Tohoku J. Exp. Med., 2002, **197**, 55-65

Case Report

Primary Cerebral Neuroblastoma: A Case Report and Review

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ETUŞ, V., KURTKAYA, Ö., SAV, A., İLBAY, K. and CEYLAN, S. *Primary Cerebral Neuroblastoma: A Case Report and Review.* Tohoku J. Exp. Med., 2002, **197** (1), 55-65 —— Primitive neuroepithelial tumors are the least common among supratentorial tumors in children. They pose great diagnostic difficulty, preoperatively as well as pathologically. Being quite rare, cerebral neuroblastomas are accepted as a distinct pathological entity, which differs from other neuroectodermal tumors, although clinically, radiologically, and morphologically at operation they are indistinguishable. Also differentiation between primary cerebral neuroblastoma and the other primitive neuroectodermal tumors may be difficult on light microscopy and be misleading. A 9-year-old girl with primary cerebral neuroblastoma who was initially misdiagnosed is reported. The other cases from the literature are reviewed and the nature of this rare tumor and its differential diagnosis is discussed. ———— primary cerebral neuroblastoma; primitive neuroepithelial tumors; childhood supratentorial tumors; neuropathological differential diagnosis

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Supratentorial gliomas are uncommon tumors in children, constituting 10% to 14% of all intracranial tumors in the pediatric age group. The majority of these neuroectodermally derived neoplasms are of astrocytic and ependymal origin. They most commonly involve the cerebral hemispheres. Primitive neuroepithelial tumors are the least common of these supratentorial tumors, and they pose the greatest diagnostic difficulty, preoperatively as well as pathologically.

Being quite rare, cerebral neuroblastomas are accepted as a distinct pathological entity, which differs from other neuroectodermal tumors, although clinically, radiologically, and morphologically at operation they are indistinguishable (Horten and Rubinstein 1976; Berger et al. 1983). Also differentiation between pri-

Received November 26, 2001; revision accepted for publication June 22, 2002
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mary cerebral neuroblastoma and the primitive neuroectodermal tumors may be difficult on light microscopy and be misleading (Berger et al. 1983).

Here, a 9-year-old girl with primary cerebral neuroblastoma who was initially misdiagnosed is reported.

Case Report

A 9-year-old girl was admitted to our hospital because of headache, nausea, impaired vision on her right eye and weakness of her left arm and leg.

She had experienced headache and vomiting during the last two weeks. Neurological examination showed bilateral papilledema, a mild left hemiparesis.

CT revealed a large heterogenous cystic mass lesion in the right parieto-temporal lobe, which was irregularly enhanced on the contrast studies. MRI confirmed a circumscribed heterogeneous tumor with cystic components, which was isointense and hypointense on T1-weighted images, isointense with hyperintense cysts on T2-weighted images, and also disclosed a marked compression of the right lateral ventricle and a midline shift. No evident peritumoral edema was observed. The tumor was irregularly enhanced after the administration of Gd-DTPA (Figs. 1 and 2).

The preoperative routine complete blood count, clotting profiles, electrolytes, sequential multiple analysis for chemistry, and the urinalysis findings were all within the normal limits.

Gross total removal of the tumor was performed on the day of admission. She improved progressively after the operation and CT demonstrated marked shrinkage of the tumor.

Pathological evaluation of the neoplasm revealed small, monotonous cells accompanied by spindle, elongated cells showing marked desmoplasia. The processes of the spindle cells arranged in fascicles or whorled pattern. Also a nodular pattern (multimicrocystic expansile lesion), biphasic cellular type (gangliocytoid cell and glial cell), perivascular reticulogenesis, deep subcortical vasogenic edema and calcifications were noted. Using the streptavidin-biotin peroxidase complex (ABC) method, immunonegativity of synaptophysin (clone Snp 88, diluted 1 : 100, Biogenex, San Ramon, CA, USA), neurofilament protein (NFP) (clone 2F11, Neomarkers, Lab Vision

