

Large Congenital Melanocytic Nevi: Associated Risks and Management Considerations

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Large congenital melanocytic nevi (LCMN) in neonates can cause considerable concern for parents, family members, and physicians. A detailed understanding of the medical risks, including cutaneous melanoma (CM), extracutaneous melanoma (ECM), and neurocutaneous melanocytosis (NCM), as well as the psychological stress that these lesions can cause in patients, will guide informed management decisions as well as provide comfort to parents. Current data indicate that LCMN greater than 20 cm, and more likely greater than 40 to 60 cm, are the lesions at greatest risk for complications such as CM, ECM, and NCM. Additionally, lesions on the trunk are at greater risk for developing CM, and LCMN in association with numerous satellite nevi are at greatest risk for NCM. Individualized management plans, including clinical observation, magnetic resonance imaging (MRI), and possibly surgery should be based on the risk versus benefit ratio, taking into account the size of the LCMN, its location, the number of satellite nevi, symptoms, and numerous other factors which will be reviewed. This paper will provide a detailed analysis of the risks associated with LCMN, as well as a discussion regarding management and treatment options.

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Large congenital melanocytic nevi (LCMN) are benign melanocytic neoplasms that develop in utero during the first trimester of pregnancy. The nevomelanocytes comprising the LCMN are usually located within the dermal-epidermal junction and dermis, but they can penetrate into the subcutaneous fat, fascia, and occasionally into underlying muscle. Because the presence of an LCMN may affect the normal development or function of adnexal structures, such as eccrine and sebaceous glands, it is not surprising that the overlying skin may manifest xerosis and hypohydrosis resulting in pruritus.¹ The nevomelanocytes may also disrupt the normal cutaneous architecture resulting in skin fragility that can manifest with superficial erosions or ulcerations.²

Congenital melanocytic nevi enlarge in proportion to the overall body surface area expansion but may exhibit more rapid growth during the first 6 months of life.³ Although a

variety of criteria exist defining what constitutes an LCMN, they are traditionally defined as nevi that are predicted to attain a diameter of at least 20 cm in adulthood (Fig. 1). Those LCMN that are greater than 40 to 60 cm are categorized by some as “very large LCMN” or “giant” nevi.⁴ A scaling factor can be used to predict the size a congenital melanocytic nevus (CMN) will attain in adulthood: CMN on the head of an infant will enlarge by a factor of 1.7, on the lower extremities by a factor of 3.3, and on the torso, upper extremities, and feet by a factor of 2.8.⁵ Multiple smaller satellite CMN may occur in patients with LCMN, with reported incidence ranging from 19% to 83% depending on the study population and location of the LCMN (Fig. 2).^{6,7}

Patients with LCMN are at increased risk for developing a host of medical problems, including, but not limited to, rhabdomyosarcoma, liposarcoma, tethered cord syndrome, and subcutaneous atrophy. The 2 most common problems are malignant melanoma (MM), which includes both cutaneous and extracutaneous melanoma (CM and ECM, respectively), and neurocutaneous melanocytosis (NCM). Although the absolute risk for developing MM or NCM is less than 11%, it should be intuitively obvious that the calculated relative risk will be very high.^{4,8} It is therefore imperative that dermatologists structure a management plan that adequately ad-

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Figure 1 LCMN with few satellite nevi (<20). Given its very large size and truncal location, this patient is at relatively high risk for CM. Clinical observation of such lesions can prove challenging because of the heterogeneous clinical morphology.

dresses the risk of MM and NCM while also addressing the potential cosmetic and psychosocial impact of the LCMN.

Risk of Cutaneous Melanoma

Patients with LCMN are at increased risk for developing CM and ECM. It should be noted that CM and ECM are not ideal descriptive terms. Primary melanoma within an LCMN may arise in the cutaneous tissue of the epidermis and dermis, but it may also arise from cells within the LCMN located in the subcutaneous fat, fascia, or muscle. Although the subcutaneous tissue, fascia, and muscle are not anatomically part of the cutaneous tissue compartment, and thus should technically be considered “extracutaneous,” they are by convention considered “cutaneous” if involved by the LCMN. In this article we will continue to define primary CM as melanoma arising in the skin and subcutaneous tissue of LCMN and ECM as primary melanoma arising predominantly in the central ner-



Figure 2 LCMN with numerous satellite nevi (>20). Given its very large size, truncal location, and numerous satellites, this patient is at relatively high risk for both CM and NCM. Clinical observation of this patient may prove challenging given the LCMNs heterogeneous clinical morphology.



