Neurocutaneous melanosis is not always a benign disease

Sir,

Neurocutaneous melanosis is a rare form of neurocutaneous syndrome characterized by the presence of congenital melanocytic nevi in the skin as well as proliferation of the melanocytes in the leptomeninges and the brain.[1] Patients with neurocutaneous melanosis are at risk for malignant transformation of cutaneous and leptomeningeal melanomas. The lifetime risk for development of melanoma in patients with congenital melanocytic nevi varies, being higher with those with large congenital melanocytic nevi and multiple satellites (>20 satellites).[2] In large congenital melanocytic nevi >40 cm projected adult size, it has been estimated to be 10%–15%.[3] In 40%–60% of patients with neurocutaneous melanosis, malignant transformation of leptomeningeal tumors occurs with severe neurological insults.[4]

A 22-month-old girl was brought to the outpatient clinic of Mansoura University Children's Hospital, Egypt, with multiple hairy pigmented nevi since birth which progressively increased in size and number over time. Her back was the most involved site being covered completely with a large nevus measuring 22 cm in its largest diameter [Figure 1a] together with multiple smaller satellites. It was first observed in the extremities and progressed to involve back and face (about 40 satellites) [Figure 1b]. She had skin phototype III, no organomegaly, and no palpable regional lymph nodes. Skin biopsies taken from the large nevus showed mitotic index 0/mm^2, Breslow thickness 0.8 mm, and Clark level III. Abdominal ultrasonography and chest X-ray showed normal findings. No brain or whole-spine magnetic resonance imaging (MRI) screening was done during early infancy.

Her developmental milestones were delayed as compared to her healthy peers. At the age of 18 months, she developed repeated seizures with right medial squint followed by coma. She was urgently referred to Mansoura University Children's Hospital, Egypt, where computed tomography scan and MRI brain were done showing a right cerebellar space-occupying lesion measuring 4.6 × 3.5 cm compressing the brain stem and the fourth ventricle with subsequent hydrocephalus [Figure 2a]. MRI of the spinal cord was done revealing extensive spinal circumferential dural thickening compressing the thecal sac and the cord at all spinal levels with post contrast enhancement [Figure 2b]. Also, cytochemical analysis and cerebrospinal fluid (CSF) culture were done which revealed normal glucose (76 mg/dL), increased protein (201 mg/dL), white blood cells (3 × 10^3/μL), and negative CSF culture.

As the tumor was extensively infiltrating the brain stem, it was not amenable to complete surgical resection and only subtotal excision was done by neurosurgical staff members of Mansoura University Hospital, Egypt. Pathological examination with immunohistochemical staining showed malignant round and spindle cells which focally contained melanin. A melanocyte marker, melan A, stained both small and large cells [Figure 3a and b]. According to the clinical, histopathological, and radiological findings, the diagnosis was malignant melanoma, as a part of neurocutaneous melanosis. *NRAS* gene sequencing was done in collaboration with medical genetics section of Florence University, Italy, being the most frequently implicated gene, revealing a wild variant.[5]

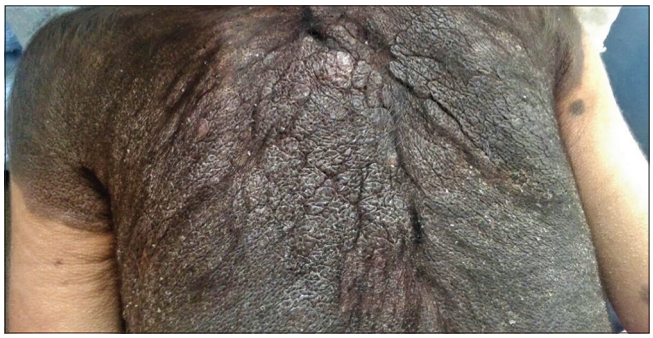

Figure 1a: A large melanocytic nevus occupying the whole trunk (bathing trunk)

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The patient was refused by the radiotherapist for irradiation because of her young age and its little value for her condition. Despite its poor efficacy, she was planned to receive palliative chemotherapy aiming to prolong the survival and improve the neurological condition. She received only one cycle of 4 weekly based chemotherapy cycles consisting of intravenous vincristine 1.5 mg/m^2 on day 1, intravenous dacarbazine 200 mg/m^2 for 5 days on days 1–5, and cyclophosphamide 750 mg/m^2 continuous intravenous infusion for 2 days on days 1 and 2.[6] With regard to seizures, levetiracetam (40 mg/kg/day bid), carbamazepine (20 mg/kg/day bid), and topiramate (started orally at 1 mg/kg/day and increased up to 6 mg/kg/day bid) were used to control seizures. Unfortunately, 2 days after starting the first cycle, the patient developed progressive deterioration of her consciousness level with irregular respiration and died. She died 4 months after the diagnosis of brain melanoma.