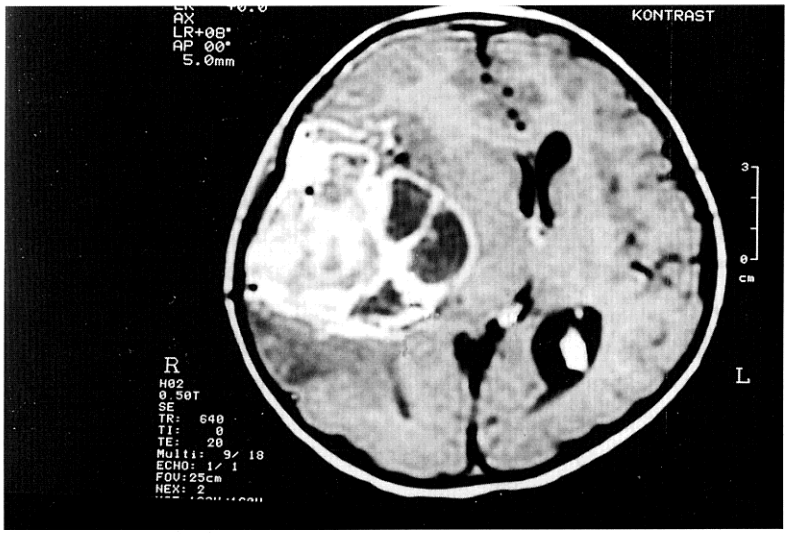


Fig. 1. Axial T1-weighted image confirming a circumscribed heterogeneous tumor with cystic components, which was irregularly enhanced after the administration of Gd-DTPA. No evident peritumoral edema was observed.

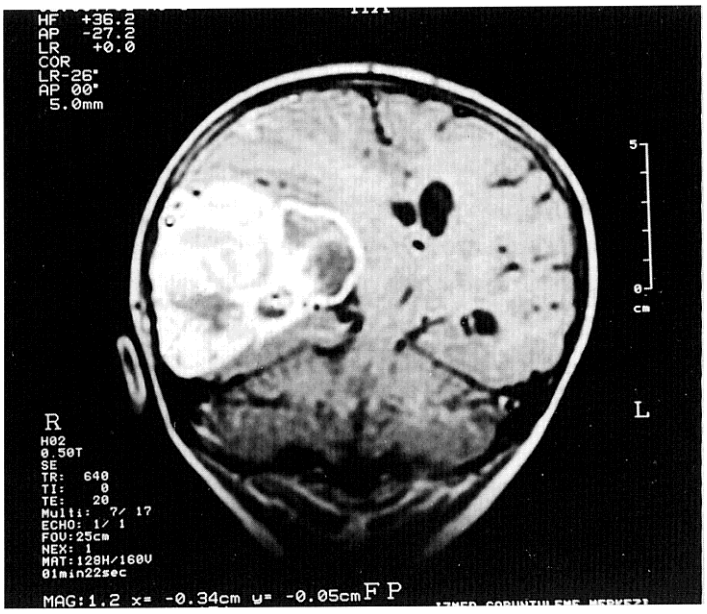


Fig. 2. Coronary T1-weighted image disclosing a marked compression of the right lateral ventricle and a midline shift. Irregular enhancement of Gd-DTPA is seen.

Corporation, Fremont, CA, USA), epithelial membrane antigen (EMA) (clone E29, diluted 1 : 20, Dako Corporation, Carpinteria, CA, USA), cytokeratin (CK) (clone CAM5.2, diluted 1 : 50, Becton Dickinson, San Jose, CA, USA), and CD45 (clone 2B11 and PD7/26/16, Biogenex) and immunopositivity of vimentin (clone V9, diluted 1 : 500, Biogenex) and glial fibrillary acidic protein (GFAP) (clone GA-5, diluted 1 : 200, Biogenex) was observed. However, the cerebral cortex above the lesion displayed dyslamellation, absence of glia limitans and the presence of balloon cells. Evaluating all these features, the neoplasm was regarded as of primary neuroepithelial origin and the histopathological examination was reported as desmoplastic cerebral astrocytoma of infantile.

