Neurocutaneous melanosis presenting with hydrocephalus

Case report and review of the literature

FRANK L. ACOSTA JR., M.D., DEVIN K. BINDER, M.D., PH.D., A. JAMES BARKOVICH, M.D., ILONA J. FRIEDEN, M.D., AND NALIN GUPTA, M.D., PH.D.

Departments of Neurological Surgery, Radiology, and Dermatology, University of California, San Francisco, California

Neurocutaneous melanosis (NCM) is a rare congenital neurocutaneous syndrome characterized by large or multiple congenital melanocytic nevi and benign or malignant melanocytic tumors of the leptomeninges. The authors report the case of a 5-month-old girl with congenital giant melanocytic nevi who presented with symptomatic hydrocephalus. A right frontal ventriculostomy was performed in the patient. Magnetic resonance imaging demonstrated melanocyte accumulation within the hippocampi, medulla, and cerebellum. Cerebrospinal fluid cytology revealed no presence of melanocytes. A ventriculoperitoneal shunt was placed; the patient’s neurological condition improved and she was discharged home in good condition. The diagnosis of neurocutaneous melanosis should be considered in a case in which an infant or child presents with hydrocephalus and either large or multiple (≥ 3) congenital melanocytic nevi. Although our patient’s neurological status improved following treatment for hydrocephalus, there is no definitive therapy for NCM and symptomatic patients have a poor prognosis. Our case illustrates to the neurosurgeon the importance of recognizing the likelihood of underlying pathological conditions of the central nervous system in a child with cutaneous melanocytic nevi.

KEY WORDS • melanosis • hydrocephalus • ventriculoperitoneal shunt • pediatric neurosurgery

Neurocutaneous melanosis is a rare, sporadic congenital neurocutaneous disorder characterized by large or numerous congenital intradermal pigmented nevi in association with melanocytic tumors of the leptomeninges. Neurocutaneous melanosis is generally believed to represent an error in embryonal neuroectodermal development, resulting in abnormal proliferation of melanin-producing cells within the skin and leptomeninges.9,16 Malignant transformation of leptomeningeal tumors occurs in 40 to 60% of symptomatic cases.16,22 Even in the absence of malignancy in the CNS, symptomatic NCM has a very poor prognosis, and chemo- and radiation therapy offer little benefit.16

We present the case of a 5-month-old girl who suffered from giant congenital melanocytic nevi and hydrocephalus; MR imaging revealed extensive leptomeningeal melanosis. We discuss the diagnosis, treatment, and prognosis of this rare disorder.

Abbreviations used in this paper: CNS = central nervous system; CSF = cerebrospinal fluid; HGF/SF = hepatocyte growth factor/scatter factor; MR = magnetic resonance; NCM = neurocutaneous melanosis.

Case Report

History. This 5-month-old girl presented with subacute onset of lethargy associated with nausea and emesis. At birth, several congenital nevi were observed on her scalp, trunk, and extremities, including a giant congenital hairy nevus over her lumbosacral area. Because of the marked irregularity and nodularity of lesions on her back, excision of the most involved area was performed when the patient was 3 months old; no evidence of malignancy was demonstrated (Fig. 1). The infant’s history included an uncomplicated delivery and normal neurological development during the first few months of life. Before admission, she was observed to be suffering from macrocephaly accompanied by an increase in head circumference of 1 cm per week for 3 weeks. Lethargy, nausea, and vomiting developed over a 24-hour period.

