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The Risk of Melanoma and Neurocutaneous Melanosis Associated with Congenital Melanocytic Nevi

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Congenital melanocytic nevi are commonly encountered in clinical practice. Although the development of malignant melanoma arising in small and intermediate congenital melanocytic nevi is rare, there is a significant risk of malignant degeneration associated with large congenital melanocytic nevi, in particular those that arise on the torso in the so-called "bathing trunk" distribution, where the risk is estimated to be about 2.5% to 5%. The risk of malignant melanoma arising within a large congenital melanocytic nevus is highest in the first 5 to 10 years of life and carries a significant mortality. Large congenital melanocytic nevi, in particular those overlying the posterior axis and occurring in the context of multiple satellite melanocytic nevi, are also associated with the development of neurocutaneous melanosis, which may result in neurologic and neurodevelopmental sequelae and is associated with a significant risk of primary central nervous system melanoma and death.
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Congenital melanocytic nevi (CMN) are common pigmented birthmarks (Fig. 1). They are noted at birth in 1% of neonates and are seen about twice as frequently in white newborns compared with black newborns.[1,2] A large study of 531,831 newborns from several hospitals in South America reported an overall prevalence at birth of 1.2%; 29% were less than 1 cm in diameter, 63% were between 1 and 4 cm in diameter, and 8% were greater than 4 cm in diameter.[3] Large CMN are uncommon and occur with an estimated frequency of 1:20,000 newborns, while giant garment-type or "bathing trunk" CMN occur with an estimated frequency of 1:500,000 neonates.[3] Although most CMN are present at birth, some may not manifest clinically until 1 to 2 years of age but demonstrate clinical and histologic features more consistent with a CMN as opposed to an acquired melanocytic nevus, suggesting that such nevi are present in nascent form at birth; these are referred to as "tardive" congenital nevi.[4]

Most CMN are relatively small. In 1979, Kopf et al[5] arbitrarily classified CMN into 3 categories defined by the greatest diameter in the adult: small: 1.4 cm or less; medium (or intermediate): 1.5 to 19.9 cm; and large: 20 cm or greater. The designation "giant" is used by some authors to refer to those CMN exceeding 50 cm in greatest diameter. Some infants born with a large CMN also have multiple smaller CMN ("satellite nevi") distributed on the head, body, and/or extremities (Fig. 2). Occasionally, multiple congenital melanocytic nevi (MCMN) may be present in the absence of a large CMN (Fig. 3). In the newborn and infant, a CMN of at least 6 cm on the body or 9 cm on the head will increase in size as the child grows and will attain a final diameter of at least 20 cm.[6]

Melanoma

There are significantly increased risks of both primary cutaneous melanoma and primary melanoma of the central nervous system (CNS) in association with large congenital melanocytic nevi (LCMN). New York University Medical Center maintains a registry of patients with large CMN (the NYU-LCMN Registry). More than one-half of the current patients in the registry were enrolled before 2 years of age and 80% by 10 years of age, thus allowing for the collection of clinical and epidemiologic data regarding complications associated with large CMN over time.[7] As of data published in 2005, 205 patients were enrolled in the registry, of whom 170 were followed prospectively. Overall, any melanoma was observed in 4.9% of registry patients and 2.3% of those patients fol-

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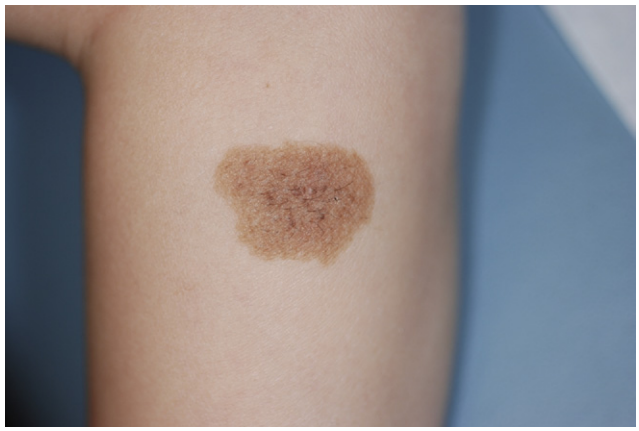