The course of neurocutaneous melanosis is quite variable; some cases have a purely benign course with normal life expectancy, while others suffer from severe neurological complications with aggressive progression and fatal outcome.[5] Neurocutaneous melanosis can affect the cerebellum, amygdala, cerebrum, medulla, pons, and spinal cord.[7,8] There are two age peaks for presentation of complications from neurocutaneous melanosis. The first peak (most common peak) occurs during the first 3 years of life and presents with increased intracranial pressure manifestations, while the other peak occurs during the second to third decades of life in the form of headache and neuropsychiatric symptoms.[9,10] The risk factors for neurocutaneous melanosis are the presence of giant congenital melanocytic nevi, multiple satellite nevi, male sex, and neck, head, or posterior midline location.[10-13] Table 1 shows a summary of some reported similar cases of brain melanoma associated with NCM.[6,14-16]

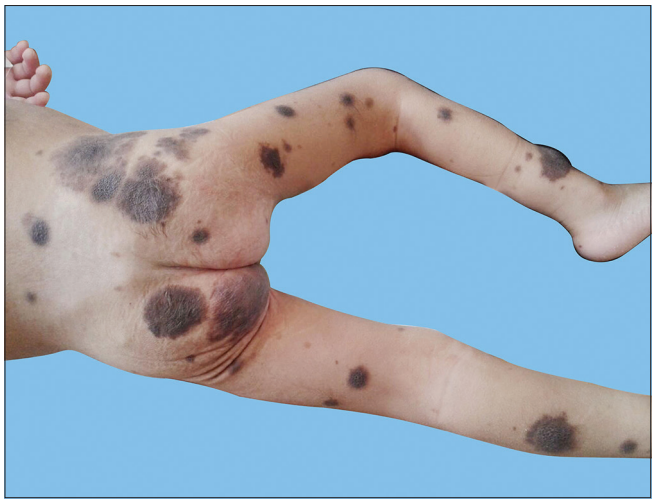

Figure 1b: Multiple smaller satellite nevi scattered over the buttocks and lower extremities

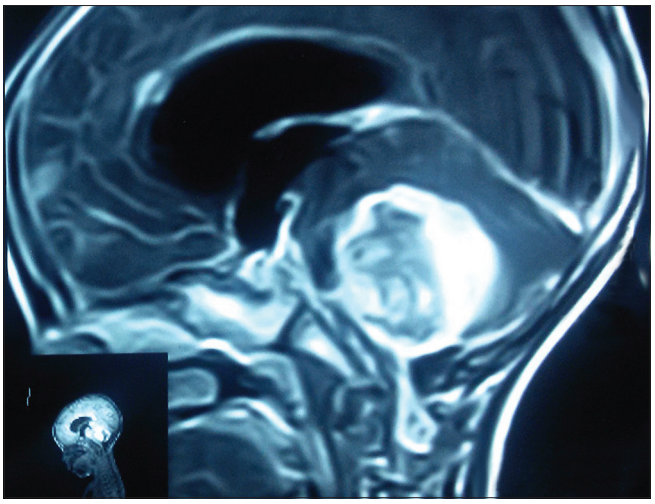

Figure 2a: A right cerebellar space-occupying lesion compressing the fourth ventricle with hydrocephalus (postcontrast magnetic resonance imaging brain)

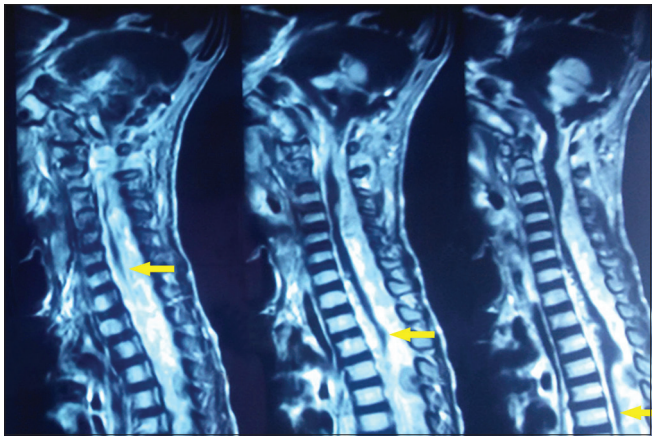

Figure 2b: The arrows point to extensive circumferential dural thickening compressing the thecal sac and the cord at all spinal levels with postcontrast enhancement (sagittal plane of postcontrast spinal cord magnetic resonance imaging)

