A 7-YEAR-OLD BOY WITH MIDLINE CEREBELLAR MASS

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CLINICAL HISTORY

A boy aged 7 years was investigated for dizziness, diplopia and occasional visual hallucinations over a period of 3 months. Examination revealed mild nystagmus and left-sided cerebellar signs, including ataxia and dysdiadochokinesis. A mass arising from the roof of the fourth ventricle was

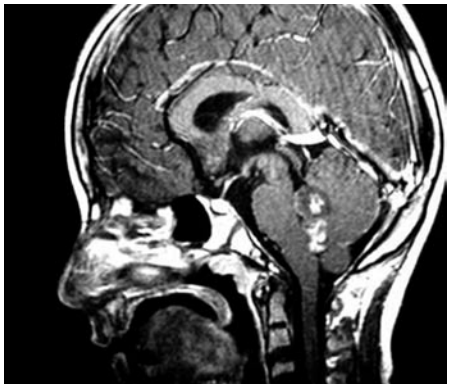

Figure 1.

demonstrated on MRI (Figure 1). No other radiologic abnormalities were present within the neuraxis. Serum AFP was 1KU/L, and HCG was <1 IU/L. The tumor was removed via a posterior fossa craniotomy. The child received craniospinal radiotherapy and cisplatin-based chemotherapy, and remains well 44 months post-surgery.

Macroscopic examination revealed pieces of tumor measuring 27 mm across altogether, and were characterized by firm gray and soft pink elements.

MICROSCOPIC PATHOLOGY

Microscopy revealed that the tumor had 2 principal components. The first consisted of undifferentiated small cells with mildly pleomorphic oval nuclei and a high nuclear:cytoplasmic ratio (Figure 2A). This component was characterized by a high mitotic count and abundant apoptotic bodies. The second was composed of mature tissues differentiating along neuroectodermal, mesodermal and endodermal lines. Most of the mature tissue appeared neuroglial (Figure 2B); ganglion cells (Figure 2C), cells with a glial nuclear morphology and occasional ependymal rosettes were scattered throughout a GFAP-immunopositive fibrillary background. Ganglion cells were positive with Neu-N immunohistochemistry (Figure 2D). However, the following elements were admixed with the neuroglial component in one region of the tumor: smooth (Figure 3A) and striated muscle (Figure 3B), cartilage (Figure 3C), and tubular/glandular structures (Figures 3D, 4A). These mature tissues showed the expected immunophenotypes, including cytokeratin and epithelial membrane antigen reactivities in the tubular structures (Figure 4B) and labeling of smooth muscle cells with anti-smooth muscle actin antibody (Figure 3A). The small cell component showed focal immunoreactivity for synaptophysin, but no labeling with antibodies to GFAP, epithelial membrane antigen, cytokeratin or smooth muscle actin. The growth fraction of this component was very high: Ki-67 immunolabeling exceeded 80% in some areas, whereas it was virtually zero in the mature tissues.

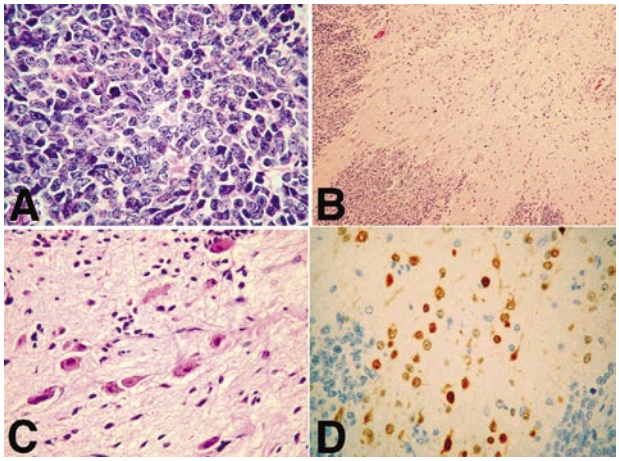

Figure 2.