However, she was readmitted with signs of increased intracranial pressure two months later and her CT revealed a recurrent tumor in the previous site.

A second operation was planned for the recurrent tumor. Performing a recraniotomy, gross total removal of the recurrent tumor was performed.

Pathological evaluation of the recurrent neoplasm revealed uniform small neoplastic cells with scant fibrillar cytoplasm and a clear organoid pattern with high mitotic index. Necrosis was evident. A nodular pattern, and a monotonous neuroblast-like cellular type were noticed. Cellular configuration displayed neuroblast-like undifferentiated monotonous cells having hyperchromatic nuclei and having clear cytoplasm in places and forming cloned islands. Homer Wright rosette formation was not observed. Using ABC method, strong immunoreactivity for NSE (clone MIG-N3, Biogenex) and for S-100 (clone 15E2E2, diluted 1 : 500, Biogenex) was present throughout the tumor. Tumor cells were negative for GFAP (clone GA-5, diluted 1 : 200, Biogenex), NFP (clone 2F11, Neomarkers), synaptophysin (clone Snp88, diluted 1 : 100 Biogenex), vimentin (clone V9, diluted 1 : 500, Biogenex), Desmin (clone 33, Biogenex), Smooth muscle actin (clone 1A4, Biogenex) Chromogranin (clone LK2H10, Biogenex) and CD45 (clone 2B11andPD7/26/16, Biogenex). Ki67 (clone MB67, Neomarkers) showed diffuse nuclear staining and proliferative index was determined

as 36.6% indicating the high proliferative feature of the neoplasm.

Comprehensive neuropathological investigation of the recurrent tumor sample and immunohistochemistry and review of the light microscopy of the initial tumor sample showed the neoplasm to have been a cerebral neuroblastoma rather than a desmoplastic infantile astrocytoma (Figs. 3–7).

Following the histopathological diagnosis, systemic examinations that included a bone survey, whole body CT scan, abdominal ultrasonography, and gallium scintigraphy did not reveal the existence of malignancy in any other organs.

Catecholamine levels and their metabolites, determined in the patient's urine and serum, showed normal values.

Diagnosis was approved as primary cerebral neuroblastoma and she underwent postoperative irradiation and received adjuvant chemotherapy.

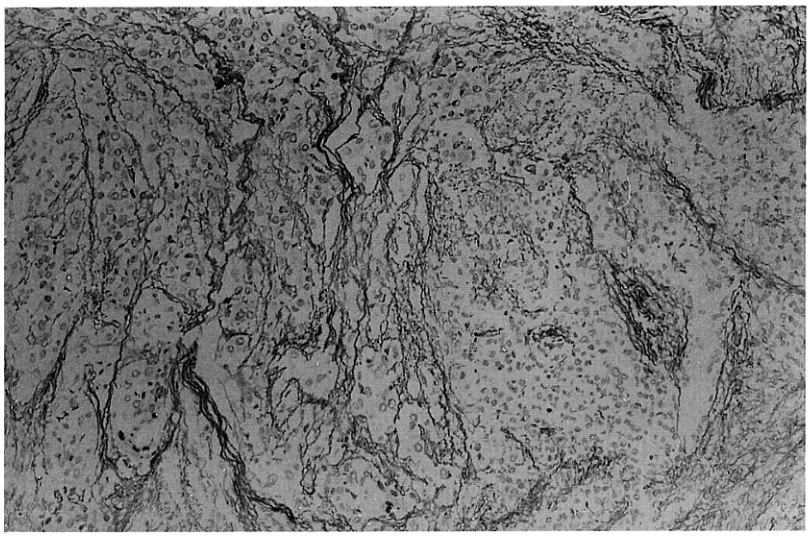


Fig. 3. 10X, Reticulin staining. Dense reticulin wrapping neoplastic cell groups and reticulogenesis.

