Congenital Melanocytic Nevi and the Risk of Malignant Melanoma: Establishing a Guideline for Primary-Care Physicians

Jeremy Nikfarjam, MD1, and Earle Chambers, MPH, PhD2
1Department of Surgery, Division of Plastic & Reconstructive Surgery, Montefiore Medical Center, Bronx, NY; 2Department of Family and Social Medicine, Department of Epidemiology & Population Health, Albert Einstein College of Medicine, Bronx, NY

Objective: The objective of this review is to determine what size congenital melanocytic nevi (CMN) increases the risk of malignant melanoma in affected patients.

Background: Congenital melanocytic nevi are benign proliferations of cutaneous melanocytes apparent at birth or in the first postnatal weeks. The Kopf system classifies nevi based on size: small, <1.5 cm in diameter; medium, 1.5–19.9 cm in diameter, and large, ≥20 cm in diameter. Great variability exists in quantifying the risk of malignant transformation from congenital nevi of different sizes. Evidence-based standard guidelines for clinical investigation need to be established.

Methods: Literature search included studies on medium, large, and giant congenital nevi in association with melanoma.

Results: Three studies pertaining to small, medium, and large congenital nevi are defined. The odds ratio of malignant transformation from small CMN was determined to be 20.9 by history and 10.5 by histology in 238 patients in the case-control study selected. No malignant transformation was found in a prospective study of 230 individuals with medium-sized melanocytic nevi. Finally, a 5% risk of malignant transformation was reported in a prospective study of patients with large congenital nevi.

Conclusion: All patients should receive total body skin and mucosal surface exams. Patients with small CMN (<1.5 cm in diameter) and medium CMN (≥1.5 cm–19.9 cm in diameter) should be closely observed over their lifetimes and given the option of specialist referral. Finally, patients with large CMN (≥20 cm in diameter) should be referred to specialists upon initial presentation. More original data and follow-up are needed for maturation of evidence-based clinical recommendations.

INTRODUCTION

Congenital melanocytic nevi (CMN) are benign proliferations of cutaneous melanocytes clinically apparent at birth or within the first postnatal weeks (Walton et al., 1976). At least 2.5% of white infants are noted to have some type of pigmented lesion at birth, but only 1% have biopsy-confirmed nevocellular nevi (Walton et al., 1976). Prevalence of CMN ranges from 0.2% to 2.7% in lesions less than 1.5 cm in greatest diameter (Pratt, 1953; Walton et al., 1976; Alper et al., 1979) to 0.005% in lesions greater than 10 cm in greatest diameter (Castilla et al., 1981).

Clinical appearance of congenital melanocytic nevi varies with respect to size, morphology, texture, age, and location. Although considered controversial in the past, the Kopf system is now the most widely accepted size-based standard for the classification of CMN: small, <1.5 cm in greatest diameter; medium, 1.5–19.9 cm in greatest diameter; and large or giant, ≥20 cm in greatest diameter (Kopf et al., 1979). In addition to size, CMN can be distinguished on the basis of having a round or oval shape, with a regular, smooth, well-demarcated border. The surface texture can be papular, rugose, pebbly, verrucous, or cerebriform, with combinations of textures in a single lesion or in different lesions. During the neonatal period, CMN may appear light in color, hairless and flat, or raised. As the child grows, the same lesion may become more uniform in color with darker pigmentation, and acquire long, coarse, dark hairs. CMN can appear anywhere on the body, with a slight predilection for giant CMN to appear on the posterior trunk (Egan et al., 1998). Anatomical location also appears to influence the progression in size of CMN with age. According to Rhodes et al. (1996), the growth rate of CMN is usually correlated with anatomic site after early infancy, with lesions on the head increasing in size by a factor of 1.5, and lesions on other anatomic areas increasing in size by a factor of 3.

