Melanotic Neuroectodermal Tumor of Infancy Disseminated by a Ventriculoperitoneal Shunt and Diagnosed from the Inguinal Sac

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Summary: Melanotic neuroectodermal tumor of infancy (MNTI) is a rare congenital neoplasm that originates from the neural crest cells, which give rise to the melanocytes of the skin and leptomeninges. We report a case of MNTI with neurocutaneous melanosis of a 28-month-old girl. She was born with hydrocephalus and several large congenital giant nevi. There were no findings except for hydrocephalus, after a ventriculoperitoneal (VP) shunt operation performed when she was 6 months old. She was operated on for a growing inguinal mass at 8 months. The specimen from the inguinal sac was positive for HMB45, vimentin, chromogranin, and neuron-specific enolase. Brain magnetic resonance imaging showed an extensive enhancing extra-axial mass with high signal intensity, along the cerebral spinal fluid space. We report a rare case of MNTI diagnosed from an inguinal hernia sac, with a disseminated clinical manifestation.

Key Words: infant, melanotic neuroectodermal tumor, neurocutaneous melanosis

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Melanotic neuroectodermal tumor of infancy (MNTI) is a rare, but distinct neoplasm in infants. 1 The tumor is primarily located on the orofacial bones, involving the maxilla in 70% of cases. There is also infrequent involvement of other sites, such as the epididymis, mediastinum, femur, and ovary. 2–5 There is no anatomic precursor, and the possibility of a phylogenetic ancestral form has been described. 6 This tumor consistently behaves in a benign manner, except for several previous examples in the literature. The potential for recurrence or metastases cannot be predicted by the gross or histologic characteristics of the tumor. 5 A review of literature revealed metastases in 13 patients (6.6%) of 195 reported cases. 7

Neurocutaneous melanosis is a rare congenital syndrome, characterized by large or multiple congenital melanocytic nevi, and benign or malignant pigment cell tumors of the leptomeninges. 8–10 The most frequent pigmented cell tumors in the central nervous system are melanomas, and MNTI associated with neurocutaneous melanosis has not been well described. We report here a case of malignant MNTI diagnosed from an inguinal hernia sac with a disseminated, malignant clinical manifestation.

CASE REPORT
A girl, aged 28 months, visited our hospital with right groin pain. A palpable, soft, reducible mass in the right groin region was noted for the 8 months before admission. As the size of the mass increased, she was operated on for a suspected inguinal hernia. No previous radiologic examinations had been performed in our hospital.

In conducting her history, we found that she was born with an oversized head, and consequently, diagnosed with hydrocephalus at 4 months after birth at which point she received a VP shunt due to increased intracranial pressure. At that time, all her radiologic examinations, including a brain magnetic resonance imaging had nonspecific findings, except for the hydrocephalus.

On physical examination, many hairy dark plaques were noted all over her body. (Fig. 1A) The clinical impression was congenital giant melanocytic nevi. On pathologic examination, the nevus was a compound type melanocytic nevus. On operation, the hernia sac was 6 cm in diameter, the wall was thin without any content, and the nature of the hernia was indirect. To remove the hernia sac, high ligation and biopsy were performed. Immunohistochemical reactions and flow cytometric analyses were carried out on the formalin-fixed, paraffin-embedded tissue.

On pathologic examination, the hernia sac was irregularly thickened due to fibrosis, and black pigments were noted in the wall. Deep sections of the same specimen, and a grosser recut showed tumor cells infiltrating the lining of hernia sac. A biphasic microscopic pattern, with alveolar or tubular collections of epithelioid round cells (Fig. 2A), and solid nests of small hyperchromatic cells were noted (Fig. 2B). The epithelioid tumor cells typically had abundant brown intracellular melanin granules, and there were occasional mitoses. The second type of lesion cell was a small, dark, round cell with a hyperchromatic nucleus and minimal cytoplasm. These cells had the appearance of neuroblasts and were aggregated in loose nests or islands in a background of fibrovascular stroma. Fontana-Masson and Prussian blue showed that the pigment were melanin (Fig. 3). Immunohistochemical staining for cytokeratin, chromogranin, vimentin, HMB45, S-100 protein, CD99, and epithelial membrane antigen revealed that the tumor cells were diffusely positive for HMB45, vimentin, chromogranin, and neuron-specific enolase, and were focally positive for S-100 protein, epithelial membrane antigen, and cytokeratin. The tumor cells were negative for CD99 and desmin. Thus, this tumor was diagnosed as a rare, disseminated, malignant form of MNTI, showing neural differentiation.

After diagnosis, abdominal computed tomography showed a large amount of ascites and peritoneal thickening. There was diffuse spinal enlargement with meningeal thickening and enhancement. Enhancing soft-tissue masses were also noted in the right cardiophrenic region and left diaphragm. Brain magnetic resonance imaging showed an extensively enhancing extra-axial mass along the cerebrospinal fluid (CSF) spaces at the meninges in the cerebrospinal fluid (CSF).
posterior fossa and in the suprasellar prepontine and premedullary cisterns. All of these masses showed high signal intensity with T1 weighted image (Fig. 1B).

