Mystery Case: Neurocutaneous melanosis with diffuse leptomeningeal malignant melanoma in an adult

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SECTION 1

A 35-year-old man presented with a history of headache, vomiting, and visual blurring of 6 months' duration. Two months after the onset of symptoms, he developed behavioral changes in the form of irrelevant talking. He was then seen at another center where the clinical possibility of tuberculous meningitis was considered. His CSF findings at this time were 4 cells, all lymphocytes, protein 221 mg/dL (2.21 g/L), and glucose 59 mg/dL (3.3 mmol/L). A non-contrast CT head showed hydrocephalus (figure, B). He was treated with antitubercular treatment (ATT)

and oral dexamethasone. He improved transiently but worsened again and presented to us with increasing headaches, recurrent vomiting, deterioration in vision, alteration in behavior, psychosis, and bilateral lower limb weakness of 10 days' duration.

General physical examination revealed the presence of a large nevus over the trunk and back in a bathing suit distribution, which he had since birth (figure, A). The lesion had been considered as a birthmark and had never been biopsied. The patient was conscious and oriented with intermittent behavior changes in form of restlessness and agitation.

Figure Neurocutaneous melanosis

(A) Large congenital nevus on trunk extending over back and thighs. (B) Noncontrast CT brain shows hydrocephalus. (C) MRI brain axial T1-weighted image shows hyperintensity along sulcal spaces (arrows) and (D) postcontrast enhanced image shows diffuse meningeal enhancement along sulcal spaces (arrows). Sagittal noncontrast T1-weighted image of spine shows hyperintensity on the dorsal aspect of the cord (arrows in G). Following contrast administration, sagittal fat-suppressed T1-weighted spine MRI shows diffuse hyperintensity in the subarachnoid space suggestive of enhancement (H). (E) Papanicolaou and (F) May-Grünwald-stained CSF cytospin show malignant cells (arrows) with cytoplasmic melanin pigment, vesicular nuclei, and prominent macronucleoli ($\times 400$). Mitotic figures are seen (E; $\times 400$). These malignant cells are immunopositive for HMB-45 (F; $\times 400$).

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There were no meningeal signs. His visual acuity was finger counting at 1 meter in both eyes and fundus examination revealed bilateral papilledema. Ocular movements and other cranial nerve examinations were normal. He had paraparesis with proximal more than distal weakness and attenuated lower limb reflexes. The plantar response was flexor.

Sensory examination was normal. There were no cerebellar signs.

Questions for consideration:

1. What is the differential diagnosis?
2. What will be the next step for a definitive diagnosis?

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SECTION 2

The patient's history of headache, vomiting, and papilledema were suggestive of raised intracranial pressure. Lack of fever, no CSF pleocytosis, high protein, mild hydrocephalus, nonresponsiveness to ATT, and worsening neurologic status raised the possibility of an alternative diagnosis of raised intracranial pressure and meningeal disease other than tubercular meningitis. Since examination revealed a large congenital nevus, the possibility of either a malignant melanoma with intracranial dissemination or neurocutaneous melanosis with malignant meningitis was strongly considered. For an etiologic workup, brain imaging, lumbar puncture, and a skin biopsy were performed.

A noncontrast CT scan of the brain showed hydrocephalus (figure, B). Noncontrast T1-weighted MRI brain (figure, C) and spine (figure, G) revealed diffuse hyperintensity along sulcal spaces of bilateral cerebral hemispheres (arrows) and spinal cord surface (arrows). Postgadolinium T1-weighted brain MRI revealed leptomeningeal and pachymeningeal enhancement (figure, D, arrows) and fat-suppressed postgadolinium T1-weighted MRI spine showed diffuse enhancement along the spinal subarachnoid space (figure, H, arrows). Lumbar puncture revealed a high opening pressure of 300 mm of CSF. There was no pleocytosis, protein was 339 mg/dL (3.39 g/L), and glucose was 26 mg/dL (1.44 mmol/L) (corresponding blood glucose 104 mg/dL [5.77 mmol/L]). CSF cultures for

bacteria, fungi, and viruses were negative. CSF for cryptococcal antigen, acid-fast bacilli, GeneXpert MTB/RIF, and PCR for *Mycobacterium tuberculosis* were negative. CSF cytopathology (figure, E and F) revealed several atypical cells with moderate to abundant cytoplasm and large vesicular nuclei with prominent macronucleoli. Many of these cells contained melanin pigment in their cytoplasm. Binucleated cells were seen. Frequent mitotic figures were identified. On immunocytochemistry, these malignant cells were immunopositive for S-100, HMB-45, and Melan-A, confirming their melanocytic nature. The skin biopsy showed features of pigmented intradermal nevus but no evidence of malignancy was observed.

Based on clinical, CSF, and MRI findings, the patient was diagnosed with neurocutaneous melanosis (NCM) with diffuse leptomeningeal malignant melanomatosis (leptomeningeal melanoma). A ventriculoperitoneal shunt was placed owing to worsening hydrocephalus and headaches. He was started on definitive treatment for NCM in the form of oral temozolomide (dose 200 mg/m² for 5 days) every 4 weeks. A recent assessment on follow-up showed worsened neurologic status and no clinical improvement.

Questions for consideration:

1. What is NCM and malignant melanoma? Are they the same entities?
2. How does one differentiate NCM from infective meningitis?