The embryological origin of melanocytes found in CMN is the neural crest. As the progression from formation to closure of the neural tube takes place, the cells of the neural crest are delineated as a separate functional entity from those of the neural tube. The neural crest cells ultimately give rise to the ectoderm, most notably melanocytes, the leptomeninges, and the peripheral nervous system. Cramer (1998) proposed a theory of the melanocytic differentiation pathway, describing the migration, plasticity, and differentiation of pluripotent stem cells of the neural crest. The consequences of this theory account for aberrations in the melanocyte differentiation pathway, namely the capability of melanoma to arise in a nevus and leptomeninges as observed in neurocutaneous melanocytosis. Furthermore, nevi may also contain pluripotent cells capable of differentiation and proliferation throughout the lifetime of the nevi (Soyet et al., 2007).
The inception of CMN in utero has not been definitively evidenced by imaging modalities or in utero studies. Nevertheless, Hamming (1983) reported a case of a “kissing nevus” in which a congenital melanocytic nevus developed on adjacent parts of the upper and lower eyelids and appeared as a single, contiguous lesion when the eyelids were closed. Based on this observation, CMN were estimated to develop between the 9th and 20th weeks of gestation.

Histological analysis can aid in differentiating CMN from acquired nevi. Although there are no pathognomonic features of CMN, histological analysis can be employed when CMN are suspected in the absence of documentation of nevus presence at birth (Cribier et al., 1999). In contrast to acquired nevi, nevomelanocytes of CMN proliferate in the subjacent dermal tissue and can spread to the deep dermis and even subcutis (Zaal et al., 2004). These nevomelanocytes can extend between collagen bundles of the reticular dermis, within and around hair follicles, sebaceous glands, vessel walls, and nerves (Mark et al., 1973; Rhodes et al., 1985; Barnhill and Fleischli, 1995). The depth and the pattern of nevus cell migration are directly related to the size of the CMN in infants (Barnhill and Fleischli, 1995). Nevertheless, nevus cell migration may continuously occur even after birth. Walton et al. (1976) studied biopsies of small CMN taken within 72 hours after birth, and concluded that the spread of congenital nevi into deeper layers of the dermis and subcutis occurs largely after birth. In addition, Mark et al. (1973) demonstrated that the epidermal-dermal junction aspect of a nevus may disappear with time, rendering a dermal nevus without epidermal involvement. On the other hand, malignant melanoma arising within CMN usually originates at the epidermal-dermal junction (Reed et al., 1965).

Thus, the determination of malignancy is of far greater importance than the question of whether the nevus is congenital or acquired (Zaal et al., 2004). Studies attempting to quantify the percentage of primary melanoma originating from a CMN have shown inconsistent results. In a study conducted by Schmid-Wendtner et al. (2002), 9 of 6,931 (0.13%) patients under the age of 18 years developed cutaneous melanoma associated with a congenital nevus. Previous to this analysis, Illig et al. (1985) reported that at least 2.8% of melanoma cases arose from congenital nevi, mostly those that were single and less than 10 cm. In a study assessing the risk of melanoma from CMN in a lower-risk black population, Shpall et al. (1994) calculated an actual risk in blacks up to age 75 to be approximately 1 in 2,000 (0.05%). The level of risk reported among these studies results varies from tenfold to a hundredfold and thus is of limited aid to clinicians in gauging the risk of malignancy in patients with CMN.

Several studies assessing the lifetime risk of malignant melanoma from CMN based on size have been undertaken in order to empower clinicians with practical and simple measures for evaluating malignancy risk in their patients. Among patients with giant CMN, a lifetime risk of malignancy of 5% to 60% has been reported in the literature (Kaplan, 1974; Kang et al., 1992; Sober and Burstein, 1995). Marghoob et al. (1996) concluded a lifetime increased risk of 3.3% for melanoma in large CMN measuring 20 cm or more in largest diameter, or CMN predicted to attain this size by adulthood. Quaba and Wallace (1986) calculated an 8.52% lifetime risk for melanoma in a retrospective analysis of 39 patients with giant CMN.