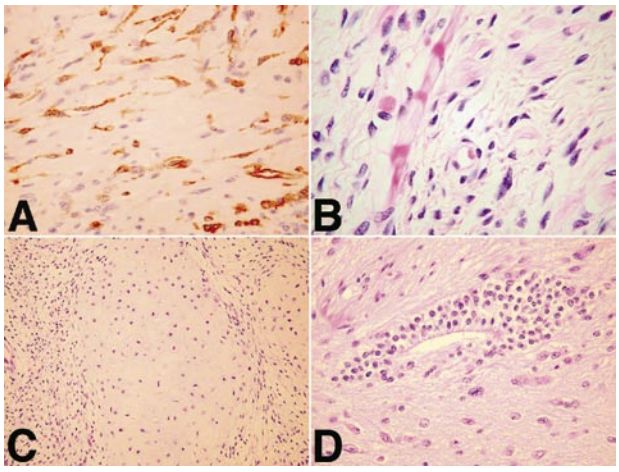

Figure 3.

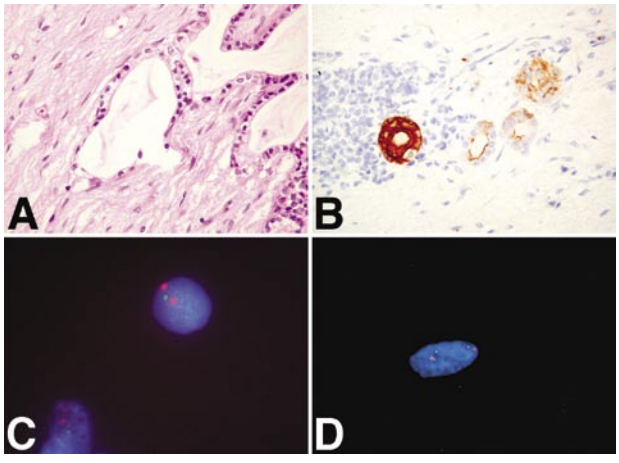

Figure 4.

Imbalance on chromosome 17 was assessed in both components of the tumor using fluorescence in situ hybridization (FISH) on both microdissected preparations of whole nuclei and paraffin tissue sections. Loss of 17p (Figure 4C) was combined with gain of 17q (Figure 4D) in both the primitive small cell and mature components.

DIAGNOSIS

Primitive neuroectodermal tumor (PNET) showing multilineal differentiation.

DISCUSSION

The differential diagnosis of this extremely unusual CNS tumor rests between PNET with multilineal differentiation and germ cell tumor. A diagnosis of atypical teratoid/rhabdoid tumor is not tenable, because the tumor contains mature tissues and does not comprise the polymorphic small cells of the atypical teratoid/rhabdoid tumor, which characteristically show focal immunoreactivities for a range of epithelial and mesenchymal markers (11). A diagnosis of mature teratoma seems pragmatic, because of the presence of tissues derived from different cell lineages. Furthermore, the development of a PNET in a teratoma is an uncommon, but well recognized, phenomenon (9). However, the cerebellum would be a very unusual site for a CNS germ cell tumor; nearly all are suprasellar or pineal (8). In contrast, more than 90% of CNS PNETs arise in the cerebellum, and the question of whether a PNET (medulloblastoma) could differentiate into such diverse mature tissues then arises.

The medulloblastoma, with its capacity for neuroepithelial differentiation along neuronal or glial lines, is considered to be the archetypal PNET (8). This differentiation occasionally manifests as a neuronal (ganglionic) or astrocytic morphophenotype, but is more usually expressed as immunoreactivity for a neuronal marker or GFAP (6). In addition to neuroepithelial differentiation, PNETs can show evidence of differentiation along other embryonic lines. The current WHO classification recognizes the medullomyoblastoma and melanotic medulloblastoma as examples of this phenomenon (8), and there are reports of children with cerebellar PNETs that contain myeloid and epithelial elements (± melanin producing cells), or cartilage (1, 2, 7). In addition, one tumor from a series of three childhood medullomyoblastomas contained a "teratoma," with mature tissue from all three germ layers including cartilage, hair follicles and sweat glands (5), and another cerebellar tumor from a boy aged 5 years combined what was described as a medulloblastoma and mature teratoma (4).