Figure 1 Small CMN.

lowed prospectively.[7] 70% of melanomas were diagnosed within the patient's first 3 years of life, and the remaining were diagnosed at age 35 years or older. Primary cutaneous melanoma occurred within a LCMN involving the trunk in 5 patients, or 2.5% of patients in the registry. One adult patient developed a primary cutaneous melanoma outside of their LCMN. Other sites at which a primary melanoma developed were the CNS (2 patients), retroperitoneum (1 patient), and metastatic disease with an unknown primary (1 patient). No melanomas were noted in any patient with a LCMN confined to the head and neck or to an extremity. In 1997, DeDavid et al[8] reviewed the data on 117 patients in the NYU-LCMN Registry and 177 cases of LCMN reported in the literature; there were 3 cases of primary cutaneous melanoma arising

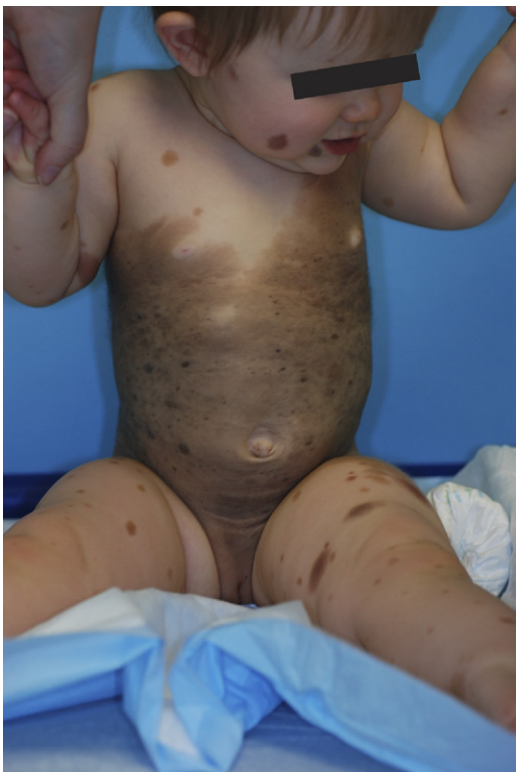

Figure 2 Large "bathing trunk" CMN with multiple satellite nevi.

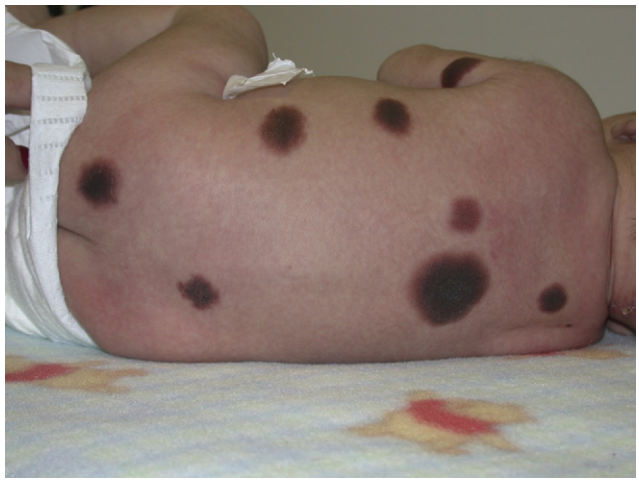

Figure 3 Multiple CMN of small and intermediate size.

within a LCMN in the NYU-LCMN Registry and 31 cases reported in the literature. All primary cutaneous melanomas arose within LCMN involving the torso with the exception of 2 in which the LCMN involved the head only. Satellite nevi were reported in 91% of patients with primary cutaneous melanoma. The age at diagnosis of melanoma ranged from birth to 52 years; 50% of patients with cutaneous melanoma were diagnosed before 5 years of age with a median age of 4.6 years. A total of 62% of patients were dead of disease, with a median age of death of 7.1 years. No primary cutaneous melanomas arising in a satellite nevus or in a LCMN involving an extremity were reported.