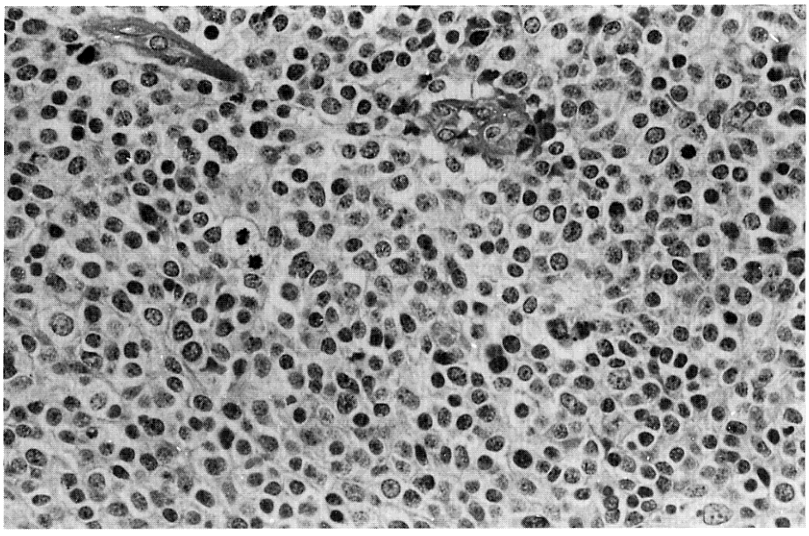


Fig. 4. 400X, Hematoxilene and eosine staining. Neoplasm showing a high mitotic index.

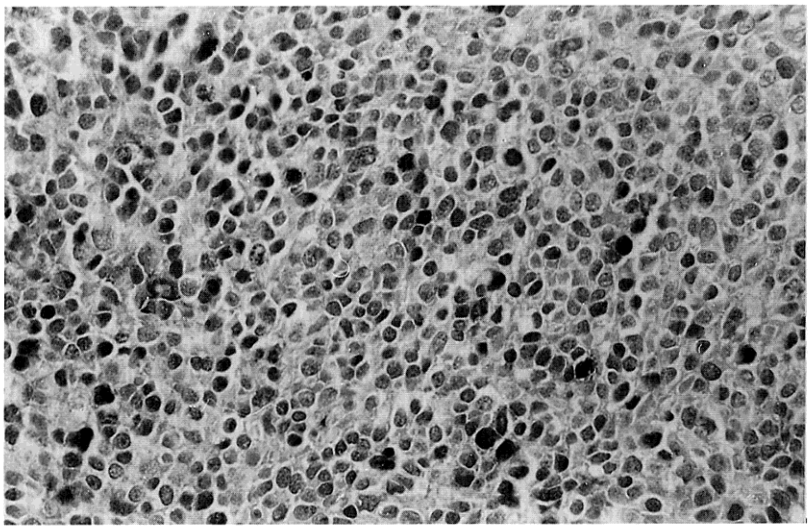


Fig. 5. 400X, S-100. Diffuse nuclear positivity and diffuse cytoplasmic positivity.