We hypothesized that if this cerebellar tumor is a PNET with multilineal differentiation its cells might show a cytogenetic abnormality more consistent with this diagnosis than with a diagnosis of germ cell tumor. An isochromosome 17q (i17q) is present in about one third of medulloblastomas (3, 6), but is not characteristic of intracranial germ cell tumors (10). Our FISH results are compatible with the presence of an i17q in both the small cell and mature components of the tumor, providing support for a diagnosis of PNET with multilineal differentiation. The case suggests that PNETs have a more diverse repertoire of differentiation than previously recognized.

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A 10-MONTH-OLD BOY WITH A LARGE PINEAL TUMOR

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CLINICAL HISTORY

A 10-month-old boy was admitted because of spasticity of both legs and a history of developmental arrest. He had problems with coordination of movements and particularly difficulty in holding position of his head. The head circumference was enlarged.

RADIOLOGY

CT scan revealed occlusive hydrocephalus and a large tumor obstructing the 3rd ventricle. MRI confirmed enlargement of the lateral and third ventricles with periventricular edema (Figure 1). The tumor measured 3.2 × 2.8 × 3.2 cm and compressed the thalami and the quadrigeminal plate. The MRI intensity at T1W, T2W, T2W/flair appeared to be close to that of normal gray matter, and there was a less homogenous part in the center of the lesion, showing contrast enhancement (Figure 1). The large cerebral veins were dislocated by the tumor.

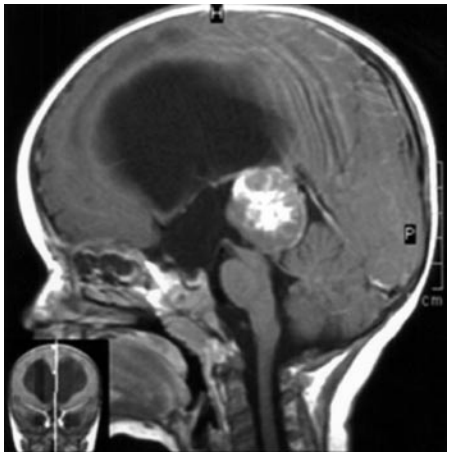


Figure 1.

A gross total resection was reached by transcortical and transventricular approach.

MICROSCOPIC DESCRIPTION

Histologic examination showed a tumor composed of disorderly arranged mature neuronal and glial cells (Figure 2A, B). The glial cells were invariably immunopositive for GFAP (Figure 2C). Some cells had bipolar shapes, while most had the morphological characteristics of reactive astrocytes with interconnecting cell processes. The neuronal cells expressed synaptophysin and neurofilament (Figure 2D). Another tumor component consisted of mature striated muscle cells aligned in bundles and slender fascicles with variable orientation, and in which cross striation was discernible (Figure 3A). These cells were immunopositive for desmin (Figure 3B). The third distinct tumor component was represented by clusters of heavily pigmented cells grouped in sheets and small tubules (Figures 2B, 4). No rosettes or fleurettes were present. The cells of the sheets and tubules had round to polygonal nuclei. There were scattered small calcifications. Broad strands of collagenous tissue divided the tumor tissue in ill-defined areas and lobules. There were rather inconspicuous tumour vessels. Endothelial proliferation was not seen. There were no primitive elements and no anaplastic or dedifferentiated tumor parts. Immunohistochemistry for MIB-1 (Ki-67 antigen) shows a very low labeling index of all tumor components including the pigmented epithelium, ie, less than 1 % of tumor cells. Positivity was found in the nuclei of some striated muscle cells, some fibroblasts and scattered glial cells.