Figure 3 Smooth, fairly homogeneous LCMN of the trunk without satellites. This patient is probably at lower risk for developing CM and NCM compared with patients in Figures 1 and 2. This LCMNs smaller size, absence of satellites, and homogeneous morphology makes clinical follow-up less challenging.

vous system (CNS), which most researchers now consider to be one of the potential complications encountered in patients with NCM.

The risk of CM in patients with LCMN, compared with those without, is quite high, with reported relative risk estimates ranging from 52 to more than 1000.^{9,10} When viewed as an absolute risk, the numbers are somewhat more comforting, with a reported range between 0% and 11% of patients with LCMN developing CM.^{10,11} However, when CM does develop in LCMN, it often arises below the dermal-epidermal junction, presumably from nevomelanocytes of the LCMN that are located in the deeper dermis and subcutaneous tissue.¹² This phenomenon can make the early clinical detection of these deeply seated CM via visual inspection challenging. More than 70% of CM in patients with LCMN are diagnosed by age 10, presumably because of a higher density of immature, possibly genetically unstable, melanocytes present during early life.⁵

In general, most studies reporting on the risk of CM in LCMN enrolled any patients with LCMN that were at least 20 cm in diameter, and most studies did not stratify the risk calculations based on the absolute size of the LCMN or its clinical appearance (ie, flat, raised, rugous, speckled, etc). It is currently unknown whether flat, homogeneous light brown, and relatively smaller sized LCMN (Fig. 3) carry the same risk for developing CM compared with very large LCMN (>40-60 cm) that are darkly pigmented, raised, and rugous (Fig. 4). However, some recent data suggest that the risk for CM may be highest for lesions greater than 40 cm.^{4,7,10} In the Registry of LCMN of the New York University School of Medicine (NYU-LCMN), 14 of 15 patients with MM and/or NCM had LCMN larger than 50 cm.⁴ In 2006, Krengal and colleagues found the risk of MM to be markedly elevated in LCMN having diameters greater than 40 cm.¹⁰ The optimal LCMN size stratification that best predicts who is at high risk for MM and/or NCM has yet to be determined and may be larger than originally thought. It is important to



Figure 4 Rugous LCMN on the trunk with few satellites (<20). This patient's lesion is probably at greatest risk for developing a cutaneous malignancy and, despite meticulous clinical follow-up via inspection and palpation, it may prove difficult to discover CM at an early stage.

stress that regardless of exact size, it appears that the larger the size of the LCMN, the greater the risk for developing CM, ECM, and NCM.^{4,7,10}

Another factor associated with increased risk of CM is location of the LCMN on the torso. In a 2005 retrospective review of 1008 patients with large or multiple CMN, Bett⁶ demonstrated that the absolute risk of CM developing in LCMN located on the trunk was 2.9% (15/525), whereas the absolute risk of CM developing on head and limb LCMN was 0.3% (1/336).

Risk of Extracutaneous Melanoma and Neurocutaneous Melanocytosis

Researchers^{4,7,10,13} have demonstrated an increased risk of ECM and NCM in patients with LCMN. Although the overall risk for developing melanoma in LCMN is well documented, the contribution of CM compared with ECM towards the overall melanoma risk remains unknown. In the past, melanomas located in the CNS were often presumed to be a metastatic manifestation of an occult primary CM believed to be located somewhere within the LCMN. However, it is now known that melanoblasts normally migrate from the neural crest, along the leptomeninges, before migrating to the skin during embryogenesis. Aberrant migration of these cells may result in the deposition of melanocytes along the leptomeninges, resulting in NCM.^{4,14-17} Rarely the melanocytes deposited along the leptomeninges may give rise to primary melanoma in the CNS.^{14,15} Even the limited and controlled proliferation of benign melanocytes along the leptomeninges can result in increased intracranial pressure and its associated neurologic signs and symptoms, including headache, seizure, and focal neurological deficits.^{17,18} During the remain-

der of this manuscript we consider ECM to be a complication related to NCM.