Bett[9] reviewed data ascertained from 1008 patients with LCMN who were enrolled in Nevus Network, Inc, an Internet-based support group and patient registry. Although this cohort has some degree of ascertainment bias because patients with complications attributable to their LCMN may be more likely to enroll, the prevalence of cutaneous melanoma in patients with LCMN involving the torso was 2.9%, similar to that reported by the NYU-LCMN Registry.[9] Of the 15 patients who developed primary cutaneous melanoma, the age at diagnosis ranged from birth to 58 years of age; 9 patients were age 8 years or younger at diagnosis, and 2 patients, one age 8 years and one age 34 years, had undergone partial excision of their LCMN previously. One patient, who was diagnosed with melanoma at age 7 years and who was treated with excision, also developed a second primary melanoma within a satellite nevus at age 18 years. Four patients died, including 1 child aged 4 years at diagnosis. In this cohort of patients there was also one 20-year-old patient with a facial CMN that had been previously treated with dermabrasion who developed cutaneous melanoma within the treated area; of the 392 patients with a LCMN involving an extremity or the head exclusively, this was the only reported cutaneous melanoma. In addition, 1 patient of 17 (6.7%) without a large CMN but with MCMN developed a primary cutaneous melanoma at 6 months of age. Both of these patients were alive. It is unclear whether patients with MCMN truly have a significantly risk of cutaneous melanoma given

the small number of patients with MCMN enrolled in this registry.

Kinsler et al[10] presented data on a cohort of 301 patients with a CMN, 122 of whom had a large CMN greater than 20 cm in diameter; 2 patients (1.6%) developed cutaneous melanoma over a mean follow-up of 9.2 years; the mean and median patient age at entry into the study was 2.9 and 1.2 years, respectively.[10] Both LCMN in the patients with melanoma involved the torso and were associated with multiple satellite nevi; ages at melanoma diagnosis were 2 and 7 months, and both children died. In a cohort of 46 patients with LCMN, of which 91% involved the torso and who were therefore at significant risk for the development of cutaneous melanoma and who were followed for a mean of 7.3 years, Egan et al[11] reported 2 patients who developed 3 primary cutaneous melanomas diagnosed at ages 2.7 and 3.5 years, one of which was fatal. The cumulative 5-year risk of cutaneous melanoma was reported to be 5.7%.

It is intuitive that excision of LCMN should reduce the risk of cutaneous melanoma. However, several investigators have reported the development of cutaneous melanoma in patients treated previously with excision or other surgical modalities, such as dermabrasion. Marghoob et al[12] reviewed the data from 4 studies encompassing 954 patients with LCMN, 68% of which had received surgical treatment previously (predominantly partial or complete excision). The prevalence of cutaneous melanoma in patients who had surgical intervention previously was 0.6% versus 7.5% in patients who received no treatment. Although it appears that surgical treatment may decrease the risk of cutaneous melanoma in this patient population, it cannot reduce the risk of extracutaneous melanoma, in particular the risk of primary CNS melanoma in patients with symptomatic neurocutaneous melanosis. In addition, there are concerns that excision with skin grafting may obscure the detection of subsequent cutaneous melanoma, thus delaying diagnosis. Some experts also caution that the biological behavior of residual melanocytes may be altered by surgical procedures, such as excision, dermabrasion, or chemical peels, which may result in increased malignant potential over time.[13] Increased pigmentation involving residual melanocytic nevus and the development of new melanocytic lesions both at the edges of the resected nevus and at distant sites have been reported in patients who have undergone surgical intervention previously.[14]

In addition to malignant melanoma, benign melanocytic proliferations may also occur within large CMN. These proliferative nodules may initially be difficult to differentiate from melanoma both clinically and histologically, although these benign proliferative nodules generally regress.[15] Clinically, proliferative nodules may present as small dermal nodules, usually less than 1 cm in diameter, that may be present at birth or may arise during childhood, or as larger dermal nodules greater than 1 cm in diameter that may proliferate rapidly, appear darkly pigmented, and ulcerate.[15] Histologically, proliferative nodules may manifest atypical epithelioid melanocytes with maturation, few mitoses, and gradual blending into the surrounding congenital nevus, or as sharply demarcated proliferations of epithelioid cells without significant mitoses.[15] Near universal expression of c-kit in proliferative nodules (97%) versus CMN (3%) has been suggested as a useful immunohistochemical marker for the histologic distinction of these benign proliferations.[16] Chromosomal aberrations have also been reported to occur with high frequency in proliferative nodules associated with CMN and typically occur as gains or losses of entire chromosomes.[17] The lack of detectable chromosomal aberrations as detected by comparative genomic hybridization, however, has also been suggested to be helpful in distinguishing benign proliferative nodules from melanoma, which almost always display genomic instability with high frequency of partial chromosomal anomalies manifest as structural aberrations involving chromosome fragments (95%).[17,18]