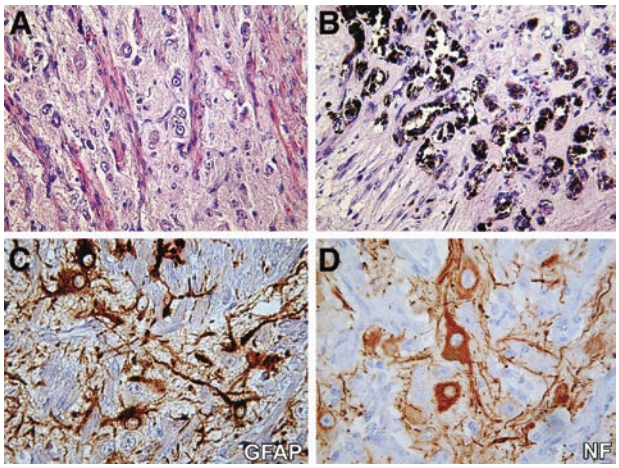
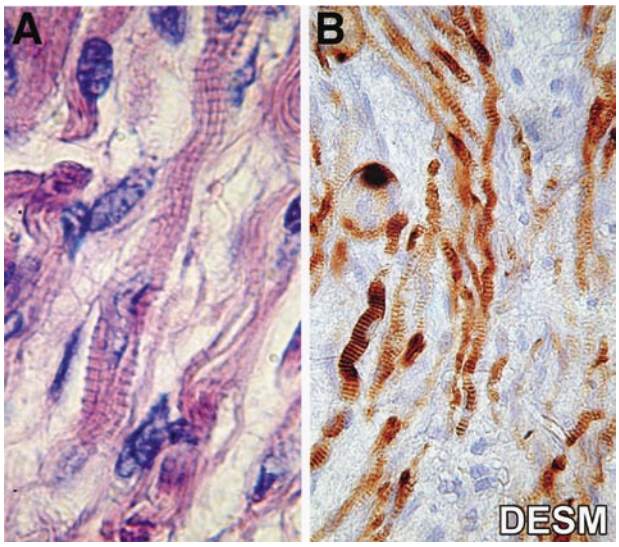


Figure 2.



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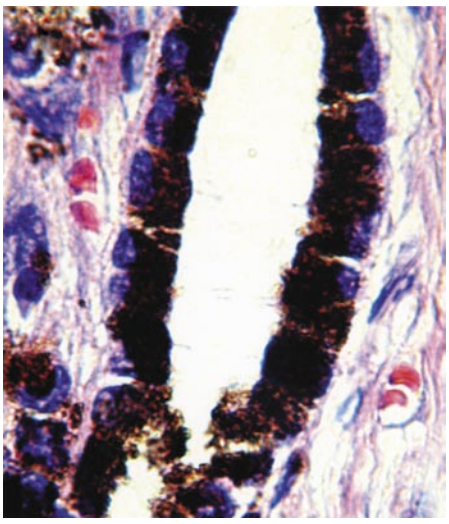

Figure 4.

DIAGNOSIS

Pineal anlage tumor (without immature components).

DISCUSSION

The presence of the melanin-containing cell clusters in this case may evoke the association with tumors designated as "retinal anlage tumors" (Table 1). These lesions, also known by the term "melanotic neuroectodermal tumor of infancy" (MNTI) or "melanotic progonoma" are usually found in the infant jaws. Similar tumors have been described intracerebrally where they generally carry an unfavorable prognosis (9). MNTI-like tumors have been reported in the pineal region and were named "pineal anlage tumours" (2, 3, 5). Primary pineal parenchymal tumors may give rise to a broad spectrum of differentiation (5, 8, 10) reminiscent of embryonic pineal cells which are able to differentiate into striated muscle fibres, pigmented epithelial cells and neuronal cells (1, 11). Apart from differentiated and undifferentiated neuronal cells, retinal receptor-like cells, ependymal cells and the melanotic epithelial cells, mature and immature cartilage and striated muscle cells have been described in the pineal anlage tumor (6, 9, 11). While the MNTI is generally a benign lesion, its cerebral counterpart usually harbors primitive tumor cells and is definitely malignant. Extracerebral MNTIs differ from the malignant cerebral tumors in immunoreactivity for HMB-45, EMA and cytokeratin. Since the pineal gland is a derivative of the neural crest, the pineal anlage tumors may also have derived from neural crest cells (ectomesenchyme) and thus overlap with the constituents of the ectomesenchymomas is obvious.