The risk of NCM in patients with LCMN is well known and has been documented in 2 prospective cohort studies, the results of which suggest that the risk of NCM may be greater than for developing CM.^{4,18} In the data from the Nevus Outreach, Inc-LCMN (NOI-LCMN) registry of 379 LCMN patients, 6.9% of patients with LCMN developed NCM, whereas no patients developed CM.¹⁸ Similar results were found in an analysis of data from NYU-LCMN of 160 patients with LCMN, in which again, 7% of patients followed over 5.5 years developed NCM, whereas no patients developed CM.⁴ The NYU-LCMN registry reported the 5-year cumulative risk of developing MM to be 2.3%, NCM to be 2.5%, and the risk for developing MM and/or NCM to be 3.3%.⁴ Although no CM has been diagnosed during prospective follow-up, recent retrospective studies have documented the development of CM. However, even in these retrospective studies the risk for developing NCM appeared to be greater than for developing CM.⁷

Kinsler and colleagues⁷ reviewed 120 patients with CMN and found that although only 1.7% of patients developed melanoma (2 cases of metastatic disease, 1 with MM arising within the LCMN and the other with unknown primary), 18% had magnetic resonance imaging (MRI) and/or clinical neurological abnormalities indicative of NCM. In the reviews by Bett of patients with LCMN or multiple CMN, 5.1% of patients (51/1008) developed NCM, whereas 2.0% developed CM (17/876).^{6,13} When evaluating the aforementioned data, it is important to be aware that many patients (or guardians) elect to undergo partial or total surgical excision of the LCMN, potentially leading to an underestimation of the risk of CM.¹⁹ With that being said, the risk of NCM and ECM is of great consequence, especially when considering potential screening and management strategies for LCMN, as many patients with CNS disease are initially asymptomatic.^{7,13}

As mentioned previously, the risk for developing CM is greatest for patients with very large LCMN located on the torso. It appears that the association of very large LCMN and increased risk of MM is also true regarding risk for NCM.^{4,7} However, location of LCMN with respect to risk of NCM, which on univariate analysis suggested a risk association with posterior midline (axial) LCMN, was not found to be associated with an increased risk of NCM on multivariate analysis.^{7,20} In a multivariate analysis performed by Marghoob and colleagues²⁰ of 379 patients from the NOI-LCMN registry, 22 of whom had NCM, patients with more than 20 satellite lesions had a 5.1-fold increased risk for NCM ($P < 0.001$; 95% CI – 1.9 to 14.0). To dichotomize the data, the number of satellite nevi in their study was set at 20, but it is important to note that new satellite nevi continue to arise in patients with LCMN over time, with a peak incidence occurring at age 5.^{20,21} Although Marghoob and colleagues²⁰ did not correlate the number of satellite nevi with age, they did demonstrate the concept that, in patients with LCMN, as the number of satellites increases, so does the risk of NCM. This is in contrast to risk of developing CM in an LCMN, which although dependent on the size of the LCMN, appears to be indepen-

Table 1 Summary Table: Risk of CM and NCM in LCMN

	Size of LCMN	Location of LCMN	Satellite Nevus
Risk of CM	Larger the nevus the greater is the risk for melanoma (20 < 40 < 60 cm)	Lesions located on the torso appear to be at increased risk for CM compared with LCMN located on the head, neck, or extremities	Number of satellite nevi does not confer an increased risk of CM because no CM has ever been reported to have developed in a satellite nevus
Risk of NCM	Larger the nevus the greater is the risk for NCM (20 < 40 < 60 cm)	Location of the LCMN does not appear to be a significant predictor of NCM	The greater the number of satellite nevi the greater is the risk for NCM

dent of the number of satellite nevi present. In addition, although CM can develop in LCMN, no CM has ever been reported to have developed in a satellite nevus.

