Neurocutaneous Melanosis Presenting with Hydrocephalus & Malignant Transformation: Case Report and Review of the Literature

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Abstract

Background: Neurocutaneous melanosis (NCM) is a sporadic condition characterized by congenital melanocytic nevi and melanocytic thickening of the leptomeninges. We describe the case of a 5-month old boy who presented with giant congenital melanocytic nevus and hydrocephalus. MR imaging and CSF immune histo chemistry confirmed leptomeningeal melanosis. He required placement of right sided ventriculoperitoneal shunt to control hydrocephalus. The patient tolerated the procedure well and was discharged home with normal neurological function, but eventually succumbed to malignant transformation of leptomeningeal disease. We discuss the diagnosis, treatment and prognosis of this rare disorder in the light of recent published literature.

Conclusion: Cutaneous manifestations of NCM are usually congenital, and neurological manifestations develop early in life. Patients with large or multiple congenital nevi should therefore be investigated early to facilitate treatment. MR imaging is the investigation of choice which can further assist in performing biopsy. Symptomatic NCM is refractory to radiotherapy and chemotherapy and has a poor prognosis. A multidisciplinary approach is necessary in the management of NCM patients.

Keywords: Neurocutaneous melanosis; Hydrocephalus; Melanocytic nevi; Leptomeningeal melanosis

Abbreviations: NCM: Neurocutaneous Melanosis; CNS: Central Nervous System; HGF/SF: Hepatocyte Growth Factor/Scatter Factor; NRAS: N-type Rat Sarcoma gene; MAPK: Mitogen-Activated Protein Kinase; MEK: MAPK/Erk Kinase; FDA: Food and Drug Administration; CSF: Cerebral Spinal Fluid; DWC: Dandy-Walker Complex; PET: Positron Emission Tomography

Introduction

Neurocutaneous melanosis (NCM) is a rare syndrome characterized by congenital melanocytic nevi and melanocytic thickening of the leptomeninges [1]. Although mostly sporadic, a few familial cases of NCM have been reported [2]. In most cases NCM presents with symptoms of raised intracranial pressure [3]. NCM is believed to result from congenital dysplasia of melanin producing-cells within the skin and leptomeninges [4].

Although first described by Rokitanski et al. [1], but the term Neurocutaneous melanosis was coined by van Bogaert [5]. The initial diagnostic criteria of NCM included large or numerous pigmented nevi without malignant transformation [6], which was later revised to include malignant transformation and distant metastasis [7]. Since its first description 100 or so cases have been described in the English literature [8].

Two-thirds of patients with NCM have a giant congenital melanocytic nevus; the remaining third have multiple small lesions [9]. Nevi are usually present at birth, but more may develop later in life. Almost all nevi have a lumbosacral (bathing trunk) distribution [7].

In the majority of cases NCM exhibit symptoms of raised intracranial pressure within the first 2 years of life [4]. As in the case reported here, most cases present with symptoms and signs of increased intracranial pressure, including irritability, lethargy, recurrent vomiting, increased head circumference, bulging anterior fontanelle and photophobia [3]. Hydrocephalus develops in two-thirds of patients.

Case Report

A 5-month-old male was delivered via caesarean section at 36-week gestational age. At birth, two extensive congenital...
hairy nevi had been observed; the first a giant hairy nevus in bathing trunk distribution the second 1cm wide on the left upper back. Figure 1 illustrates the bathing trunk distribution of the giant nevus. There were no issues with his feeding, weight gain or neurological development. At 5 months, he presented with a 5 day-history of drowsiness, poor feeding, high pitched cry, nausea and vomiting. His skin was dry and flaky. His mother had mild psoriasis (elbows & knees) and benign moles, but there was no other relevant family history. At the time of presentation, he was alert but irritable, and his anterior fontanel was full and tense. Downward gaze (“setting-sun” sign) was also noticed intermittently but there was no neck rigidity. A non-enhanced computerized tomography (CT) scan demonstrated communicating hydrocephalus and significant transependymal oedema, as illustrated in Figure 2.

Figure 1: Giant hairy nevus in bathing trunk distribution.

Figure 2: Axial CT. A showing communicating hydrocephalous and transependymal oedema, B showing decompressed ventricles after shunt placement.

An emergency right ventriculoperitoneal shunt was performed. The patient recovered well from the procedure and was discharged home on postoperative day one. The CSF was xanthochromic and cytological examination revealed medium-sized epithelioid non-pigmented cells with oval nuclei and relatively high nuclear cytoplasmic ratios. Such appearances have been described in children with NCM [11,26]. Immuno histochemistry highlighted scattered lymphoid cells (CD45) and epithelioid cells were negative for melanoma markers (MelC, HMB45) as illustrated in Figure 3. MR imaging demonstrated meningeal enhancement in the periphery of the left and right cerebellum as well as in the thoracic spine and conus suggestive of melanin deposition. A presumptive diagnosis of NCM was made based on the MR characteristics, CSF cytology and clinical presentation. Follow up MR five months after the procedure showed decompressed ventricles with oedema over the thalamus and diffuse enhancement over the spinal cord again in keeping with CNS melanosis, as illustrated in Figure 4.

At 19 months of age, a repeat MRI showed arachnoid loculations at the ventricular outflow foramina as well as thalamic oedema and diffuse spinal enhancement in keeping with NCM. Skin and leptomeningeal biopsies were subsequently taken at 21 months of age, which showed N-type Rat Sarcoma gene (NRAS) mutated melanoma, although PET scan showed no hypermetabolic foci within brain, spine or upper half of the body. For 7 months, he received Trametinib, a MAPK/Erk kinase (MEK) inhibitor which inhibits cellular proliferation. During this time, he continued to develop normally and was attaining appropriate social and motor milestones. At 30 months of age, he developed left sided weakness and status epilepticus requiring PICU admission and ventilator support. No acute changes were demonstrated on head and spine CT. He was extubated successfully, but continued to deteriorate neurologically. He received palliative treatment and died at the age of thirty-two months.