The term "ectomesenchymoma" was coined for tumors consisting of ectodermal components (usually neuronal cells and S100-positive spindle cells) in combination with embryonal rhabdomyosarcoma . Ectomesenchymomas have been described in a variety of tissues (4) including the orbit (6) and the CNS (5). A problem in making the diagnosis ectomesenchymoma in the present case is the lack of a primitive tumor component, ie, rhabdomyoblastoma. For the same reason, namely, the absense of immature rhabdoid cells, the present case also differs from medullomyoblastomas occurring in the cerebellum (regarded as variant medulloblastomas) and an even more rare tumor called "myoneurocytoma" that was described in the cerebellum of a 6-year-old boy and consisted of immature muscular cells with a mature neuronal component (8). The diverse cell populations of these various tumors is, however, suggestive of an origin from pluripotential neural crest cells (ectomesenchyme) or neural groove.

The present tumor cannot unequivocally be classified into any current classification or nomenclature and we have not found an equivalent case in the literature. Therefore, various diagnoses may be appropriate but we prefer to classify it within the group of pineal anlage tumors. Strictly, diagnoses as "bidermal mature teratoma of the pineal gland" or "melanotic benign ectomesenchymoma," "ectomesenchymal hamartoma" would be even appropriate. The pathogenesis, key to a definite term for this neoplasm, remains obscure.

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	Site	Pigmented (neuro) epithelium	Ganglion cells	Neuro-blasts	Glia	Striated Muscle	Rhabdo-myoblasts	Cartilage	Schwann cells
MNTI	Jaw	+	-	+	+	-	-	-	-
Pineal anlage tumor	Pineal gland	+	+	+	+	+	+	+	-
Ectomesenchymoma	Soft parts; CNS	+	+	+	-	-	+	-	+
Medullomyoblastoma	cerebellum	-	-	+	-	+	+	-	-
Teratoma	various	+	+	+	+	+	+	+	+
Present case	Pineal gland	+	+	-	+	+	-	-	-

Table 1. Components of the respective tumor entities as described in various case reports in the literature. + = sometimes or always present; - = never or very unusually present.

A 15-YEAR-OLD FEMALE WITH PROGRESSIVE MYELOPATHY

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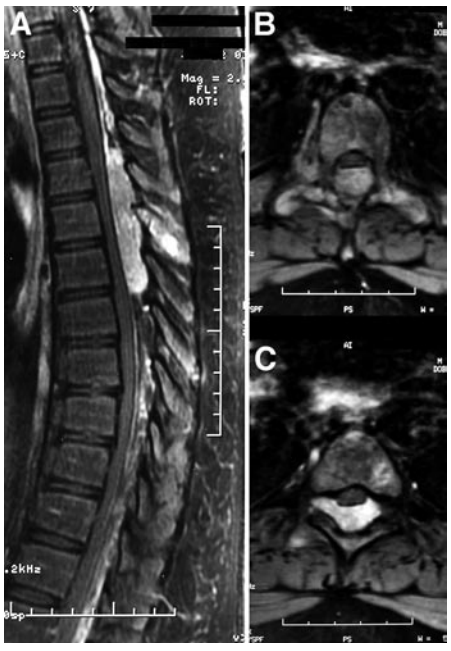
CLINICAL HISTORY

A 15-year-old female presented to the Emergency Room with urinary retention and inability to walk. She had developed progressive low back pain and bilateral leg pain about 2 months prior to presentation. Physical examination demonstrated bilateral positive Babinski reflex, bilateral positive Hoffmann reflex, positive Romberg reflex and positive bulbocavernous reflex. Sagittal T1-weighted MRI scan post Gadolinium (Gd) using fat saturation technique showed an intensely enhancing intraspinal, extradural, 6.5 × 0.8 × 2.3 cm (cranial-caudal, anterior-posterior, transverse) mass, with anterior displacement and compression of the spinal cord (Figure 1A). The mass extended from T3 to T7. Axial T1-weighted MRI scan post Gd at T5 showed bilateral transverse process and spinous process involvement (Figure 1B). Axial T1-weighted MRI scan after Gd showed enhancing tumor in the spinal canal and neural foramina from T4 to T7 (Figure 1C, scan was taken at T5). A decompression surgery was performed.



