NOVEMBER 2004: INTRADURAL MASS OF THE CAUDA EQUINA IN A WOMAN IN HER EARLY 60s

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Clinical history. A 63-year-old woman presented with a history of continuously aggravating lower back pain, sometimes radiating down the back of her thighs, of approximately 4 months duration. In the weeks preceding the initial clinical evaluation, she experienced urinary urge incontinence. There were no pareses or sensory disturbances. The other aspects of the clinical history were completely unremarkable.

Radiology. T1-weighted magnetic resonance imaging of the spinal cord revealed a sharply-delineated, partly cystic intradural mass with inhomogenous contrast-enhancement at the level of the cauda equina (Figure 1). T2-weighted imaging showed serpentine structures at the upper pole, corresponding to ectatic vessels. Axial sections revealed that the tumor filled the entire spinal canal but had not caused bony erosion. An ependymoma of the cauda equina was suspected and the patient was operated.

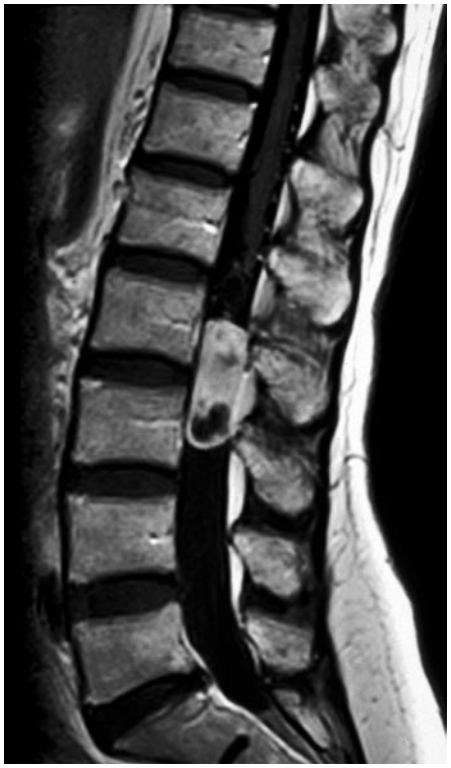

Figure 1.

Macroscopic findings. Intraoperatively, the cranial end of the tumor was found to be attached directly to the conus. A single arterial feeder was present between the lower end of the conus and the mass, and was accompanied by several ectatic veins. The oval-shaped tumor was ensheathed by a delicate collagen capsule and displayed a soft, homogenously brown-reddish cut surface. The tumor mass was removed in toto.

Microscopic findings. At low magnification, the tumor appeared moderately cellular, relatively monomorphic, and contained several areas with cystic structures. At higher magnification, regions composed of small uniform cells were found to be interrupted by areas of diminished cellularity. In addition, the tumor cells often formed perivascular pseudorosettes with tumor cell processes arranged radially around blood vessels (Figure 2A). In several regions, structures resembling ependymal canals were identified that were composed of columnar cells lined around a central lumen (Figure 2B). Occasionally, hemosiderin deposits were found in the vicinity of blood vessels (not shown). The tumor cells possessed small, round-to-oval, isomorphic nuclei with sharply delineated nuclear membranes, delicate stippled chromatin and small, inconspicuous nucleoli; up to 2 mitoses per 0.19 mm^2 visual field were identified. Interspersed between the predominating small-cell tumor component, occasionally mature ganglion cells with large vesicular nuclei and prominent nucleoli could be discerned; the ganglion cells were arranged either in small clusters or scattered as single cells (Figure 2C, arrows). In addition, larger islet-like fields composed of cells displaying a phenotype transitional between the small tumor chief cells and mature ganglion cells were found (Figure 2C, islet marked by arrowheads).

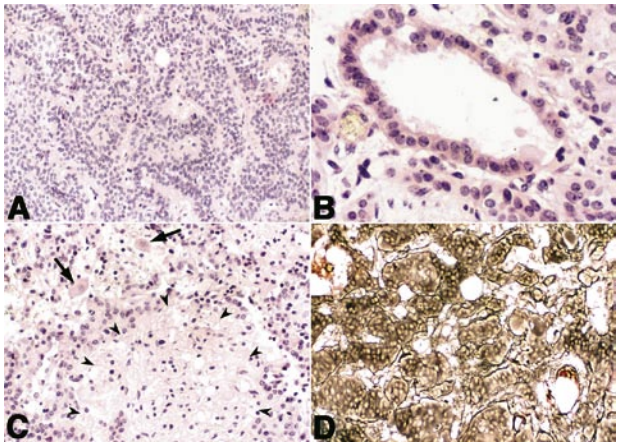

Figure 2.