There are several theories regarding the significantly increased risk of melanoma in association with large CMN. One involves the presence of a significantly increased number of "at risk" melanocytes with a fixed rate of malignant degeneration over time. Another theory is that the melanocytes that comprise large CMN are biologically different from the melanocytes found in small and intermediate melanocytic nevi and have a greater malignant potential. Differential gene expression studies have indicated that melanocytes derived from large CMN display up-regulation of genes implicated in chemoresistance in cancer.[19] Large CMN have been reported to demonstrate a high frequency of NRAS mutations (70%) and a low frequency of BRAF mutations (15%), and melanocytes derived from 2 LCMN were demonstrated to harbor a chromosomal alteration involving the BRAF oncogene predicted to result in constitutive activation, suggesting that these genes, which are implicated in melanoma, may contribute to the malignant potential of LCMN.[19,20] In contrast, small and intermediate CMN appear to demonstrate a greater frequency of BRAF mutations (70%-94%) and a lower frequency of NRAS mutations (14%-56%).

The precise risk of malignant melanoma arising in small and intermediate CMN is unknown, as no prospective study of sufficient duration and sample size has been undertaken. The authors of 2 studies have attempted to prospectively follow a cohort of patients with CMN with respect to the risk of development of cutaneous melanoma. Sahin et al[21] did not observe any melanomas arising in association with intermediate-sized CMN (1.5-19.9 cm in diameter) in a cohort of 230 patients followed for an average of 6.7 years and a median of 5.8 years; the average and median age when patients were first evaluated were 19 and 12 years, respectively. Similarly, Swerdlow et al[22] found no cutaneous melanomas arising in association with CMN involving less than 4% body surface area (correlating approximately to <20 cm in diameter) in 232 persons followed for a mean and median of 23.7 and 25 years, respectively; 89% of the person-years occurred at ages younger than 30 years.

In addition, an unequivocal history of a precursor melanocytic nevus associated with a melanoma is often lacking in large case series of cutaneous melanoma. Although large congenital nevi typically show distinctive histologic features, such as the presence of melanocytes within the lower dermis and in close association with adnexal structures, small and

intermediate congenital nevi may lack these features; in addition, these histologic features are not pathognomonic for the diagnosis of a CMN.[23] In general, the risk of malignant melanoma arising in a small or intermediate CMN is believed to be very small in children, and therefore elective excision of most small and intermediate CMN is not recommended as long as clinical follow-up can be ensured. Melanoma arising in small and intermediate CMN typically occurs at the dermal-epidermal junction and presents as a readily apparent clinical change in the appearance of the existing nevus, as opposed to melanoma arising within a large CMN, which typically develop in the dermis, making early detection before the development of a large palpable subcutaneous nodule and/or ulceration challenging.

Illig et al[24] reviewed a series of 52 cases of melanoma arising in CMN; the age at diagnosis ranged from 19 to 79 years, and 27 patients were younger than 50 years old at the time of diagnosis. Only 4 melanomas occurred in association with a CMN ≤10 cm in diameter, and the majority were superficial spreading melanomas arising either eccentrically or at the border of the preexisting nevus. Betti et al[25] presented a cohort of 190 cutaneous melanomas, of which 7.9% demonstrated either histologic or clinical evidence of an associated CMN, which ranged in size from 0.5 to 1.5 cm; the majority were either melanoma in situ or superficial spreading melanoma <0.76 mm in thickness. The patients ranged in age from 16 to 77 years, with only a single patient <21 years of age.