Examination. At the time of clinical examination, she was not awake but demonstrated purposeful movement of all extremities in response to stimulation. Extraocular movements were intact and no nystagmus was apparent. The anterior fontanel was tense. A nonenhanced computed tomography scan demonstrated enlargement of the
Neurocutaneous melanosis

Emergency Treatment and Diagnosis. An emergency right frontal ventriculostomy was performed. The infant’s initial intracranial pressure was elevated (30 cm H₂O) but decreased to 10 cm H₂O following drainage of 20 ml of CSF. The results of the patient’s neurological examinations also improved rapidly after CSF drainage. The CSF was xanthochromic, but cytological examination demonstrated that it was benign. Evaluation of the CSF revealed a cell count of one white blood cell, 2600 red blood cells, 18 mg/dl protein, and 39 mg/dl glucose. A brain MR imaging study demonstrated severe hydrocephalus and an enlarged cisterna magna with intact cerebellar vermis (Fig. 3A). Scattered foci of intrinsic T₁ signal within the cerebellar hemispheres, dorsal midbrain, and bilateral hippocampi were also noted (Fig. 3B and C). The presumptive diagnosis of NCM was made based on these findings. In addition, a spine MR imaging study demonstrated a 1 × 10 cm extramedullary fluid collection from T₁–11 that was associated with the remodeling of the posterior elements resulting from a spinal arachnoid cyst (Fig. 3D).

Operation. The patient was taken to the operating room on the 5th hospital day for placement of a ventriculoperitoneal shunt. A dural biopsy was performed during the procedure and showed no significant pathological abnormality. The patient tolerated the procedure well and was discharged home 1 day postoperatively demonstrating baseline neurological function.

Discussion

Neurocutaneous melanosis is a rare congenital but non-heritable neurocutaneous disorder characterized by excessive proliferation of melanin-producing cells in both the skin and leptomeninges. To date, only approximately 100 symptomatic cases have been reported. Neurocutaneous melanosis occurs with equal frequency in both male and female patients.

Pathogenesis of NCM

Although the exact pathogenesis is obscure, NCM is generally believed to represent an embryonal neuroectodermal dysplasia. Specifically, NCM is thought to result from an abnormality in the development of neural crest-derived melanocyte precursors, or melanoblasts, of the skin and pia mater. In the CNS, melanoblasts differentiate into melanocytes that are normally found within the pia mater, the substantia nigra, and the medullary reticular formation. A deregulation of HGF/SF signaling has been implicated in the pathogenesis of NCM. A cytokine that stimulates the proliferation, migration, and morphogenesis of different types of cultured epithelial cells, HGF/SF is known to play an important role in the normal distribution and prolif-
feration of melanocytes. Transgenic mice with overexpression HGF/SF have been found to develop multiple pigmented nevi in both the skin and leptomeninges; moreover, abnormal expression of the HGF/SF receptor, Met, has been immunohistochemically detected in a congenital nevus of an infant with NCM.

Criteria for Diagnosis

The original clinical criteria for the diagnosis of NCM proposed by Fox in 1972 include the following: 1) large or numerous pigmented nevi in association with leptomeningeal melanosis or melanoma; 2) no evidence of malignant change in any cutaneous lesion; and 3) no evidence of melanoma in any organ other than the meninges. Since Fox’s description, however, both malignant transformation of cutaneous nevi and distant metastases of leptomeningeal melanoma have been described. The current diagnostic criteria for NCM were subsequently proposed by Kadonaga and Frieden (Table 1). Although confirmation of the diagnosis of NCM can only be made by histological findings, often only at autopsy, MR imaging allows the diagnosis of excessive melanotic cells in the meninges (leptomeningeal melanosis) to be made. The potential diagnostic role of MR imaging is especially relevant to NCM; some investigators have found that in only approximately 40% of patients is the evidence of malignancy demonstrated using CSF cytology. The sensitivity of MR imaging has also permitted detection of melanosis in approximately 25% of infants with giant nevi who are neurologically asymptomatic. This finding together with data from a giant nevus registry demonstrates that symptomatic CNS disease is at least as important, if not more important, as melanoma arising in the skin as a morbid sequela of giant nevi.