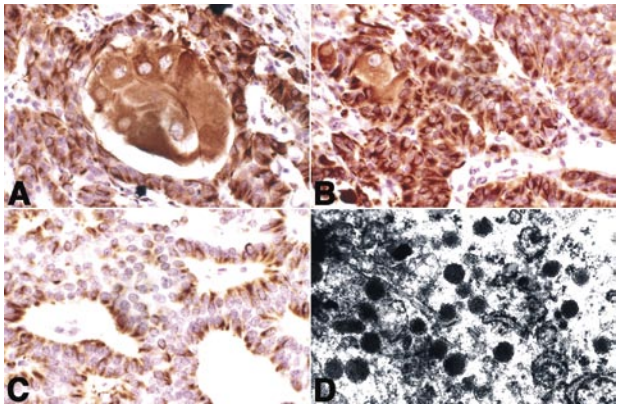

Figure 3.

Reticulin staining revealed that aggregates of tumor cells were circumscribed by a delicate connective tissue framework (Figure 2D).

Immunohistochemically, both the ganglionic cells and the small tumor chief cells were strongly immunoreactive for neurofilament (Figure 3A) and synaptophysin (Figure 3B), as well as neuron-specific enolase and chromogranin (not shown). GFAP expressing sustentacular cells were clustered in the vicinity of small nests of ganglion cells, and were also scattered between the small chief cells. Many tumor cells displayed perinuclear immunoreactivity for cytokeratin, and especially the columnar cells that surrounded lumina reminiscent of ependymal canals were strongly cytokeratin-positive (Figure 3C). The MIB-1 labeling index focally reached 5% (not shown). Ultrastructurally, numerous perinuclear dense-core granules were detected in the tumor cells (Figure 3D).

Diagnosis. Paraganglioma of the cauda equina, gangliocytic variant.

Discussion. The clinical and radiological findings, as well as the first-glance morphological impression lead to the preliminary assumption, that the tumor in this 63-year-old woman was an ependymoma. In particular, the perivascular pseudorosettes, ependymal canal-like structures and the monomorphic cellular pattern seemingly supported this diagnosis. However, the presence of a tumor capsule, the compartmentalization of tumor cells into zellballen surrounded by reticulin fibers, and the presence of ganglionic cells were untypical of ependymoma and instead were indicative of paraganglioma with a gangliocytic component. Immunoreactivity of the tumor cells for neuroendocrine antigens, the detection of GFAP-positive sustentacular cells and the ultrastructural confirmation of neurosecretory granules substantiated this diagnosis.

Paragangliomas arise from specialized neural crest cells associated with autonomic ganglia throughout the body. Most frequently, they occur in the glomus caroticum or the glomus jugulare. In the CNS, paragangliomas are almost exclusively located in the cauda equina (9). The first case of spinal paraganglioma was reported in 1970; interestingly, this tumor was described as "secretory ependymoma" (6). To date, more than 120 cases of paragangliomas of the CNS have been reported. Paragangliomas of the cauda equina usually occur in adults; the mean age at presentation is 47 years (10) with a reported age range of 12 to 71 years (8, 9). The male:female ratio is 1.4:1. Cauda equina paragangliomas correspond to WHO grade I and are usually cured by surgical resection. The recurrence rate is approximately 4%, and CSF-seeding or distant metastases are extremely rare (1). In a study of 31 cases, ganglionic differentiation was detected 45% of the tumors (10). In another study of 30 patients with spinal paraganglioma, ganglion cells were detected in only one case (7).

Clinically, the most common symptom of cauda equina paraganglioma is lower back pain accompanied by sciatica. Endocrine activity of these tumors is extremely rare, and only 2 cases with functional hormonal activity have been reported (2, 11). Radiologically, paragangliomas of the cauda equina are typically hypo- or isointense to the spinal cord on T1-weighted images, hyperintense on T2-weighted images, and strongly contrast-enhancing (9). Serpentine vessels, as observed in the present case, are not uncommon and are considered a major clue to the diagnosis of a highly vascular lesion (1).

