Neurocutaneous Melanosis with Malignant Leptomeningeal Melanoma
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Neurocutaneous melanosis (NCM) is a rare congenital syndrome characterized by the presence of large or multiple congenital melanocytic nevi with either benign or malignant pigmented cell tumors of the leptomeninges. We report a case of NCM in a patient with previously robust health. No neurological deficit was noted in the patient. At the age of 21 years old, blurred vision initially appeared. We were consulted to evaluate cutaneous lesions in the patient. We found an unduly large, hairy, congenital melanocytic nevus predominantly over the patient’s torso with multiple variously sized scattered hairy nevi over his trunk. The patient was diagnosed as NCM with malignant leptomeningeal melanoma following pathologic evaluation of the specimen taken during frontal craniotomy for removal of tumor and decompression. No other malignant change of the cutaneous lesions and internal organs was noted except in the meninges. The patient received treatment with radiotherapy. However, he died within 3 months.(Dermatol Sinica 23: 162-167, 2005)

Key words: Large congenital melanocytic nevus, Melanoma, Neurocutaneous melanosis

神經皮膚性黑色症合併惡性軟腦膜黑色素瘤
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神經皮膚性黑色症為有巨大或多發的先天性黑色素細胞母斑合併軟腦膜有良性或惡性的黑色細胞腫瘤。我們報告一例神經皮膚性黑色症，病人過去之健康狀況良好且無神經學之異常，於二十一歲時以視力模糊為初始神經學症狀表現。我們被會診而發現病人有一過度巨大，具毛髮的先天性黑色素細胞母斑及數個大小不等之毛髮母斑散佈於頭幹處，病人接受前額開顱手術取出腫瘤及減壓處置後，發現為軟腦膜黑色症及黑色素瘤。皮膚上之病灶無惡性病變之證據，且腦膜以外之器官無惡性黑色素瘤之發現。病人確定診斷為神經皮膚性黑色症合併惡性軟腦膜黑色素瘤後，接受放射線治療，於三個月後仍不幸死亡。(中華皮誌 23: 162-167, 2005)
INTRODUCTION

NCM is a rare, congenital, non-inheritable phakomatosis, first described by Rokitansky. This syndrome is characterized by the association of giant or multiple congenital melanocytic nevi with benign or malignant melanocytic tumors of the central nervous system (CNS). Most NCM patients display apparent neurological deficit during the first 2 years of life, but there is minor percentage of reported cases with initial presentation of neurological symptoms in the teens or twenties. To date, about 100 cases have been reported in the literature. Herein, we report a case who presented a rare initial symptom of blurred vision when he was 21 years old. After a thorough process of clinical and pathological evaluation, we confirmed this was a typical case of NCM.

CASE REPORT

A 21-year-old male was referred to our hospital on account of progressive blurred vision, and his visual acuity declined to only light perception in a short time. He was admitted for further evaluation and management. We were consulted to evaluate the cutaneous manifestations, especially the unduly large birthmark over his torso. Physical examination of his dermatological condition revealed an asymptomatic large, blackish congenital hairy melanocytic nevus with a pattern of “bathing trunk” over the torso (Fig. 1). Four satellite hairy melanocytic nevi and fifty-two spilus nevi were noted over his entire surface.

On neurological examination, the patient was alert and oriented. The twelve cranial nerves were intact with the exception of visual acuity at the level of light perception. Results of sensory examination were normal. Serial routine laboratory examinations including complete blood count, urinalysis, and blood biochemistry were normal. Roentgenograms of the alimentary and renal tracts, chest, and lumbar region were normal.

Fig. 2
The T1-weighted magnetic resonance imaging with gadolinium of the brain showed a large mass over the left superficial frontal lobe. Heterogenous-density tumor with upward pattern produced a protruding contour. A protruding contour was produced by the upward outgrowth of a heterogeneous-density tumor.

Fig. 3
Intraoperative finding of the leptomeninges revealed leptomeningeal melanosis and tumor mass.
The T1-weighted magnetic resonance imaging (MRI) with gadolinium of the brain showed a large mass lesion measuring 7 X 6 X 6.5 cm in size over the left superior frontal lobe, resulting in focal edema and mass effect (Fig. 2). The patient received frontal craniotomy for removal of the tumor. Intraoperative gross finding of the leptomeninges revealed leptomeningeal melanosis and tumor mass (Fig. 3). Pathological examination of the brain tumor revealed tumor cells with hyperchromatic nucleus and prominent nucleoli. Focal melanin pigment deposition was noted in the tumors. Immunohistochemistry study with HMB-45 staining was positive (Fig. 4). Skin biopsy of the flank and left thigh was also performed. The skin biopsy revealed intradermal nevus with congenital features (Fig. 5).

Combining the clinical manifestations of giant hairy congenital melanocytic nevus and multiple scattered nevi, with the MRI study and pathologic findings, the diagnosis of NCM was confirmed. The patient received radiotherapy for the brain tumor, but the deterioration persisted and brain edema developed. He passed away 3 months later.