Clinical Manifestations

A giant congenital melanocytic nevus, usually of the lumbosacral region, is present in two thirds of patients with NCM, whereas numerous small- to intermediate-sized melanocytic nevi without a single large lesion are observed in one third of patients. Nevi are first present at birth, although more can develop later in life. Nevi are dark pigmented lesions circumscribed with irregular borders, that can be raised or flat. The “nevus of Ota” is a hyperpigmented lesion, often unilateral and involving the eyelid, conjunctiva, and adjacent facial skin, which is often associated with leptomeningeal melanosis. Almost all nevi appear on the posterior midline, head, and/or neck.

FIG. 3. Magnetic resonance images. A: Sagittal T1-weighted image demonstrating panventricular enlargement and a large cisterna magna. Note the cerebellar vermis appears abnormally small. B: Axial T1-weighted image at the level of the fourth ventricle, demonstrating multiple small foci of T1-signal shortening, presumably melanin-containing cells, in the cerebellar hemispheres. C: Axial T1-weighted image at the level of the midbrain, demonstrating foci of T1-signal shortening just anterior to the temporal horns. D: Sagittal T1-weighted image of the cervical and upper thoracic spine, demonstrating the dorsal arachnoid cyst compressing the thoracic portion of the spinal cord.
Neurocutaneous melanosis

### TABLE I

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>large or multiple congenital melanocytic nevi in association with meningeal melanosis or melanoma</td>
</tr>
<tr>
<td>2</td>
<td>no evidence of cutaneous melanoma, except in patients in whom the examined portions of the meningeal lesions are histologically benign</td>
</tr>
<tr>
<td>3</td>
<td>no evidence of meningeal melanoma, except in patients in whom examined areas of the skin are histologically benign</td>
</tr>
</tbody>
</table>

* Criteria are modified from the original by Kadonaga and Frieden. Large denotes greater than or equal to 20 cm in diameter in adults, greater than or equal to 9 cm in diameter on the head, and greater than or equal to 6 cm on the body in neonates and infants. Multiple refers to three or more lesions.

Although limited epidemiological data exist, the risk of the development of symptomatic NCM in a patient with a giant congenital nevus has been reported to range from 2.5 to 11%. Alcool, et al., found that almost 40% of children with primary malignant melanoma of the leptomeninges also demonstrated hairy nevi. Half of patients with symptomatic NCM will manifest neurological symptoms during the 1st year of life. The majority of patients demonstrate symptoms before the age of 2 years; less frequently, symptomatic NCM presents during the second or third decade of life. Two thirds of patients will present with neurological signs and symptoms due to hydrocephalus (irritability, lethargy, emesis, bulging anterior fontanel, enlarging head circumference), as in our case. The development of hydrocephalus in patients with NCM is believed to be secondary to a reduction of CSF absorption as a result of infiltration of arachnoid villi by melanocytes, or from obstruction of CSF flow by the thickened leptomeninges. Hydrocephalus can also result from an associated Dandy–Walker complex. Focal or generalized seizures, aphasia, and motor or cranial nerve deficits may develop in patients with intracranial melanocytic tumors. Spinal involvement occurs in approximately 20% of cases and may result in myelopathy, radiculopathy, and bowel or bladder dysfunction.

Neurocutaneous melanosis can be associated with other neurocutaneous disorders, such as neurofibromatosis Type 1 and Sturge–Weber syndrome. The association of NCM with Dandy–Walker complex is rare, with approximately 11 cases reported in the literature to date. It is currently theorized that in cases involving NCM with Dandy–Walker complex, the leptomeningeal melanosis interferes with normal development of the cerebellum and fourth ventricle. Chaloupka, et al., have proposed that leptomeningeal melanosis interferes with the ability of primitive meningeal cells to induce normal deposition of the extracellular matrix, neuronal migration, and formation of CSF resorption pathways, resulting in the formation of posterior fossa cysts and vermis aplasia characteristic of Dandy–Walker complex. Barkovich, et al., have proposed that leptomeningeal melanosis interferes with normal ectodermal–mesodermal interaction, causing abnormal formation of the cerebellum and fourth ventricle.