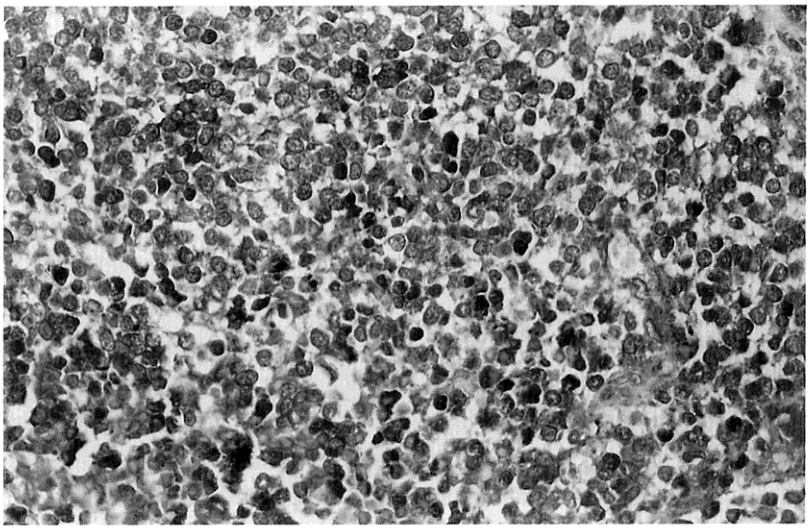


Fig. 6. 400X, NSE. Diffuse nuclear positivity and diffuse cytoplasmic positivity.

Follow-up examinations revealed a slight hemiparesis without any cranial nerve and cognitive function impairment. MRI performed 8 months after surgery revealed no evidence of tumor recurrence.

Discussion

Classification

Primary CNS neuroblastoma was initially considered a subset of primitive neuroectodermal tumors, and this categorization remained controversial for a long time. Although some authors have proposed that neuroblastoma was an "unfortunate" (Feigin and Budzilovich 1974) or "restrictive" (Kosnik et al. 1978) term and have doubted its validity (Willis 1967), majority of the relevant reports proposed that neuroblastoma was a distinct pathological and clinical entity (Hassin and Munch-Petersen 1951; Robertson et al. 1964; Voorhess and Watkins 1969; Boesel et al. 1978; Sakaki et al. 1981; Berger et al. 1983).

A broad classification was suggested in 1973 as a descriptive term for predominantly

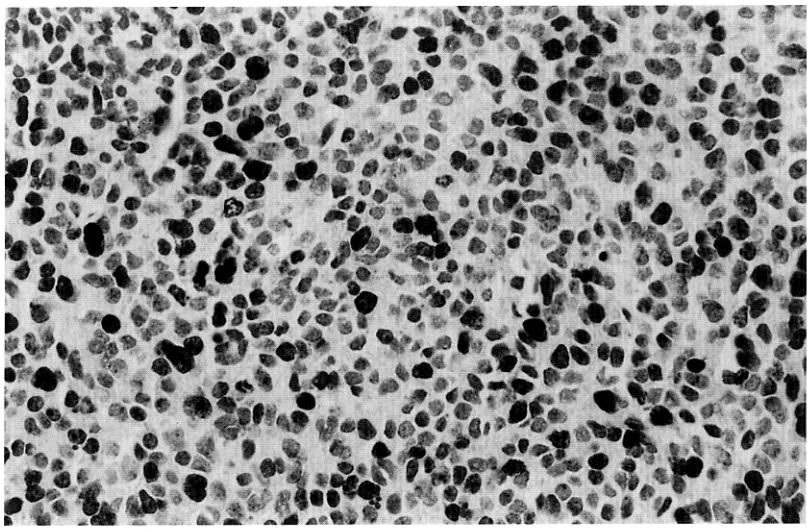


Fig. 7. 400X, Ki 67. Diffuse Ki 67 positivity of the neoplasm.

undifferentiated, or at times undiagnosed supratentorial tumors in children, which microscopically (without electron microscopy) were thought to originate from the primitive neural tube. These were malignant, often cystic, compressed adjacent brain, and could exhibit foci of glial and/or neuronal differentiation (Hart and Earte 1973).

The primitive neuroectodermal tumor group was reported to include medulloblastoma, medulloepithelioma, neuroblastoma, spongioblastoma, ependymoblastoma, and pineoblastoma (McComb and Burger 1985).