With the data present in the literature, we can begin stratifying patients with LCMN who are at greatest risk of developing CM and/or NCM. Although location seems to play a role in defining the risk of CM, and the number of satellite nevi plays a role in defining the risk of NCM, the size of the LCMN influences the risk of both CM and NCM.^{4,6,7,10,20} These findings are summarized in Table 1.

Psychosocial Consequences of LCMN

In addition to the medical risks conferred by LCMN, these nevi greatly influence the lives of patients because of the psychosocial issues they impart. Approximately 30% of children with LCMN feel their social lives are negatively impacted by the aesthetic appearance of their nevi, and 26% are reported to have behavioral and emotional issues.²² The knowledge of the risk of malignancy can also be psychologically disturbing to these patients and their families.

Management of Large Congenital Melanocytic Nevi

The management of LCMN must be considered on an individual basis. Numerous factors to consider include location and depth of penetration of the nevus; risk of CM and NCM; patient age; ease of examining the nevus for suspicious changes; and the cosmetic and psychological impact associated with the nevus or subsequent scar resulting from removal. Current management options for LCMN include expectant observation, prophylactic treatment to theoretically decrease risk of malignancy, and treatment to improve cosmesis. Treatment interventions include surgical excision, dermabrasion, laser therapy, chemical peels, and curettage. Regardless of whether surgical interventions are pursued, management of these patients should always include serial examinations by a dermatologist experienced in monitoring such lesions. Because of the large number of variables involved in managing patients with LCMN, a multidisciplinary approach, including a pediatrician, dermatologist, dermatopathologist, plastic surgeon, neurologist, radiologist, psychologist, and primary care physician, along with patient (if

age appropriate) and family input, is most helpful. Setting realistic expectations for the patient and family regarding the possible aesthetic and functional outcomes when discussing treatment options, while at the same time addressing the small but real risk for developing CM and NCM, is important.

There is only 1 absolute medical indication for surgical intervention in the management of LCMN—the development of a malignancy. Relative indications for surgical intervention include prophylactic treatment to theoretically reduce the risk for developing CM, and for cosmetic purposes. It is well documented that the risk of CM and NCM increases with increasing size and perhaps thickness of the CMN. Unfortunately, lesions that are most challenging to remove surgically are those that may be at greatest risk for developing a malignancy.

All patients with LCMN should be screened periodically for MM and NCM. Visual inspection can be facilitated by obtaining baseline images to use for comparison, which may help in the detection of subtle focal changes indicative of early CM. Dermoscopy may also prove useful in this endeavor, although it cannot be used to detect tumors developing below the cutaneous layer. Palpation of the LCMN can assist in identifying these deeply seated tumors, and some have suggested that scanning with techniques, such as positron emission tomography (PET) may be useful.²³

For those considering prophylactic treatment, it is important to note that a critical review of the literature is unable to answer the question of whether surgical intervention reduces the risk of CM.²⁴ Clearly, surgical intervention cannot reduce the risk of CM to zero because it is impossible to remove every nevus cell, and cases of CM developing from residual cells have been reported.^{6,12,25} In our opinion, the intervention that most thoroughly addresses the risk of malignancy and cosmesis is surgical excision. Current evidence indicates that the risk of developing melanoma in an LCMN is greatest before puberty, and therefore any prophylactic surgical intervention would be most beneficial if performed early in life. Therefore, the burden of this decision often rests squarely on the shoulders of the parents. Other advantages to early surgical intervention are based on the belief that infants may better tolerate tissue expanders, serial stage excisions and surgical recovery, as well as exhibit better wound healing resulting in improved cosmetic result. However, general anesthesia is not without risks, and this also must be considered when counseling families of very young infants about sur-

gery. Surgical removal of the LCMN will have no effect on the risk for NCM. Hence, prophylactic surgical interventions should be postponed in patients with NCM until it is determined that their NCM is not progressing to symptomatic disease.