Primary cutaneous melanoma is exceedingly rare in children; the Surveillance, Epidemiology, and End Results Section of the National Cancer Institute reported only 698 cutaneous melanomas arising in patients younger than 20 years of age who were diagnosed between 1973 and 1996; these patients accounted for only 1.2% of all reported cutaneous melanomas during this period.[26] In a case series of children and adolescents with cutaneous melanoma who were diagnosed before 20 years of age, Sander et al[27] reported that an associated CMN was noted either histologically or by history in only 5 (4.4%) of 113 patients; none were reportedly associated with a large CMN. Similarly, Temple et al reported the presence of an associated CMN in only 2 (6.5%) of 31 children and adolescents younger than 20 years of age diagnosed with cutaneous melanoma, and Spatz reported the presence of an associated CMN in only 4/60 (6.7%) children and adolescents younger than 16 years of age diagnosed with cutaneous melanoma.[28,29] The greatest reported prevalence of an associated CMN was reported by Schmid-Wendtner et al,[30] who noted the presence of an associated CMN in 8 (22%) of 36 of children and adolescents younger than 18 years of age diagnosed with cutaneous melanoma.

Neurocutaneous Melanosis

Neurocutaneous melanosis (NCM) is a rare, sporadic disorder usually seen in the context of a LCMN or MCMN and is characterized by the presence of excessive proliferation of melanocytes within the CNS, including the leptomeninges as well as the brain parenchyma. It is believed to represent a congenital error in morphogenesis of embryonal neuroectoderm, which in less pronounced form may also underlie the genesis of CMN.[31] Diagnostic criteria were refined in 1991 by Kadonaga and Frieden; a definitive diagnosis includes the presence of a large (>20 cm in diameter in the adult) CMN or multiple (>3) CMN in association with histologic confirmation of leptomeningeal melanocytosis or CNS melanoma; absence of cutaneous melanoma unless there is no evidence of CNS melanoma; and no evidence of meningeal melanoma, unless there is no evidence of cutaneous melanoma.[32] Because it can be difficult to differentiate primary CNS melanoma from metastatic melanoma, in the rare patient with the presence of both cutaneous and CNS melanoma, these criteria make a diagnosis of NCM difficult. A provisional diagnosis of NCM may be made when the above criteria are met without histologic confirmation of leptomeningeal melanosis.

Several investigators have demonstrated that posterior axial location of a LCMN and the presence of multiple satellite nevi are risk factors for the development of neurocutaneous melanosis, with the highest risk in those patients with multiple satellite nevi.[7,33-36] In a cohort of 26 patients with NCM, Marghoob et al[33] reported a 5.1-fold increased risk of NCM in those patients who had more than 20 satellite nevi compared with those who did not. In addition, in a review of 35 cases of NCM reported in the literature, Kadonaga concluded that the majority (33/35 cases) also had involvement of the head and/or neck, and while 66% of patients had a LCMN (96% of which involved the posterior axis), 34% of patients had MCMN in the absence of a single large CMN.[32]

Symptoms of NCM are often related to increased intracranial pressure and include seizures, hydrocephalus, cranial nerve palsy, hemiparesis, and developmental delays. Most children with symptomatic NCM present within the first 5 years of life, with many presenting by 2 years of age.[34-37] Delayed presentation in older children, adolescents, and adults has also been reported, usually with symptoms such as headaches or neuropsychiatric manifestations.[38] Both Lovett and Bittencourt reviewed small cohorts of 26 and 30 patients, respectively, with LCMN who underwent magnetic resonance (MR) imaging to evaluate for NCM; the overall prevalence of NCM diagnosed either by suggestive radiologic findings on MR imaging and/or on the presence of neurologic symptoms was reported as 17% to 23%, of which 60% to 67% of patients with NCM were symptomatic.[35,37]

