIMITIVE NEUROECTODERMAL TUMORS
OF THE BRAIN IN CHILDREN

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Predominantly undifferentiated tumors occurring in the cerebrum of young individuals are referred to as “primitive neuroectodermal tumors.” Twenty-three of these cases were collected which had certain common features. Grossly they tended to be cystic and compressed adjacent brain. Microscopically they were malignant-appearing and demonstrated a prominent mesenchymal component. Sixteen cases showed focal evidence of glial and/or neuronal-appearing differentiation. It is suggested that the mesenchyme is also an aspect of tumor differentiation. The biologic behavior of these tumors was malignant, with an average duration of 18 months from onset of symptoms to death.

PRIMITIVE NEUROECTODERMAL” OR “NEURO-
EPITHELIAL” are names used to describe tumors composed of undifferentiated cells resembling germinal or matrix cells6 of the embryonic neural tube. Implied in both of these names is the capacity of these tumor cells to differentiate along either neuronal or glial lines. Neuroectodermal is the preferable name for our purposes since neuroepithelial implies a covering or lining tissue, and also because there is a specific tumor named neuroepithelioma. The term neuroectoderm has long been in use to describe the total substance of central nervous system tissue minus the mesenchymal elements of blood vessels and microglia.

In a recent address concerning specific types of primitive neuroectodermal tumors, Rubinstein12 cited the medulloepitheliomas, cerebral neuroblastomas, polar spongioblastomas, ependymoblastomas, pineal parenchymal tumors, and cerebellar medulloblastomas as tumors that have earned special designations because of their more or less predictable location and histologic appearance.

In contrast to these tumors, there remains a group of largely undifferentiated cerebral neoplasms occurring in children. These tumors remain a classifier’s enigma because they are uncommon, are sometimes mistaken for metastatic tumors, and often show focal areas of glial and/or neuronal differentiation in addition to a prominent mesenchymal component, thereby adding to the confusion. For these reasons, primitive neuroectodermal tumors are generally called by a variety of names: “neuroblastoma,” “cerebral medulloblastoma,” “undifferentiated small cell neoplasm,” and “unclassified glioma.” We prefer the designation primitive neuroectodermal tumor because it allows for a spectrum of histologic appearances ranging from completely undifferentiated tumors to those showing focal or diffuse areas of neuronal and/or glial differentiation. At the same time, these tumors display certain common clinical, gross, and microscopic features justifying this grouping. The following 23 cases from the files of the Armed Forces Institute of Pathology illustrate these features.

MATERIALS AND METHODS

Twenty-three cases were selected from the files of the Armed Forces Institute of Pathology with the diagnoses of “primitive neuroectodermal tumor,” “unclassified glioma,” “cerebral neuroblastoma,” and “cerebral medulloblastoma.”

All sections were stained with hematoxylin and eosin. In 11 cases special stains of Nissl, phosphotungstic acid hematoxylin, reticulin, and Bodian or Bielschowsky were performed in order to enhance detection of differentiation.

CLINICAL FEATURES

Fifteen patients were male and eight were female. The age range was stillborn to 24 years with the average age being 8.1 years. Present-
ing signs or symptoms in 18 cases where this information was available included: headache, 9 cases; vomiting, 6 cases; seizure, 5 cases; eye signs, 4 cases; hemiparesis, 4 cases; and hydrocephalus, 2 cases. Duration of symptoms from onset to diagnosis ranged from zero (sudden unexpected death in two cases) to 3 years, with the average being 4.8 months. If one case in which symptoms lasted for 3 years is eliminated, then the average duration of symptoms was 3.0 months. Follow-up until death was obtained in 6 cases with the average duration of symptoms from onset until death being 18 months. Again, if the same case in which the patient lived 5 years after onset of symptoms is eliminated, then the average duration of symptoms from onset until death was 10 months.