The histogenesis of cauda equina paragangliomas remains enigmatic. Interestingly, Caccamo et al have described a cauda equina tumor with both ependymal as well as paraganglionic differentiation, confirmed both immunohistochemically and ultrastructurally (3). The authors speculated that this tumor arose from elements normally found in the human filum terminale, such as ependymal cells, ganglionic neurons and neuroblasts. Interestingly, in teleost fish, ependymal cells lining the central canal of the distal spinal cord, can differentiate into large neurosecretory cells (4). Moreover, in human newborns the existence of ependymal cells with neurosecretory activity has been reported in the filum terminale (6). In rodents, cerebral ependymal cells have even been described as origin of neural stem cells (5). Despite these studies, any transdifferentiation-hypotheses regarding ependymal and neuroendocrine/neuronal cells in humans are at present highly speculative.

To conclude, the clinical, radiographic and morphological similarity between ependymomas and paragangliomas in the cauda equina region has repeatedly lead to substantial diagnostic confusion. Ependymal tumors are far more common in this region than paragangliomas, which can therefore easily be overlooked on conventionally stained sections. Immunohistochemical and/or ultrastructural analyses are essential to distinguish these tumors in the cauda equina region.

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DECEMBER 2004: ONE-YEAR-OLD GIRL WITH AGGRESSIVE SKULL TUMOR

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Clinical history. A 12-month-old girl was admitted to the hospital with an ill-defined subcutaneous mass in the left parietal region. When she was 4 months, the mother noticed a small swelling on the left side of the head, just above the ear. It enlarged quickly until it reached a disfiguring size. Outside radiological studies revealed a tumor arising in the left parietal bone. She underwent excision of the mass and reconstruction of skull defect with bone graft. The child was well until 8 months of age, when skin ulcers and multiple masses developed in the vicinity of previous excision, complicated by CSF leak and infection of bone graft. She was referred to KFSH&RC for further management. On admission, she was febrile and lethargic but alert. There were multiple, firm and tender skull masses in left temporo-parietal area, the biggest of which measured 6 × 7 × 4 cm, and an ulcer measuring 2 × 3 cm in the left supra-auricular area over the exposed bone flap.

CT and MRI examinations showed a skull tumor in the left temporo-parietal area, infiltrating the soft tissue around cranioplasty flap, dura mater and cerebellum as well as the left temporal and parietal lobes, and the content of left orbit (Figure 1). The neoplasm was markedly enhancing after contrast injections. Craniotomy was performed in order to repair CSF leak, rebiopsy and debulk the extracranial and part of the intracranial tumor component.

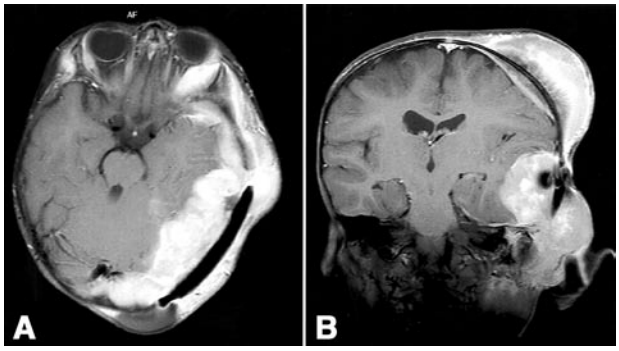
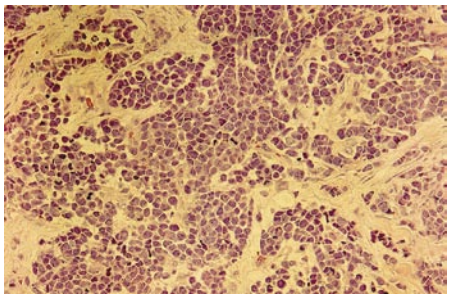


Figure 1.

Pathological findings. Microscopic examination revealed highly anaplastic small cell tumor (Figure 2). Neoplastic cells showed, nuclear hyperchromasia and atypia, high nuclear/cytoplasmic ratio, frequent mitotic figures, numerous apoptotic nuclei, and scattered small foci of necrosis. There was also a scanty component of pigmented cuboidal epithelioid cells, distributed at the periphery of anaplastic cell nests, as minute tubular structures (Figure 3A), or in small foci surrounded by a dense connective tissue stroma. Pigmented epithelium was positive with a Fontana-Masson stain (Figure 3B) and more frequently seen in the specimen from the first surgery. The tumor cells were uniformly positive for synaptophysin (Figure 4A, red) while epithelial cells were positive for AE1/AE3 cytokeratins (Figure 4A, dark brown), epithelial membrane antigen, S-100 protein and HMB45 (Figure 4). Double immunostains revealed intermediate cellular forms with overlapping immunoreactivities for synaptophysin and cytokeratins (Figure 4A, white arrow) as well as cytokeratins and HMB-45 (Figure 4B, black and red labeling respectively), indicating origin of both cellular components from a common precursor. MIB-1 was positive in more than 80% of tumor nuclei. There was no immunoreactivity for desmin, smooth muscle actin or GFAP. Only occasional tumor cells contained melanin but were slightly positive for neurofilament or HMB-45 antibodies.