Surgical intervention may also help address some of the cosmetic concerns. The significant psychosocial burden endured by patients with LCMN is well documented.²² Although surgical excision may lead to unappealing, disfiguring, or physically restrictive scars, 76% of patients prefer scars to LCMN, whereas only 24% regretted having surgery (A.A. Marghoob, Department of Dermatology).²² This finding may be because scars tend to be more socially acceptable compared with LCMN. Early surgical intervention has also been shown to relieve the stress and anxiety of patients and their families regarding the threat of malignancy.²⁶ It is important to be aware that many LCMN will spontaneously lighten over time and this fact may influence the decision regarding whether or not to pursue treatments aimed at improving cosmesis.

Dermabrasion and curettage are other options that may reduce the risk of CM and improve cosmesis. These procedures are best performed within the first 4 to 6 weeks of life when it is apparently easier to find a tissue plane separating the nevus cells from underlying tissue.²⁷ Laser therapy may also improve the appearance of LCMN. Although these treatment modalities may improve the overall cosmetic outcome and reduce the risk of CM, they cannot fully eliminate the risk and the cosmetic results are variable. In addition, superficially altering the appearance of an LCMN with scar tissue may make it more difficult to clinically monitor for the development of CM.

Because of the risk of NCM in patients with LCMN, one of the key management questions is whether they should all be screened with an MRI of the CNS. In a study by Agero et al²⁸ of 148 asymptomatic patients with LCMN located on the posterior axis, 6% had positive findings consistent with NCM on MRI. A study by Foster et al²⁹ demonstrated that out of 43 patients with LCMN overlying the dorsal spine or scalp, 14 patients had NCM, and only one went on to develop symptoms over an average of 5 years of follow up. A more recent review by Kinsler et al⁷ of 120 high-risk patients (LCMN, many satellites, multiple CMN) found that 15% had abnormal MRI findings, and 72% of those patients developed symptomatic disease by age 2. Although not all asymptomatic patients with NCM go on to develop symptomatic disease, longer follow up will be necessary to determine the real long-term prognosis in asymptomatic patients. Theoretically, screening MRI scans of the CNS should be performed by 4 to eight months of age, before myelinization can interfere with visualization of the leptomeningeal melanin deposits.³⁰ From a practical standpoint, this may not be necessary, as follow-up MRIs of patients with positive initial findings did not show a reduction in signal intensity at a later age.⁷

It is clear that all symptomatic patients with LCMN should obtain an MRI of the CNS, and an MRI scan should be strongly considered for asymptomatic patients with LCMN, especially those with very large LCMN and/or many satellite

nevi. Negative imaging studies can be reassuring for patients and families, while positive findings may lead to therapeutic interventions aimed at preventing or limiting progression to symptomatic disease (ie, surgical resection or ventriculoperitoneal shunt placement) as well as potentially altering plans for elective cutaneous surgery. If the initial screening MRI is negative then the general recommendation is that no follow-up MRI scans are necessary unless the individual develops neurological symptoms suggestive of NCM. By contrast, if the initial screening MRI is positive then the patient should be followed by a neurologist and decisions regarding the need for repeat MRI scans will depend on multiple factors, such as the presence or absence of symptoms and type of initial MRI finding (ie, mass lesion, hydrocephalus, etc).

Conclusions

LCMN in neonates can cause considerable concern for parents, family members, and physicians. A detailed understanding of the medical risks, including CM, ECM, and NCM, as well as the psychological stress associated with these lesions, will guide informed management decisions and provide comfort to parents. Current data indicate that LCMN greater than 20 cm, and more likely greater than 40 to 60 cm, are the lesions at highest risk for complications, such as CM, ECM, and NCM. Additionally, lesions on the trunk are at higher risk for developing CM, and LCMN in association with numerous satellite nevi are at highest risk for NCM. Individualized management plans, including clinical observation, MRI, and possibly surgery should be based on the risk versus benefit ratio, taking into account the size of the LCMN, its location, the number of satellite nevi, symptoms, and other factors as discussed above. Regardless of what type of management is decided upon, be it surgical or observation, it must be remembered that most LCMN patients lead healthy, productive lives.

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