Discussion

Criteria for the diagnosis of NCM were first proposed in 1972 and included large or numerous pigmented nevi in patients without malignant transformation in cutaneous lesions and without evidence of melanoma except in the leptomeninges [6].

Since then, both malignant transformation of cutaneous nevi and distant metastases of leptomeningeal melanoma have been recorded [7]. This led to revision of the diagnostic criteria which currently comprise: 1. Large (diameter more than 20 cm in adults or 6-9 cm in infants) or numerous (three or more lesions) congenital nevi in association with Leptomeningeal melanosis or melanoma. 2. No evidence of cutaneous melanoma, except in patients with histologically benign meningeal lesions. 3. No evidence of meningeal melanoma, except in patients with histologically benign cutaneous lesions [9].

Confirmation of the diagnosis is still based on histological findings, often only at autopsy. However, MR imaging allows...
a presumptive diagnosis of CNS melanosis to be made [10,11]. Leptomeningeal melanosis demonstrates a distinctive hyperintensity on T1-weighted MR images and a hypointensity on T2-weighted MR images [7,12]. Patients may also present with intraparenchymal lesions without meningeal involvement [13].

NCM is a sporadic syndrome with few reported familial cases [14,15]. Animal models of NCM have been developed. Transgenic mice over expressing hepatocyte growth factor/scatter factor (HGF/SF) demonstrate extensive pigmented nevi in both skin and leptomeninges of the central nervous system, thus resembling human NCM. HGF/SF is growth factors that control the proliferation of neural crest melanocytes during embryogenesis [16]. Dysregulation of these growth factors may explain associated cystic malformations of the posterior fossa such as the Dandy–Walker complex (DWC) [16].

Oncogenic missense mutations (affecting the NRAS gene) have been identified in affected neural and cutaneous tissue in NCM patients. However; these mutations were not found in unaffected tissues and blood. The mutations are thought to be the result of somatic mosaicism, which occurs in a progenitor cell in the developing neural crest or neuroectoderm [2]. This suggests that these mutations would be lethal if they occurred in germ line cells [2].

The resultant phenotype is dependent upon the type of mutation, affected cells and timing [17]. NRAS mutations have only been found in benign melanocytic nevi. This indicates that they are of themselves insufficient for malignant transformation to occur. Given that malignant transformation is an indicator of poor prognosis in NCM (as discussed in prognosis and outcomes), a better understanding of molecular genetics pathogenesis is required [18]. NRAS mutations could represent a potential therapeutic target for NCM [19]. NRAS melanomas are thought to proliferate through the MAPK pathway which could be inhibited by MEK inhibitors. Trametinib for a MEK inhibitor has been approved by the Food and Drug Administration (FDA) for the treatment of certain NRAS mutated melanomas [20].

The histopathological patterns of NCM cutaneous lesions are indistinguishable from those seen in congenital melanocytic nevi without CNS involvement. Nevus cells spread into the dermis and encircle nerves and blood vessels [9,21]. Leptomeningeal melanosis most evident in areas of physiological melanin distribution such as the base of the brain, the ventral surface of the pons, cerebral peduncles, the medulla and cerebellum [7]. Several features have been identified to distinguish meningeal melanosis from melanoma which can develop in about half of the cases [22]. Necrosis, invasion of basal lamina and cell atypia can distinguish melanoma from melanosis. Although the prognostic significance of this distinction is unclear [4], CSF cytology is used to investigate malignancy but its sensitivity is reported to be around 40% [4].

### Management

For cutaneous manifestations, the management remains controversial. Some dermatologists support prophylactic surgical excision of large melanocytic nevi to reduce the risk of malignant transformation, which occurs in 5% to 15% of patients [9] and to improve cosmetic appearance. For neurological manifestations, outcome remains poor even with the use of radiotherapy and chemotherapy [23,24]. Early neurosurgical intervention however; can assist in tissue diagnosis and has the potential to effect early decompression [10]. The usual surgical intervention is shunt insertion with a filter to prevent potential seeding into the abdominal space [25].

### Prognosis and Outcomes

Prognosis in NCM is generally poor, with half of patients dying within 3 years of the onset of neurological symptoms, as in the case discussed earlier [9]. However, the course of asymptomatic patients is variable and unpredictable [4]. The worst prognosis is seen in NCM patients with Dandy–Walker complex (DWC). DWC is thought to be a marker of melanocytic infiltration into the CNS and confers an increased risk for malignant transformation [26].

### Conclusion

NCM is a rare syndrome characterized by congenital melanocytic nevi and melanocytic thickening of the leptomeninges. Cutaneous manifestations of NCM are usually congenital, and neurological manifestations develop early in life. Patients with large or multiple congenital nevi should therefore be investigated early - even in the absence of neurological manifestations – to facilitate treatment plan and prognosis. Because of the uncertain value of CSF cytology, MR imaging is the investigation of choice especially if biopsy cannot be carried out. As in the case reported here, symptomatic NCM usually presents with increased intracranial pressure and hydrocephalus, and requires ventriculoperitoneal shunt insertion. Symptomatic NCM is refractory to radiotherapy and chemotherapy and has a poor prognosis. A multidisciplinary approach is necessary in the management of NCM patients. This should include routine neuro development assessments and dermatologist input.

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