Pathology

Nine tumors were located in a frontal lobe, 4 in a temporal lobe, 4 in a parietal lobe, 2 in an occipital lobe, 2 in the corpus callosum, 1 at a foramen of Monro, and 1 bilateral in the hemispheres. Relationship of the tumors to ependymal lining, other than the specimen located at the foramen of Monro, was not stated. Most of the hemispheric tumors appeared to reside in the white matter, but exact location in most cases was not known. Grossly, 9 tumors were described as being cystic; the others were variously described as hemorrhagic, soft, lobulated, and well demarcated from surrounding parenchyma. Three tumors were stated to be encapsulated.

Microscopically these tumors were composed predominantly of small, undifferentiated cells with dark, oval to irregular nuclei and usually without observable cytoplasm (Fig. 1). All tumors were histologically malignant using the parameters of cellularity, pleomorphism, endothelial hyperplasia (Fig. 2), numbers of mitotic figures, and areas of necrosis (Fig. 3). A mesenchymal component was prominent in 18 cases; 9 cases showed collagenous trabeculae, and 4 cases showed an alveolar pattern with the alveolar walls composed of reticulin. Focal perivascular arrangement of cells was present in 6 cases (Fig. 4) and rosettes (with either central canal or central tangle) were present in 7 cases (Fig. 5). Mitotic figures were seen readily in 20 cases. Confirming the gross impression, the margins of tumor were noted to be compressing adja-

cent brain in 17 cases where margins of tumor were present in the specimen (Fig. 6). Characteristically, a few cells were usually noted infiltrating adjacent brain beyond the compressing margins. Areas of necrosis were present in 15 cases (Fig. 5). Each tumor was carefully screened for areas demonstrating differentiation along either glial or neuronal lines (Figs. 7, 8). Spongioblastic appearance, and fine cellular and intercellular processes were accepted as evidence of probable glial differentiation. Flexner-Wintersteiner rosettes (so-called "true" rosettes with a central canal) were considered to be evidence of either ependymal or retinal differentiation. Electron microscopy will be necessary in the future to determine whether or not the Flexner-Wintersteiner rosettes show features of photoreceptor cells as demonstrated in some retinoblastomas by Ts'o, Fine, and Zimmerman or whether they show features of ependymal cells as suggested by Rubinstein and observed in some of our cases of ependymoma. Neuronal differentiation was acknowledged when two or more of the following criteria were present: increase in cell size, increase in amount of cytoplasm, presence of prominent nucleoli, and presence of Homer-Wright (central fibrillary tangles) rosettes. Whether or not these cells with histologic features of neurons are truly neurons or not will require electron microscopy for determination. Zimmerman, Font, and Andersen have shown that cells that appeared to be neurons in some of their cases of intraocular medulloepithelioma, were in fact rhabdomyoblasts by electron microscopy. Many of their medulloepitheliomas of the eye showed mixed features of neuroepithelial, mesenchymal, and undifferentiated elements similar to some of our neoplasms in the brain. It was further noted that in areas showing what appeared to be obvious glial differentiation, the supposed glial fibrils stained positively with PTAH in less than half the cases, with staining in several cases being equivocal. Three cases showed focal areas of glial differentiation only. Seven cases showed focal areas of neuronal differentiation only, and 6 cases showed focal glial differentiation plus focal neuronal differentiation. Another 7 cases were judged as showing no evidence of either glial or neuronal differentiation. Four of the latter group were among those cases showing prominent collagenous trabeculae. There was no correlation between amount or degree of differentiation and the age of the patient.
FIG. 1 (top). Typical histology of primitive neuroectodermal tumor illustrating undifferentiated cells and fine stromal network (AFIP Neg. 72-11232; H and E, x305). FIG. 2 (bottom). Tumor with undifferentiated cellularity and prominent endothelial hyperplasia (AFIP Neg. 72-11231; H and E, x110).
Fig. 3 (top). Undifferentiated pattern with prominent vessels and "pseudopalisading" of tumor cells around areas of necrosis (AFIP Neg. 72-11228; H and E, x80). Fig. 4 (bottom). Focal perivascular arrangement of cells in an otherwise undifferentiated tumor (AFIP Neg. 72-11229; H and E, x110).
Fig. 5 (top). In the center of the picture are islands of darkly staining tumor cells containing rosettes with central tangles. The surrounding tissue is mesenchymal and stained positively with reticulin stains (AFIP Neg. 72-9843; H and E, ×100). Fig. 6 (bottom). Abrupt margin of tumor. This section also shows trabeculae coursing through tumor (AFIP Neg. 72-9836; H and E, ×35).
FIG. 7 (top). Focus of enlarged cells with increased cytoplasm and large nuclei with prominent nucleoli suggesting neuronal differentiation. Large cell in center closely resembles a ganglion cell. (AFIP Neg. 72-11771; H and E, x440).