Limited electron microscopic examination revealed cells containing premelanosomes.



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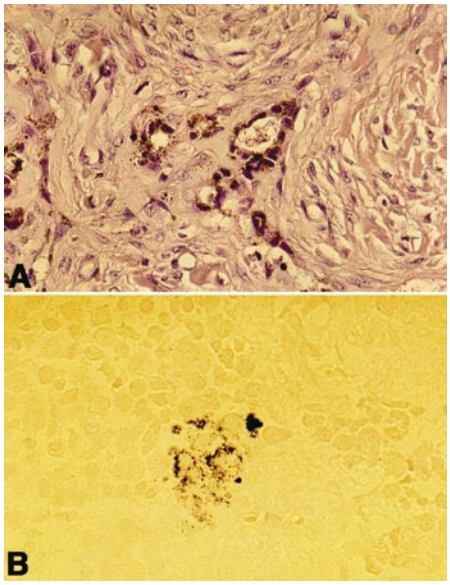

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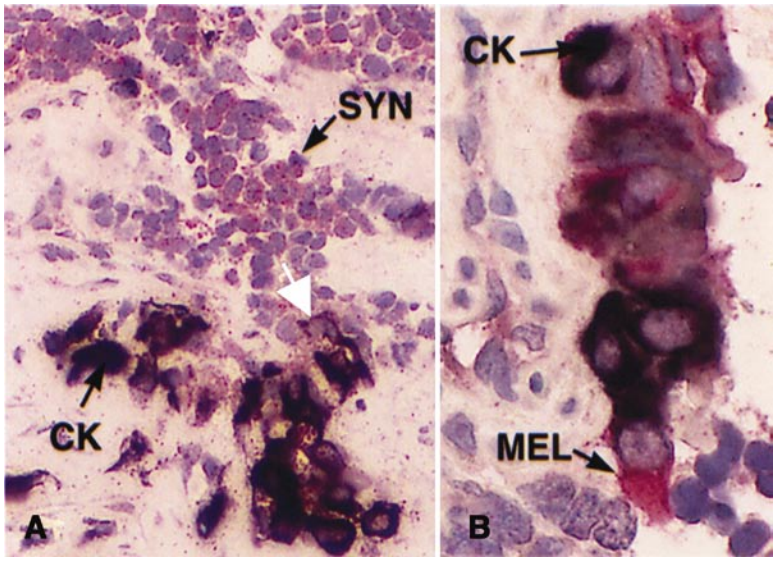

Figure 4.

Diagnosis. Malignant melanotic neuroectodermal tumor of infancy

Discussion. The melanotic neuroectodermal tumor of infancy (MNTI) is a rare, usually benign pigmented lesion that characteristically involves the maxilla (70%), and less frequently other sites such as skull (10%), mandible (6%) and brain (1%-4%). On rare occasions, the neoplasm has been found in the skin, epididymis, uterus, ovary and mediastinum (3). In approximately 6% to 9% the tumour could be multifocal (3). MNTI was first described by Krompecher in 1918 as a congenital "melanocarcinoma." Since then, other synonyms such as a melanotic epithelial odontoma, retinal anlage tumour and melanotic progonoma were also used. However, the modern terminology is restricted to "melanotic neuroectodermal tumor of infancy." Due to usually extra-axial location of MNTI, the present WHO classification of the brain tumors does not incorporates this neoplasm. Despite of some morphological similarities to the melanotic medulloblastoma (6), MNTI is considered an unrelated, benign tumor entity that can be easily distinguished from medulloblastomas on the basis of immunoreactivity for EMA, HMB-45 and cytokeratins. These immunohistochemical properties of MNTI, separate this entity also from other pigmented neuroectodermal tumors, such as melanotic Schwannoma, melanocytoma or pineal gland neoplasm (6). Electron microscopic studies consistently show the presence of pigmented epithelial cells with abundant premelanosomes and melanin granules, non-melanotic neuroblastic cells, and poorly differentiated anaplastic cell component (3). Molecular studies revealed strong expression of melanotransferrin within the tumor and provided proof for origin of neoplasm from the neural crest precursors (4). Borello and Gorlin reported increased 3-methoxy-4-hydroxy melanic acid (VMA) in urine supporting this hypothesis (1). On the basis of immunohistochemical studies, it has been suggested the MNTI recapitulates retina at fifth week of gestation (5). Review of the previously reported MNTI, indicates that approximately 3% of cases can behave in a malignant fashion (3). The malignant variant of MNTI is an aggressive neoplasm that more often spreads by local extension rather than metastases. This tendency to a local recurrence rather to dissemination in CSF or extracranial sites, further distinguishes this tumor from medulloblastoma. Recurrence rate remains approximately 15% and metastases to the lymph nodes, liver and bone have been described on a few occasions. Increased signal intensity on T1 and decreased signal on T2 weighted images may suggest the presence of melanin content on MRI, and guide to a correct diagnosis on radiological studies. The malignant variant of MNTI almost invariably has a poor prognosis. Only in 2 cases (2,6), disappearance of metastases was observed after the treatment with Cyclophosphamide and Carboplatin. However, the extent of the disease in our patient reached the point beyond any justification for an aggressive therapy, and she died 2 months after the last surgery, approximately 8 months from the onset of the disease.