GO TO SECTION 3

SECTION 3

NCM is a noninherited disorder and was first described by Rokintansky in 1861 and the term NCM was coined by Von Bogaert in 1948.¹ This is one of the pigmentary disorders of the nervous system that include focal, diffuse, benign, or malignant pathologies, either arising primarily within the nervous system (neurocutaneous melanosis, meningeal melanocytoma, primary leptomeningeal melanomatosis, and melanoma) or disseminating from a systemic lesion.² Our patient fulfilled the revised criteria of NCM laid down by Kadonaga and Frieden^{2,3} which include a large nevus (>20 cm in adults, 6–9 cm in infants) or multiple nevi (at least 3) in association with CNS melanosis or melanoma, no evidence of a cutaneous melanoma except in patients with no evidence of brain melanoma, and no evidence of meningeal melanoma except in patients without cutaneous malignant lesions.

NCM is thought to represent a phakomatosis, which possibly results from an abnormality in the development of neural crest–derived melanocyte precursors, or melanoblasts of the skin and leptomeninges⁴; a form of neuroectodermal dysplasia.⁵ Malignant transformation in the CNS occurs in about 40%–50% of cases of NCM, with grave outcomes.^{3,5} It has been proposed that melanin-containing cells are either derived from neural crest–derived nerve sheath precursor cells and migrate to skin via the nerves, paraspinal ganglia, blood vessels, and adnexal tissue or they are neural crest cells that have been genetically or phenotypically altered as melanin-containing cells.^{6,7} One hypothesis suggests that in patients with NCM, the migration occurs along the pia-arachnoid during meningeal invagination of blood vessels during the formation of perivascular spaces.⁶

NCM has been reported to manifest most commonly in childhood, generally within the first 2 years of life, and less commonly in adults.^{3,8–11} So far, only 12 adult cases have been described in the literature,^{11,12} of which only 3 had leptomeningeal melanocyte infiltration. The condition can be asymptomatic or symptomatic in its presentation¹⁰ and no sex or racial predilection is reported. The diagnosis in adults may be delayed or missed owing to late onset of symptoms. The neurologic presentation in these cases can be variable depending upon the age, site, and extent of involvement, with features of obstructive hydrocephalus, headache, vomiting, neuropsychiatric manifestations, seizures, ataxia, intracerebral hemorrhage, or, less commonly (about 20%), spinal cord involvement with arachnoiditis, syringomyelia, or radiculopathy.^{3,9}

Imaging using MRI and CT scan can reveal features of NCM. MRI is the optimal method of imaging.³ Leptomeningeal disease characteristically presents

as hyperintensity on unenhanced T1-weighted images, usually hypointense on T2-weighted sequences, hyperintense on fluid-attenuated inversion recovery images, and shows diffuse enhancement following gadolinium injection.^{3,6,9,10} However, melanin deposits without signal abnormality on unenhanced MRI may also be seen. The imaging features are believed to be derived from the paramagnetic effect of the melanin, which shortens the T1 and T2 relaxation times,¹⁰ possibly reflecting interactions of unpaired electrons in melanin with water protons.^{13,14} The leptomeningeal involvement in NCM is different from that seen in primary melanoma of the meninges. In NCM, the dura mater is not typically affected, but involvement of the cerebral parenchyma, choroid plexus, and ventricular ependyma has been observed.³

Although histopathology with positive meningeal biopsy is required for definitive diagnosis, a positive CSF cytology can help confirm the diagnosis. Our patient had a positive CSF cytologic specimen for malignant cells confirming the diagnosis. Anti-melanoma antibody (HMB-45) positivity (as seen in CSF cytology in our case) is observed in primary melanocytic lesions of the nervous system.⁹ Treatment options for patients with NCM are restricted to radiotherapy, chemotherapy, or CSF diversion strategies. Prognosis remains poor and therapies offer little benefit. The overall prognosis of diffuse leptomeningeal disease limits survival to less than 3 years.^{3,9}

This rare case suggests that adult patients presenting with neurologic symptoms and benign congenital dermal nevi may harbor NCM and herald a malignant leptomeningeal disease. Careful investigation and a high index of suspicion are mandatory for a correct diagnosis.

AUTHOR CONTRIBUTIONS

Rohit Bhatia: manuscript editing and writing. Vijay Kataria: manuscript writing and editing. Deepti Vibha: manuscript editing. Aanchal Kakkar: cytology review, manuscript writing. Kameshwar Prasad: manuscript editing. Sandeep Mathur: cytology review, manuscript writing and editing. Ajay Garg: radiology review, manuscript editing. Sameer Bakhshi: oncology review and manuscript editing.

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DISCLOSURE

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MYSTERY CASE RESPONSES

The Mystery Case series was initiated by the *Neurology*® Resident & Fellow Section to develop the clinical reasoning skills of trainees. Residency

programs, medical student preceptors, and individuals were invited to use this Mystery Case as an educational tool. Responses were solicited through a group e-mail sent to the American Academy of Neurology Consortium of Neurology Residents and Fellows and through social media.

Of the 14 respondents to this mystery case, many suggested potential diagnoses, but only 4 respondents first described the cutaneous and neuroimaging findings presented, which would be a key step in working through an uncommon case of this nature. Of these 4 respondents, 2 correctly identified the patient's cutaneous abnormality as a large congenital nevus, 2 identified the neuroimaging finding of hydrocephalus, and 3 (75%) identified the presence of meningeal hyperintensity and enhancement. Of all the respondents, 6 (43%) offered the correct diagnosis of NCM. Another 36% suggested metastatic melanoma, including metastasis to the meninges, or another neurocutaneous syndrome like primary leptomeningeal melanoblastosis. Indeed, this patient did have a diffuse leptomeningeal melanoma in addition to the congenital NCM.

This patient was initially misdiagnosed with tuberculous meningitis and the skin finding was overlooked. This case highlights the enduring relevance of appropriate exposure of the patient during examination as part of the diagnostic process. NCM with leptomeningeal disease is important to consider in patients who present with neurologic symptoms and dermal nevi.

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