Russell and Rubinstein suggested that this classification was misleading since it combined a histologically inhomogeneous group of tumors as if they were pathologically indistinguishable (Russell and Rubinstein 1989).

Horten and Rubinstein however, previously suggested that primary cerebral neuroblastoma was a nosologic entity distinct from primitive neuroectodermal tumors and characterized by a cellular tumor of neuronal origin, without glial differentiation; the presence of a fine fibrillary matrix of axonal material; occasional differentiation to mature ganglion cells; and the frequent exhibition of well-formed Homer Wright rosettes (Horten and Rubinstein 1976).

In a subsequent study, recognition of neurosecretory granules on electron microscopy was reported to allow a precise diagnosis for primary cerebral neuroblastoma (Zulch 1986).

As a result, today there is sufficient evidence to warrant the conclusion that neuroblastomas belong in a classification distinct from other primitive neuroectodermal tumors, the primary feature of which being glial elements and precursors, and varying degrees of neuronal cell differentiation.

Apart from the cerebral neuroblastomas, International Neuroblastoma Pathology, classification was established by International Neuroblastoma Pathology Committee in 1999 for peripheral neuroblastomas. The International Neuroblastoma Pathology Classification, a system based on a framework of the Shimada classification with minor modifications, was proposed for international use in assessing neuroblastic tumors (Shimada et al. 1999). Tumors were classified as having favorable or unfavorable histology on the basis of Schwannian stroma, neuroblastic differentiation and mitosis-karyorrhexis (fragmenting nucleus) index, which is the cellular density sum of mitotic and karyorrhectic cells in the tumor in the context of age at diagnosis. High Ki-67 scores ($>25\%$) correlate with poor prognosis (Rudolph et al. 1997) as amplified N-myc proto-oncogene

(MYCN) (Shimada et al. 1995).

According to histological classification of tumors of the central nervous system proposed by WHO, in 2000, neuroblastoma is classified under supratentorial primitive neuroectodermal tumors group with ganglioneuroblastoma. Supratentorial primitive neuroectodermal tumor group is the subgroup of embryonal tumors group, which is classified under the tumors of neuroepithelial tissue (Kleihues and Cavenee 2000).

Differentiation and outcome

Neuronal tumors of the central nervous system have been shown to exhibit different degrees of neuronal differentiation toward various kinds of mature neurones. Cerebral neuroblastomas were reported to have probability to differentiate into gangliocytomas or gangliogliomas manners similar to those of cerebellar and sympathetic neuroblastomas (Warzok et al. 1983; De Chadarevian et al. 1987).

In a study, intraventricular neuroblastomas were compared with hemispheric neuroblastomas. It was reported that, neuronal morphologic or epitope differentiation was associated with a longer survival time than lack of differentiation by Kaplan-Meier product-limit estimates and with a better survival rate (chi-square) for intraventricular neuroblastomas but not for hemispheric neuroblastomas. It was concluded that intraventricular neuroblastomas follow a more benign course when neuronal differentiation is present (Rhodes et al. 1994).

In another study, the outcome was evaluated in 70 patients with primary cerebral neuroblastoma.

No correlation could be made between survival times and histological variant of the tumor or the presence of ganglionic differentiation. It was notified that, postoperative irradiation with or without chemotherapy did not improve length of survival, but an occasional favorable clinical response to chemotherapy did occur. Because of the high incidence of local recurrence and the relative frequency of cerebrospinal metastasis, prophylactic whole brain and spinal irradiation was justified (Bennett and Rubinstein 1984).

In comparison with patients who have primitive neuroectodermal tumors, those with primary cerebral neuroblastomas were reported to have a much better prognosis for long-term survival (Berger et al. 1983).

Differential diagnosis

Cushing was one of the early proponents of the term "cerebral neuroblastoma." After reevaluating 11 supratentorial tumors that he had originally described as medulloblastoma, he decided that five of the lesions, although they resembled medulloblastoma, had clinical features different from those of medulloblastoma.