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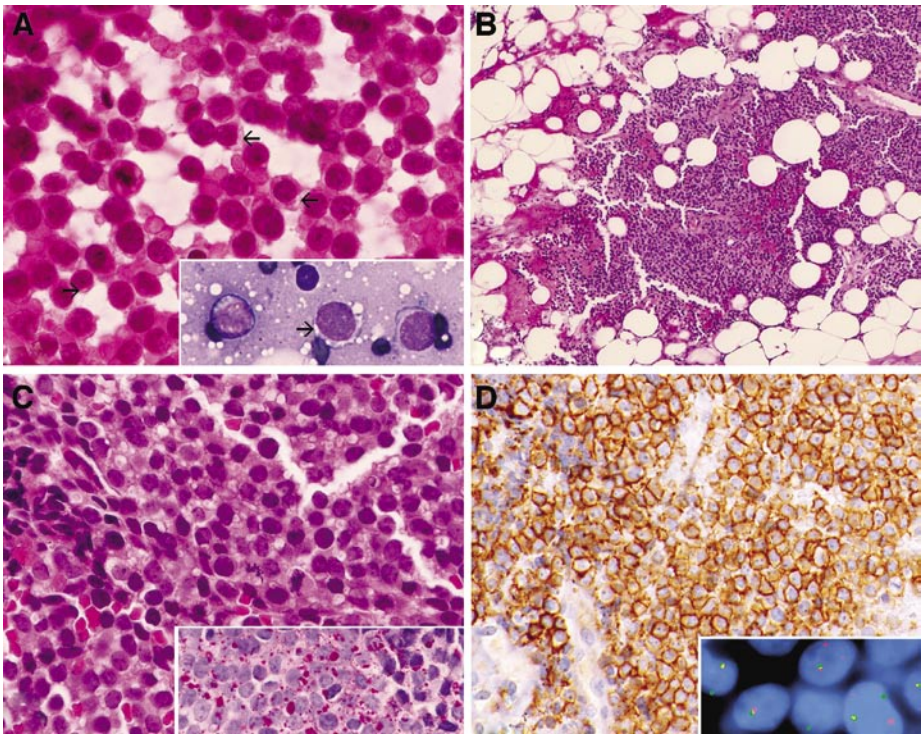

Figure 2.

MICROSCOPIC DESCRIPTION

The surgery yielded a 3.5 × 3.0 × 0.8 aggregate of tan soft tissue fragments. Intraoperative cytologic preparation (squashed preparation) revealed a rather monotonous population of small blue cells with round, centrally located hyperchromatic nuclei; the cytoplasmic membrane was distinct; the cytoplasm was granular (Figure 2A) and contained small cytoplasmic vacuoles (Figure 2A, arrows). These vacuoles were best visualized with DiffQuick stain (Figure 2A, insert). The cytoplasmic vacuoles could not be well appreciated on frozen sections.

Formalin fixed, paraffin embedded sections showed tumor invasion into bone and fibroadipose tissue (Figure 2B). The neoplastic cells were small to medium sized and had mild variation in nuclear size with the smaller ones hyperchromatic to the larger ones. Mitotic figures were common. The cytoplasm was delicate to granular and had small cytoplasmic vacuoles (Figure 2C) that contained substantial amount of periodic acid Schiff (PAS) positive (Figure 2C, insert) diastase sensitive material. The tumor cells demonstrated strongly positive membranous immunoreactivity for CD99 (Figure 2D) but no immunoreactivity for S-100 protein, HMB45 and leukocyte common antigen.