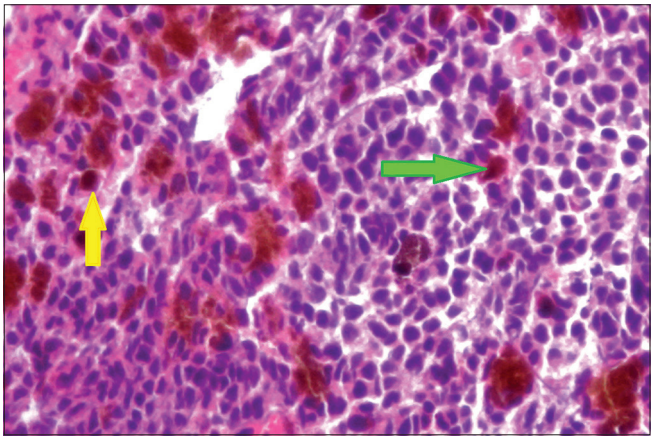

Figure 3a: Brain mass section showed malignant tumor cells (yellow arrow points to spindle cell, green arrow points to round cell, and both cell types contain melanin) (hematoxylinand eosin, ×200)

Table 1: Summary of some reported cases of brain melanoma associated with neurocutaneous melanosis[6,14-16]

Study	Patient's age	Presenting symptoms	Associated hydrocephalus	Treatment	Outcome
Vanzieleghem *et al*. (1999)	24 months	Somnolence, headache, vomiting, and ocular cranial nerve palsy	No	Stereotactic biopsy	Died 1 month after biopsy from intralesional Bleeding and brain stem compression
Chu *et al*. (2003)	36 months	Seizures and impaired consciousness	No	Systemic and intraventricular chemotherapy	Died 7 months after initial presentation
Livingstone *et al*. (2009)	18 months	Vomiting and hypokinesia of the lower limbs	Yes	Subtotal surgical resection	Died at home few days from surgery
Sung *et al*. (2014)	14 years	Headache, vomiting, dysarthria, and right hemiparesis	Yes	Total surgical resection	Died 4 months after surgical resection

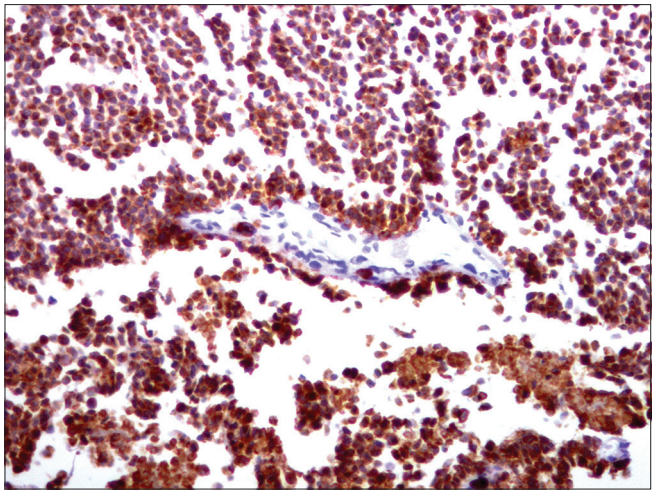

Figure 3b: Brain mass section shows diffuse positive staining with melan A (melan A, ×200)

Our case showed all neurological sequences of the disease starting with developmental delay progressing to repeated seizures and hydrocephalus because of diffuse circumferential thickening of the meninges secondary to melanin deposition. Unfortunately, she had a giant trunk nevus with multiple satellites putting her at a higher risk of development of brain melanoma.[17]

Brain melanoma has very poor prognosis because of disappointing results of conventional therapy. Radical surgical resection is often impossible as the tumor commonly infiltrates the adjacent brain structures massively. Also, the tumor responds poorly to chemotherapy and radiotherapy.[6] In 2014, Küsters-Vandevelde *et al*. reported a trial of treatment of brain melanoma of neurocutaneous melanosis syndrome using a novel target therapy (MEK162; mitogen- activated protein kinase, MEK inhibitor) against the somatic mutation of *NRAS*.[18] More recent efforts are being carried out for finding targeted therapy in the future as the conventional therapeutic options have dismal results. In 2016, Patel *et al*. postulated that insulin-like growth factor binding proteins' downregulation enhances the proliferation and viability of neurocutaneous melanosis cells. They assumed that inhibition of insulin-like growth factor 1 receptor may lead to loss of viability of neurocutaneous melanosis which may represent in the future a therapeutic target for this rare fatal disease.[19] Our patient led a downhill course and died shortly after appearance of neurological deficits in spite of surgery and palliative chemotherapy.

We concluded that though neurocutaneous melanosis is a well-known disease, it is important for dermatologists and pediatricians to remember the risk of a potentially fatal association of giant congenital melanocytic nevi. We recommend brain and whole-spine MRI screening for infants with giant congenital melanocytic nevi, multiple medium sized congenital melanocytic nevi, or multiple satellite nevi (especially >20 satellite nevi). Also, apart from imaging, these infants need to be followed up with serial head circumference measurement, neurological examinations, and development assessment, to pick up any abnormality early and also for repeat imaging if required. The MRI screening should be gadolinium-enhanced and should ideally be done during the first 6 months of life before myelination, as the latter may obscure the evidence of melanosis.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the legal guardian has given consent for the child's images and other clinical information to be reported in the journal. The guardian understands that the child's name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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