Conversely, Foster et al[39] presented prospective data on 42 asymptomatic patients with LCMN overlying the posterior axis or involving the head and neck who underwent MR imaging; the average age at presentation was 5 months and clinical follow-up averaged 5 years. Abnormal MR findings consistent with NCM were seen in 10 patients (23%), of which only 1 patient (10%) became symptomatic during the follow-up period. Agero et al[36] reviewed data on a cohort of 379 patients with LCMN participating in Nevus Outreach, Inc, a nonprofit, Internet-based registry and patient support group for patients with CMN, of which 26 (6.9%) reported NCM, with 17 reporting neurologic symptoms (4.5% of the entire registry and 65% of patients reporting NCM); of 186

patients who had undergone MR imaging, 23 (12.3%) had abnormal MR findings; 14 were symptomatic (7.5% of the entire registry and 61% of the patients with abnormal MR findings). The prognosis of symptomatic NCM is poor; DeDavid et al[34] presented a cohort of 33 patients with symptomatic NCM; 79% of patients were deceased with the median age of death being 3 years; 50% died before 5 years of age. Death is attributable in a significant number of symptomatic patients to the development of primary CNS melanoma, although death may also occur as the result of neurologic complications. Care is palliative because chemotherapy and/or radiotherapy has not proven to be effective in the treatment of NCM.[32,38] There is a significant risk of primary CNS melanoma in patients with symptomatic NCM, with a reported prevalence of 50% to 64% and a median age at death of 3 years.[32,34,37]

Characteristic findings of NCM on MR imaging are focal T1 and less commonly T2 shortening, consistent with increased melanization, involving the anterior temporal lobes and amygdala, cerebellum, thalamus, and/or base of the frontal lobe (Fig. 4).[40] These areas correlate with the normal distribution of melanocytes within the leptomeninges. Diffuse leptomeningeal enhancement on postgadolinium T1-weighted MR imaging of the convexities of the cerebral and cerebellar hemispheres, posterior surface of the brainstem, and quadrigeminal and superior vermian cisterns may also be seen but is believed to occur less frequently and may be more frequently seen with symptomatic NCM.[41-43] The presence of vasogenic edema and areas of necrosis and/or hemorrhage are associated with malignant degeneration.[40]

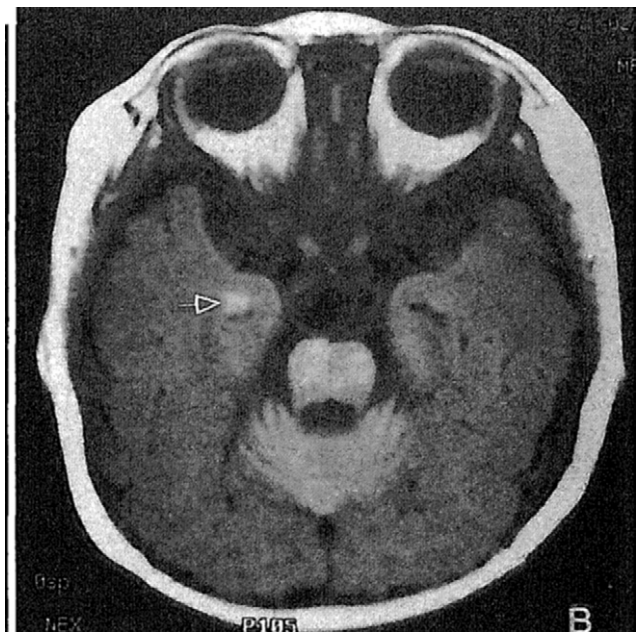

Figure 4 MR imaging of neurocutaneous melanosis demonstrating foci of high signal intensity on T1-weighted images in the cerebellum, pons, and right anterior temporal lobe.

Conclusions

Infants with a LCMN or MCMN are at significant risk for the development of cutaneous melanoma arising within their LCMN, in particular if the LCMN involves the torso. The significant risk of primary cutaneous melanoma within the first 5 to 10 years of life necessitates close clinical follow-up of affected infants and children. Those infants with a LCMN overlying the posterior axis, in particular if associated with greater than 20 satellite nevi, and those patients with MCMN are also at high risk for neurocutaneous melanosis, which carries a significant risk for neurodevelopmental sequelae and primary CNS melanoma. Consideration should be given for evaluation of at-risk infants with a LCMN or MCMN with magnetic resonance imaging of the brain and spinal cord, ideally before 4 to 6 months of life.

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