Fluorescent in situ hybridization (FISH) demonstrated fusion signals consistent with reciprocal translocation of t(11;22)(q24;q12) (Figure 2D, inset). The cytoplasmic vacuoles were well demonstrated in resin embedded section (Figure 3, insert). Ultrastructurally, the tumor cells had sparse, inconspicuous cytoplasmic organelles and prominent non-membrane bound cytoplasmic vacuoles that were devoid of cytoplasmic organelles (Figure 3A). Some of these vacuoles contained residual glycogen particles (Figure 3B).

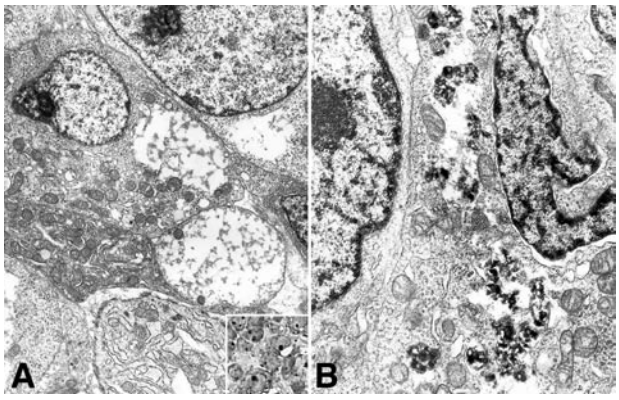

Figure 3.

DIAGNOSIS

Ewing sarcoma/peripheral primitive neuroectodermal tumor.

DISCUSSION

Ewing sarcoma/peripheral primitive neuroectodermal tumor (EWS/pPNET) is a common small round cell sarcoma of bone that occurs predominantly in the metaphysis of long bones in skeletally immature patients and accounts for 6% to 8% of all primary malignant bone tumors. Its peak incidence is in the second decade of life and there is a male predilection. Patients of African descent are rarely affected. Although long bones, pelvis, and ribs are the common sites, any bone can be affected. Primary vertebral EWS/pPNETs are well documented and should be seriously entertained when a vertebral extradural/epidural mass occurs in young patients (1, 4, 5). The prognosis of patients with EWS/pPNET arising in the spine is worse than those with tumors occurring in the limbs but better than those with tumors arising in the pelvis (1); vertebral EWS/pPNETs have increased frequency of cerebral and skeletal metastases as compared to EWS/pPNETs occurring in other locations (1). There is no significant correlation between the level of vertebral involvement and the length of disease-free survival, overall survival, or incidence of metastasis (4).

Histologically, EWS/pPNET have features of undifferentiated mesenchymal cells. The tumor cells are typically small cells with round, centrally located hyperchromatic nuclei and a small amount of cytoplasm; the tumor cells grow in solid, densely packed sheets and nests filling intertrabecular space and necrosis is frequent. A biphasic population of light and dark cells is common. Differentiation of EWS/pPNET from lymphoma is always a concern during intraoperative consultation. A cytologic preparation will greatly assist the identification of lymphoglandular bodies that are typical for lymphomas but not EWS/pPNET.

The amount of cytoplasmic glycogen in EWS varies from scant to substantial. In this case, a large amount of glycogen gives rise to vacuolated cytoplasm in cytologic preparation, paraffin sections, and at ultrastructural level. This feature may be of diagnostic help but is probably limited only to EWS/pPNET with substantial amount of glycogen. The cytoplasmic vacuoles have been described in so-called atypical EWS; cells from these tumors are larger than those in conventional EWS, exhibit greater heterogeneity, and may have focal spindle-cell features. These features are more often seen in recurrent and treated EWS but can also be present in primary EWS. There is no difference in the clinical behavior of classic and so-called atypical Ewing sarcomas (2). Our present case, however, does not possess features of the so-called atypical EWS other than cytoplasmic vacuoles.