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CASE OF THE MONTH: ABSTRACT

October 2004. **A 49-year-old right-handed man developed progressive cognitive difficulties over a 4-month period. There was impairment in recent memory, calculations and language. He also developed fatigue, weight loss, gait imbalance and urinary incontinence. Past history included transfusion- associated Hepatitis C. Neurologic exam showed mild dysarthria, dysnomia, left sided neglect, bilateral Babinski signs, and a prominent grasp reflex. Laboratory testing provided no positive etiologic data. An EEG showed generalized intermittent slowing suggestive of a diffuse encephalopathy and decreased background in the right hemisphere, suggestive of a structural lesion. MRI showed multiple areas of high signal on FLAIR imaging and patchy enhancement. FDG-PET showed multi-focal areas of increased uptake, correlating with the abnormal areas on MRI, on a background of decreased uptake. A 4-vessel cerebral angiogram showed no abnormalities. A brain biopsy showed diffuse infiltrates of large malignant cells that were immunoreactive with antibodies to CD20, diagnostic of diffuse large B cell lymphoma. In summary, the clinical presentation suggested bilateral hemispheric involvement, which was supported by physical examination, EEG, MRI, and PET scans. The differential diagnosis for this presentation is limited to demyelinating disease such as multiple sclerosis, vascular dementia, and infiltrating neoplasm such as glioblastoma multiforme or lymphoma. Diagnosis was made by morphologic and immunohistochemical analysis of brain tissue.**

November 2004. **A 63-year-old woman presented with slowly aggravating lower back pain and recent urinary urge incontinence. MRI revealed a sharply-delineated, partly cystic intradural mass with inhomogenous contrast-enhancement and ectatic vessels at the upper pole. An ependymoma was suspected, and the tumor was resected in toto. Histologically, at first glance, the tumor strongly resembled an ependymoma, showing a monomorphic cellular pattern, perivascular pseudorosettes and ependymal canal-like structures. However, the finding of a delicate collagen capsule, compartmentation of tumor cells into zellballen and the presence of ganglionic cells were untypical. These features were indicative of a paraganglioma with a gangliocytic component. Immunoreactivity of the tumor cells for neuroendocrine antigens, the detection of GFAP-positive sustentacular cells and the ultrastructural confirmation of neurosecretory granules substantiated this diagnosis. The clinical, radiological and morphological similarity between ependymomas, which are far more common in the cauda equina region than paragangliomas, has led to substantial diagnostic confusion in the past.**

December 2004. **Twelve-month old girl presented with recurrent subcutaneous lesion in the left parietal region, one year after excision of a "benign" tumor. An MRI demonstrated left temporo-parietal skull tumor infiltrating the soft tissue, surrounding craniotomy flap, and extending to the brain parenchyma. Biopsy revealed biphasic neoplasm displaying nests of poorly differentiated neuroblastic cells positive for synaptophysin and pigmented cuboidal epithelioid cell positive for keratins, epithelial membrane antigen and MHB-45. In addition, some neoplastic cells were immunoreactive for synaptophysin as well as HMB-45 and epithelial markers, suggestive of their origin from a common progenitor. Interestingly, cell with the neuroblastic immunophenotype displayed 80% nuclear MIB-1 reactivity indicating that the aggressiveness of the neoplasm was confined mostly to this pattern of differentiation. The overall histological features are consistent with a rare malignant variant of a melanotic neuroectodermal tumor of infancy.**

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.