FIG. 8 (bottom). Focal spongiofastic-like arrangement of cells with fine cellular processes suggesting glial differentiation (AFIP Neg. 72-11776; H and E, x350).
DISCUSSION

We have presented 23 tumors with the common features of (a) predominance in early life, (b) clinical malignancy, (c) occurrence in the cerebrum (usually hemispheric and deep), (d) grossly cystic and hemorrhagic with sharp borders, (e) microscopically malignant and predominantly undifferentiated with evidence of focal attempts to differentiate along glial and neuronal lines, and (f) prominent mesenchymal component. It is to be emphasized that not all, but most of these characteristics are present in each tumor, justifying their common grouping. It is also to be recalled that the specific neuroectodermal tumors mentioned in our introduction as well as malignant gliomas display many of the anaplastic features similar to this group of tumors. At what point a tumor should cease to be considered a “primitive neuroectodermal tumor” and named according to its avenue of predominant differentiation is arbitrary; for our purposes, we have restricted the present series to those tumors appearing at least 90–95% undifferentiated.

The appearance of mesenchyme as a prominent histologic component of many of these tumors is interesting. We feel that this probably represents a third avenue of differentiation open to tumors of neuroectodermal origin. Mesenchyme is often distributed heavily throughout cerebellar medulloblastomas, and in our experience is not uncommonly found forming a prominent part of oligodendrogliomas and glioblastomas.

Most reviews of brain tumors in children do not list a category such as ours but in general concede that certain specific neuroectodermal tumors such as cerebral neuroblastomas or ependymoblastomas may be predominantly undifferentiated. Willis, however, mentions six tumors in his collection entitled “Gliomas of Uncertain Nature,” which he felt were glial but preferred to leave unclassified. Although several of his tumors are quite bizarre, others certainly were very close in their pathology to our primitive neuroectodermal tumors. Bodian reported 15 cases of supratentorial medulloblastomas in a series of 129 brain tumors which he termed “differentiating medulloblastomas.” He reported these tumors to be slow growing, however. In a series of 116 gliomas, Cushing had 6 cases in his “unclassified” category in children which were atypical or transitional. Some of these may have been what we are describing as primitive neuroectodermal tumors.

In a recent analysis of 167 brain tumors occurring in children under two years of age, Leestma and Earle listed 19 cases which were difficult to classify because of lack of differentiating features. They referred to four of these as “blue tumors”; so named because of their dense, undifferentiated cellular patterns with a strong affinity for hematoxylin. These tumors are included in the present series.

It cannot be explained why this tumor occurs only in younger individuals. In general, however, many primary cerebral neoplasms of children tend to appear more histologically primitive than their adult counterparts. Cellular rest theories cannot explain why these tumors would lie dormant for so long and then become suddenly so aggressive. More plausible is the hypothesis that whatever the carcinogenic agent is, the substrate cells of the child’s central nervous system respond to this agent differently than do adults.

In our series, contributors’ diagnoses of these tumors were most often neuroblastoma, glioblastoma, undifferentiated tumor (or some variation), cerebral medulloblastoma, malignant ependymoma, or astroblastoma, reflecting the desire to place each tumor in a known category for which there is ample justification. We are fully aware that each of these tumors, with slightly more differentiation or de-differentiation, might fit into one of these categories. However, once it is recognized that these largely undifferentiated brain tumors share common biological and pathologic properties, then focal areas of divergent differentiation can be tolerated without losing sight of the ultimate reason for any classification—prediction of clinical outcome.

REFERENCES