#### Neuroimaging Evaluation

Contrast-enhanced MR imaging is the most useful diagnostic tool for detecting leptomeningeal involvement in patients with NCM. Leptomeningeal melanosis demonstrates a characteristic hyperintensity on T1-weighted MR images without contrast and a hypointensity on T2-weighted MR sequences as a result of paramagnetic properties of melanin. Frieden, et al., reported that T1-signal shortening of the infratentorial structures was the most common finding in asymptomatic children with NCM, and Barkovich, et al., found meningeal enhancement to be uncommon. Patients may also present with intraparenchymal lesions in the absence of meningeal involvement. Magnetic resonance imaging is also useful in evaluating associated posterior fossa malformations, such as Dandy–Walker complex, because it can delineate the cerebellar vermic hypoplasia as necessary for diagnosis. Magnetic resonance imaging of the spine is also useful to diagnose associated anomalies such as tethering of the spinal cord, lipomas, and cysts (as in the current case).

#### Histopathological Studies

The histopathological features of NCM lesions are identical to those seen in congenital melanocytic nevi without CNS involvement. Nevus cells extend into the dermis or, occasionally, into the deep dermis, and surround nerves and blood vessels.

Neuropathological examination reveals leptomeningeal melanosis with dural sparing. This melanosis is most prominent in areas of physiological melanocytic distribution—the inferior surface of the cerebellum, the frontal, temporal, and occipital lobes, and the ventral surface of the pons, medulla, and cerebellar peduncles, and upper cervical cord. The anterior temporal lobes and cerebellum are the most common locations for melanocyte accumulation, whereas the temporal lobe is most often affected in parenchymal NCM. Melanocytic infiltration of ependymal cells and perivascular spaces can also occur; this condition is characteristic of NCM because melanocytes are absent from perivascular spaces in healthy patients. Malignant degeneration of leptomeningeal melanosis to leptomeningeal melanoma has been reported to occur in 40 to 60% of cases; however, it is not clear that this number is accurate in asymptomatic patients, and it is certainly not accurate in the short term. Very few patients in whom the diagnosis was made using MR imaging have been found to have malignant degeneration of their intracranial melanotic lesions. Long-term outcome of asymptomatic patients with MR imaging–detected NCM is unknown.

#### Prognosis for NCM

Even in the absence of CNS melanoma, prognosis for patients with symptomatic NCM remains very poor; approximately 50% of patients die within 3 years of the onset of neurological symptoms. The association of NCM with Dandy–Walker complex has a particularly poor prognosis. Patients with both conditions experience rapid neurological deterioration and usually die by the age of 4 years. It is thought that this deterioration is due to the malignant degeneration of NCM, and therefore the Dandy–Walker complex may be a marker of a profound infiltration of melanocytes in the CNS and increased risk for malignant transformation.
Treatment Options

The treatment of congenital melanocytic nevi remains controversial. Malignant transformation of these lesions occurs in 5 to 15% of patients.20 Because of this risk, some dermatologists advocate prophylactic resection of these nevi, which also improves cosmetic outcome.20 When neurological symptoms are present, NCM has an extremely poor prognosis, whether or not malignant cells are present.15 More than half of all patients die within 3 years after presenting with neurological symptoms.25 Neither chemoradiation therapy improves outcome.25

Conclusions

Neurocutaneous melanosis is a rare congenital neurocutaneous disorder characterized by congenital melanocytic nevi in association with leptomeningeal melanosis. As in the case reported here, symptomatic NCM often presents with symptomatic hydrocephalus requiring ventriculoperitoneal shunt placement. Because CSF cytology is often nondiagnostic, MR imaging is the examination of choice when biopsy cannot be performed. Our case illustrates to the neurosurgeon the importance of recognizing the likelihood of an underlying CNS pathological entity in a child with cutaneous melanocytic nevi. Unfortunately, there is currently no effective treatment for this disorder, and symptomatic NCM has a poor prognosis.

References


F. L. Acosta, et al.