**DISCUSSION**

Although NCM was first described in 1861, the criteria for diagnosis of NCM was proposed in 1972.\(^1\) giant or multiple pigmented nevi in patients without any malignant change in skin lesions and without any malignant melanoma in any organ other than the leptomeninges. Further refinement of the diagnosis of NCM was proposed by Kadonaga and Frieden in 1991\(^3\) as follows:

1. Large or multiple congenital nevi in

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**Fig. 4A**
The crowded tumor cells revealed hyperchromatic nucleus and prominent nucleoli. Focal melanin pigment deposition was noted. (Brain, H&E stain, 40X)

**Fig. 4B**
Cells are arranged in clusters and large sheets. (Brain, H&E stain, 200X)

**Fig. 4C**
The epitheloid cells exhibit severe uniform cytologic atypia, usually with readily evident mitoses. Most nuclei are large, irregular and hyperchromatic. (Brain, H&E stain, 400X)

**Fig. 4D**
The brown reaction in the lesional cells, as shown by HMB-45 immunohistochemical staining, is striking. (Brain, 400X)
association with meningeal melanosis or melanoma. “Large” refers to a lesion that is, or is estimated to become, $\geq 20$ cm in diameter in an adult. This includes lesions in neonates and infants that approximate 9 cm in diameter on the head or 6 cm in diameter on the body. “Multiple” means three or more lesions.

2. No evidence of cutaneous melanoma, except in patients whose examined results of the meningeal lesions are histologically benign.

3. No evidence of meningeal melanoma, except in patients whose examined results of the cutaneous lesions are histologically benign.

NCM occurs sporadically with an equal sex ratio. There are no population-based reports of different racial incidence. NCM is not hereditary. The pathogenesis of this disease is not clear. It is thought that NCM might originate from a congenital developmental disorder of the skin and pia mater melanoblasts among the neural crest cells during embryogenesis. Happle proposed a concept of autosomal lethal genes surviving in a mosaic state as the genetic basis of several serious birth defects with cutaneous involvement which are characterized by sporadic occurrence, scattered or asymmetrical distribution of skin lesions, no diffuse involvement of other organs, and equal sexual ratio. Based on the concept of autosomal lethal mutations surviving by mosaicism, NCM can fit the definition of birth defects proposed by Happle.

The clinical cutaneous features of NCM were reported in a study by DeDavid of 289 patients with large congenital melanocytic nevi (LCMN). Thirty-three cases (11.4%) manifested with CNS melanosis, and were categorized as symptomatic NCM. LCMNs were present in a posterior axial location on the head, neck and/or buttock. Satellite nevi were noted in 93.9% of the 33 patients. On the other hand, two-thirds of patients with NCM have LCMNs and one-third have numerous satellite nevi without a single giant lesion. According to this analysis, patients with LCMN in a posterior axial location, especially when associated with satellite melanocytic nevi, are at a higher risk for the development of NCM than patients with LCMN limited to the extremities or in those lacking of satellite nevi. The patient we reported had a giant garment hairy nevus, four satellite hairy melanocytic nevi, and 52 spilus nevi over the entire body surface.

Neurological manifestations of NCM usually occur before the age of 2 years. In half of the symptomatic patients, the manifestation of CNS involvement has shown in the first year of life already. The spectrum of neurological manifestations of NCM is broad and depends on the location, extension, and type of lesions. Therefore, symptoms and signs of NCM are variable. Increased intracranial pressure, seizure, motor deficits, aphasia, psychosis, unstable gait, headache, vomiting, spinal cord compression, stool and urine incontinence all have an acute onset owing to associated meningeal, subdural, or intraparenchymal hemorrhages. Other combined clinical conditions reported in the literature include Dandy-Walker complex, syringomyelia, intraspinal lipoma, and transposition of the great arteries and renal agenesis. Our case presented initially as blurred vision.

For diagnostic and laboratory evaluation, MRI with gadolinium contrast injection is the
standard diagnostic examination in patients with suspected NCM.9, 10 Cerebrospinal fluid (CSF) pressure in NCM was elevated frequently. CSF typically showed elevated protein, normal glucose levels, and a sterile leukocytosis.17

The histopathological features of the non-malignant cutaneous lesions are identical to congenital melanocytic nevi. Nevus cells extend into the deep dermis between collagen bundles and surrounding nerves, blood vessels and adnexa.

Neuropathological examination of CNS lesions in NCM shows leptomeningeal melanosis generating from the melanocytes of the pia mater. The pathogenesis of malignant leptomeningeal melanoma in the presence of NCM is not entirely clear. Statistically, there is a much higher incidence of malignant transformation of leptomeningeal melanosis than cutaneous melanosis.18, 19 However, this distinction has little prognostic significance because of the poor outcome of symptomatic NCM patients even in the absence of melanoma.3, 7, 10, 17, 20

Rarely, NCM may be asymptomatic and discovered incidentally at postmortem examination. Long-term prognosis for these patients is unknown.21 However, the prognosis of patients with symptomatic NCM is poor. The interval between the patient’s age at initial presentation with NCM and death ranged from immediate to 21 years; more than half of the deaths occurred within 3 years of their initial presentation with neurological manifestations.3, 4, 5 Due to the poor prognosis regardless of whether malignancy is present or not, neither radiotherapy nor chemotherapy seems to improve the outcome.3, 4, 20 In our case, the patient suffered from a neurological attack till his 21 years old and died within 3 months.

In practice, most NCM patients are seen in early infancy and dermatological consultation is usually required. Head circumference should be measured regularly because a disproportionate increase could be an early sign of hydrocephalus.3, 4 Physicians should be watchful of the symptoms and signs of increased intracranial pressure, which include lethargy, irritability, headache, recurrent vomiting, seizures and photophobia. MRI with gadolinium contrast injection is required when NCM is highly suspected. Recently, the establishment of transgenic mice overexpressed hepatocyte growth factor/scatter factor (HGF/SF) provides an important animal model to research the underlying mechanisms of pathogenesis in NCM.22 This would be a fruitful area for further investigation.

REFERENCES