They had a propensity to become large and calcify, and were composed principally of neuroblasts (Berger et al. 1983).

Rubinstein also believed that the tumors many authors labeled "medulloblastoma," "ependymoma," "poorly differentiated oligodendroglioma," or "undifferentiated primary sarcoma" were probably neuroblastomas (Berger et al. 1983).

Horten and Rubinstein classified neuroblastomas on the basis of the degree of connective tissue present, differentiating "classic" lesions with scant connective tissue from the "desmoplastic" variant, which they identified as having a more prominent stroma, especially when the tumor was located adjacent to the leptomeninges. They also distinguished a transitional type of neuroblastoma. Ganglion cells were more often found in the "classic" tumor, suggesting that mature neuronal cells may induce less of a stromal reaction than is seen with the more primitive precursor cells (Horten and Rubinstein 1976).

The cerebral neuroblastoma often appears to be confused with other tumors. Tumors concerned in neuropathological differential diagnosis of primary cerebral neuroblastoma

TABLE 1. *Tumors concerned in neuropathological differential diagnosis of primary cerebral neuroblastoma*

Neuropathological Differential Diagnosis of Primary Cerebral Neuroblastoma (PCN)
Oligodendroglioma (*the classical variety of PCN*)
Ependymoma (*the classical variety of PCN*)
Sarcoma, especially of the polymorphic type (*Transitional and desmoplastic variants of PCN*)
Medulloepithelioma
Polar spongioblastoma
Ependymoblastoma
Glioblastoma
Desmoplastic medulloblastoma
Neurolipoma
Desmoplastic infantile ganglioglioma
Central neurocytom

were summarized in Table 1.

The classical variety was sometimes mistaken for an oligodendroglioma or an ependymoma. The distinction between Homer Wright and ependymal rosettes was reported to create additional confusion (Horten and Rubinstein 1976).

In general, however, the classical form of cerebral neuroblastoma resembles the well-known peripheral tumors sufficiently closely to give rise to only minimal diagnostic difficulty.

The transitional and desmoplastic variants, on the other hand, can easily be interpreted as forms of sarcoma, especially of the polymorphic type.

A reticulin preparation, however, will display in sarcomas a uniform network of reticulin throughout the tumor, whereas in neuroblastomas small islands of cells free of reticulin will be evident. Failing this, a careful examination of the tumor for small foci of ganglionic differentiation may help in the diagnosis.

The gross histological characteristics of neuroblastomas are not helpful in differentiating them from primitive neuroectodermal tumors. Primitive neuroectodermal neoplasms, such as medulloepithelioma, polar spongioblastoma, ependymoblastoma, and cerebellar medulloblastoma, can often be distinguished from the neuroblastoma on the basis of the following histological features: glial differentiation (PTAH-positive fibrils), 90% to 95% cellular nondifferentiation, a greater degree of cellular pleomorphism and endothelial hyperplasia, and a less prominent connective tissue component.

Nonetheless, differentiation between neuroblastoma and primitive neuroectodermal tumors may be difficult on light microscopy because of the variability of their histological features (Berger et al. 1983).

It was reported that cerebral neuroectodermal tumors might express a range of phenotypic features from the exclusive neuroblastic stage to a neuronal and stromagenic phase analogous to the classic neuroblastoma of the sympathetic nervous system (Dehner et al. 1988).

In a case report it was demonstrated that a cerebral neuroblastoma was mistaken easily for a glioblastoma even by competent neuropathologists (Wyche et al. 1989).

In an other report, a case of cerebral differentiated neuroblastoma with the clinical and light microscopic appearance of an oligodendroglioma was notified and the importance of immunostaining techniques was stressed (Wilson et al. 1985).

In our case, in the first neuropathological evaluation the neoplasm was regarded as of primary neuroepithelial origin. But because of the superficially located nature of the lesion, with spindle cells and desmoplasia, the tumor was considered as a low-grade neuroepithelial tumor.