Neuroendocrine differentiation similar to pPNETs is seen in EWS, which may possess Homer Wright rosette, immunoreactivity to synaptophysin, and neurosecretory granules under electron microscope. Most authors consider pPNET and EWS to be related or indistinguishable entities within a continuum of overlapping immunohistochemical and morphological features. Immunohistochemical demonstration of the MIC2 gene product (CD99 antigen) is typically seen in EWS but can also be present in lymphomas, synovial sarcoma, and rhabdomyosarcoma (3); results must be interpreted with care (2).

Reciprocal translocation between chromosomes 11 and 22 involving bands q24 and q12, t(11;22)(q24;q12), occurs in approximately 90% of Ewing sarcomas, pPNETs and Askin tumors. The translocation produces a fusion gene EWS/FLI-1 that places the FLI-1 gene under the control of EWS promoter leading to overexpression of the FLI-1-protein, an important step in tumorgenesis of EWS. This translocation serves as an important diagnostic feature (2) for separating EWS from tumors with similar morphologic and immunohistochemical profile such as metastatic neuroblastoma and metastatic neuroendocrine carcinoma to the bone. The fusion gene, EWS/FLI-1, is well demonstrated in this case; FISH shows fusion (yellow or red-green signals) of the FLI-1 gene (green signals) with EWS gene (red signals) (Figure 2D, insert).

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CASE OF THE MONTH: ABSTRACT

January 2005. **A boy aged 7 years was found to have a tumor arising from the roof of the fourth ventricle. Histopathologically, part of the tumor appeared as a PNET, while neuroglial tissue, striated and smooth muscle, cartilage and small glandular structures were present in other regions. Tumor cells in both primitive and mature elements showed a loss of chromosome 17p accompanied by a gain of 17q, a pattern consistent with the presence of an isochromosome 17q. This abnormality is not characteristic of intracranial germ cell tumors, but is present in over 30% of medulloblastomas. On the basis of the histologic and genetic abnormalities, we propose a diagnosis of PNET with multilineal differentiation.**

February 2005. **Case report of a 10-month-old boy with a large tumor located in the pineal gland, consisting of glia, ganglion cells, pigmented neuroepithelium and striated muscle, without immature components. The combination of neuroectodermal and mesenchymal constituents includes entities as pineal anlage tumor (melanotic neuroectodermal tumor of infancy, MNTI), ectomesenchymoma, medullomyoblastoma, and teratoma in the differential diagnosis. Lack of immature elements in this case, however, eliminates ectomesenchymoma and medullomyoblastoma from the differential diagnosis. Retinal anlage tumors, to be considered as MNTI at the site of the pineal gland, usually harbor immature components as well. Therefore, the present case does not match strict criteria of any of the categories mentioned and therefore we have designated it as a "pineal anlage tumor (without immature components)".**

March 2005. **A 15-year-old female presented with urinary retention, inability to walk and low back pain. MRI disclosed an elongated epidural mass in the thoracic spine with cord compression and invasion into the surrounding bone and soft tissue. Cytologic preparation at intraoperative consultation disclosed a rather monotonous small tumor cells with hyperchromatic nuclei and vacuolated cytoplasm. These vacuoles were best visualized with DiffQuick stain. Pathologic studies revealed an Ewing sarcoma/peripheral primitive neuroectodermal tumor (EWS/pPNET) with typical features including periodic acid Schiff positive diastase sensitive cytoplasmic substance; strong membranous pattern of immunoreactivity for CD99, and a reciprocal translocation of t(11;22)(q24;q12) that was demonstrated by fluorescent in situ hybridization (FISH). The vacuolated cytoplasm was produced by glycogen as demonstrated by electron microscopy. Although primary vertebral EWS/pPNETs are uncommon, they should be considered in the differential diagnoses of extradural/epidural mass of the spine in young patients.**

For a more complete discussion of these cases, additional micrographs, and information regarding submission of cases, please access the *Brain Pathology* web site at *http://www.brainpathology.com*. We welcome comments about these or similar cases our readers may have encountered.