Cytologic examination, using CSF revealed many melanin-containing epithelioid tumor cells without free melanin granules. Bone marrow and bone scans were negative for tumors. On laboratory examinations, lactate dehydrogenase/uric acid was 1404/6.0 IU/L. Serum norepinephrine was 285 pg/mL (normal range, 100 to 450 pg/mL), epinephrine was 98 pg/mL (normal range, 0 to 140 pg/mL), and dopamine was 95 pg/mL (normal range, 0 to 30 pg/mL). Urine vanillylmandelic acid (VMA)/Cr was 5689 μg/mgCr (normal range, <13 μg/mgCr) and homovanillic acid/Cr was 53.5 μg/mgCr (normal range, <13.5 μg/mgCr). Other tumor markers, such as human chorionic gonadotropin, α-fetoprotein, and carcinoembryonic antigen, were within normal limits. Chromosome analysis, using bone marrow cultured cells, revealed an usual number of chromosomes, without any structural abnormalities (46, XX).

Flow cytometric examinations, using paraffin-embedded inguinal tissue, showed an aneuploid tumor with a DNA index of 1.3.

The patient was started on anticancer chemotherapy with mesna, ifosfamide, adriamycin, and vincristine. The size of the tumor decreased remarkably after the first and second trials of chemotherapy. The VP shunt was completely occluded after 2 cycles of chemotherapy. We removed the occluded VP shunt and performed a new VP shunt operation. In specimens from the occluded shunt lumen, histologic examinations showed deeply

FIGURE 1. Many hairy dark plaques were noted on the whole body (A) and brain magnetic resonance imaging showing an extra-axial mass along the cerebrospinal fluid spaces, at the meninges of the posterior fossa, and in the suprasellar prepontine and premedullary cisterns with high signal intensity in the T1 weighted image (B).

FIGURE 2. Biphasic tumor components with alveolar or tubular collections of epithelioid cells (A) and sheets of small hyperchromatic cells resembling neuroblasts (B) (× 400).
pigmented tumor cells, with the same immunohistochemical findings as the inguinal sac. After chemotherapy, the patient developed a leukopenic state with fever. The urine culture showed *Escherichia coli*, and the blood culture showed coagulation-negative staphlococcus. She recovered completely after supportive care and treatment with the appropriate antibiotics. However, she developed heart failure due to increased ascites and pleural effusion. She died from respiratory suppression involving the brain stem, 5 months after diagnosis. This was an exceptionally rare case of MNTI diagnosed from an inguinal hernia sac, with a disseminated, malignant clinical manifestation.

**DISCUSSION**

The rare MNTI is a congenital neoplasm of unclear histogenesis. The lesion was reported under a variety of different names, as succeeding authors attempted to identify the cell of origin. In 1966, Borello and Gorlin reported a case displaying high urinary excretion of VMA. They suggested that the tumor originated in the neural crest, and proposed the term MNTI. Since then, numerous histochemical, immunohistochemical, electron microscopic, and tissue culture studies have supported the neural crest origin and confirmed the preferred term of MNTI. This tumor is considered to arise from the neural crest cells in the embryo that are responsible for much of the development of the maxillofacial region. Extraoral tumors have been reported that arose from the mediastinum, brain, anterior fontanelle, epididymis, and soft tissues of the arm. Most patients present with the tumor in the first year of life, usually within 1 to 6 months of age. The mean age of patients with MNTI is 4.3 months. Our patient was 28 months old and had suffered from increased intracranial pressure after birth. Malignant variants represent <5% of the reported cases and thus far, only 200 cases have been reported. Our case adds 1 more case of malignant MNTI. Since then, numerous histopathologic examinations were inconclusive, the presence of multiple, large congenital melanocytic nevi, the increased intracranial pressure after birth, and the coexistence of meningieal thickening and enhancing extra-axial mass along CSF spaces strongly supported the possibility that leptomeningeal melanosis might be the origin of the MNTI.

To confirm our diagnosis, the origin of the tumor must be identified, and the pathologic distinction of MNTI from melanocytosis or melanomas. Both MNTI and neurocutaneous melanomas are postulated to represent congenital errors in the morphogenesis of the embryonal neuroectoderm. The neuroectoderm originates from neural crest cells that give rise to the melanotic cells of both the skin and leptomeninges. Increased urinary excretion of VMA and homovanillic acid, increased serum dopamine (a precursor of norepinephrine) levels, the typical histologic findings of 2 cell populations, immunohistochemical positivity for cytokeratin, neuron specific enolase, and chromogranin could rule out the possibility of melanocytosis or melanomas.

In this patient, we decided to perform intensive chemotherapy, due to the disseminated state with aneuploidy, although many cases with MNTI are first locally controlled in the orofacial area. The chemotherapy consisted of ifosfamide or cyclophosphamide, doxorubicin, and vincristine, such as neuroblastoma or primitive neuroectodermal tumor treatment strategy. Initially 2 cycles were effective for reducing tumor size in our patient, even though she reached a refractory state after 2 cycles. We did not consider chemotherapy including etoposide, in disseminated MNTI.

This case can be summarized as MNTI that might occur in the meninges in congenital neurocutaneous melanosis. This was histologically diagnosed from the inguinal hernia sac disseminated by a VP shunt.
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REFERENCES