The identification of the lesion as neuroblastic is easiest in the presence of Homer Wright rosettes. Also, the appearance of the tumor in H & E stained sections is less specific, although fibrillar rosette-like clearings suggest the diagnosis. In that setting, immunohistochemistry can be used for further identification of phenotypic clues of the tumor. Reactivitiy for

synaptophysin is essential, particularly in the absence of ganglioid cells or mature neurons. Moreover, it is strictly recommended to be cautious against over-interpreting small zones of fibrillarity as Homer Wright rosettes. In majority of cases, immunoreactivity for synaptophysin of NSE is widespread, both in fibrillated areas and within the cytoplasm and minute processes of small cells. The striking feature in our case is disseminated immunoreactivity for NSE and S100 that led us about the origin of tumor cells to be neuronal despite the negativity of the other neuronal markers (Burger and Scheithauer 1994).

Also, a densely cellular neoplasm is occasionally encountered in young patients might resemble neuroblastoma in which no specific neuroblastic features can be identified by either light microscopy or immunohistochemistry. In such cases, ultrastructural studies may be diagnostic (Burger and Scheithauer 1994). The diagnostic ultrastructural features are neurofilaments, axonal processes, formation of growth cone, and the presence of clear and dense core synaptic vesicles. However, in practical routine it is not always possible to perform an electronmicroscopic study. In our case, unfortunately we did not have the opportunity for an electronmicroscopic study of the tumor.

123I-metaiodobenzylguanidine (MIBG) scintigraphy is known to be very useful in detecting peripheral neuroblastomas. Its use in diagnosing primary cerebral neuroblastomas is not well studied. A case of olfactory neuroblastoma was reported by noting MIBG uptake revealed by single-photon emission CT (SPECT) (Sasajima et al. 2000). SPECT-revealed MIBG uptake may be clinically useful for distinguishing cerebral neuroblastomas from other tumors.

Among the entities in differential diagnosis of the neuroblastoma includes a rare neoplasm occurring in first two years of life, the desmoplastic infantile ganglioglioma (DIG). This tumor might exhibit a minor small cell component. But, it could be distinguished by its superficial location, accompanying cyst, predominant desmoplastic component containing enmeshed astrocytes, minor component of ganglioid cells and immunoreactivity for both GFAP and neuronal markers and also low Ki-67 proliferation index (Burger and Scheithauer 1994). Our case did not show immunoreactivity for GFAP or vimentin whereas it was immunoreactive with NSE.

Another well-known entity is central neurocytoma that is a low-grade intraventricular lesion. Although it is a cellular tumor, it does not appear particulary "primitive" since it exhibits remarkable cytologic uniformity with precise, round, mitotically inactive nuclei with delicate "salt and pepper" chromatin and inconspicious micronucleoli (Burger and Scheithauer 1994).

Also a specific clone directed against Ki-67 was widespread reacted in our case to be a reliable marker of its proliferative capacity. This striking feature of our case could be assumed to be reproducible finding for any high-grade tumor reflecting rapid cell turnover. Also, a high proliferative capacity could be regarded the relative risk of tumor to recur in a short period. It is our feeling that a high Ki-67 index in a tumor with cellular neuroepithelial tumor could be argued against its origin, such as central neurocytoma and DIG.

In neuropathological differential diagnosis of the primary cerebral neuroblastoma the following neoplasms should be also taken into consideration: primitive neuroectodermal tumors, primary and secondary central nervous system lymphomas, desmoplastic medulloblastoma, neurolipoma (neurocytoma/lipoma) and central neurocytoma.

In conclusion, additional to a careful radiological workup including SPECT, immunohistochemical and electron microscopic findings are crucial for the diagnosis of cerebral neuroblastoma.

Acknowledgments

We, gratefully thank Filiz Alptekin, M.D., for her assistance.

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