Among patients with medium and small-sized CMN, the risk of transformation to malignant melanoma seems to be controversial. Scalzo et al. (1997) of the Massachusetts General Hospital Pigmented Lesion Clinic reported that in a 30-year period, no child (<20 years old) developed melanoma in association with a congenital nevus less than 5 cm in diameter. Similarly, Swerdlow et al. (1995) reported that none of their 239 patients with CMN from 1 to 19 cm in diameter followed over a mean of 25 years developed melanoma. However, in a study by Illig et al. (1985), 52 patients with melanoma that arose in CMN were observed to occur in patients age 18 or older. Based on these results, the authors concluded that melanoma can, in fact, arise from congenital nevi less than 10 cm in diameter.

These disparate and sometimes conflicting study results make it challenging for primary-care physicians to develop the appropriate standard of treatment for patients with CMN. Although these congenital lesions may not be common in the population, primary-care physicians may well be the first to detect such nevi, and the ones ultimately to decide whether such skin lesions warrant referral to a specialist. More importantly, the role of the primary-care physician is critical in underserved areas, where the patient population has poor access to healthcare, is largely uninsured, and may have recently emigrated from another country with poor healthcare. These underserved patients may present with CMN for the first time well into adulthood, when risk of melanoma from CMN has been reported. Such delayed presentation may endanger the life of a patient with a preventable disease. In addition, the African American and Caribbean American population may be protected from acquired melanoma due to dark skin pigmentation, but CMN are equally present in these populations, as is the risk of melanoma from CMN. Not only may these factors contribute to physicians’ overlooking the importance of CMN in these populations, but detection of CMN may be more difficult due to dark skin pigmentation.

In order for primary-care physicians to provide the best and most efficient treatment for patients with CMN, evidence-based standard guidelines for clinical investigation need to be established. The objective of this
review is to answer the following question: What size CMN increases the risk of malignant melanoma in the affected patients?

METHODS

A literature search was performed using the biomedical bibliographical database Medline from 1966 to December 2008. Initial searches used the keywords “congenital nevus,” “congenital melanocytic nevus,” and “congenital nevocellular nevus.” We included studies on medium, large, and giant congenital nevi in association with melanoma. We excluded all articles that were not prospective analyses and/or case-control studies, articles with five or fewer CMN patients, articles that dealt only with aspects of treatment, articles that classified size by methods other than the Kopf model, and data presented in letters to the editor and abstracts. The remaining studies were individually placed into Google Scholar, and were selected based on the number of citations received. Manual cross-referencing was performed. Finally, one representative article was selected with respect to CMN classification by size: small CMN, medium CMN, and large CMN.

RESULTS

No prospective studies met our search criteria for small CMN, so a case-control study was included with the caveat that a prospective study is preferred over a case-control study for our particular assessment.

Three studies pertaining to small, medium, and large CMN met our inclusion criteria. The results are shown in Table 1.

The first article reviewed is by Rhodes and Melski (1982): “Small congenital nevocellular nevi and the risk of cutaneous melanoma.” This case-control study was created to determine the odds ratio of melanoma for persons with small congenital nevi (SCN). This was done by comparing the frequency of SCN in unselected cases of melanoma to the frequency of SCN in newborn infants. Postpubertal patients with all histological types of cutaneous melanoma invasive to at least the papillary dermis were included and divided into three groups.

The first group was composed of 134 patients who reported a detailed history of preexisting pigmented lesions (PPLs) at the tumor site, but whose tumors were not histologically examined for melanoma-associated nevocellular nevi. The 134 patients included 67 males and 67 females with an age range of 16–78 years (mean = 47.9 years) with histological documentation of primary cutaneous melanoma diagnosed between April 1960 and September 1979 at the Pigmented Lesion Clinic of Massachusetts General Hospital. In this study group, 33 patients were diagnosed at the time of interview, 40 patients were interviewed within one year of diagnosis, 23 patients were interviewed between one and two years of diagnosis, and 38 patients were interviewed later than two years after diagnosis. Interviews included questions to assess the first appearance and morphological characteristics of the PPLs, along with the source of the information obtained (parents versus patient).

The second group was composed of 234 patients who did not report a detailed history of a PPL at the tumor site, but whose tumors were histologically examined for the presence of melanoma-associated nevocellular nevi. The 234 patients included 119 males and 115 females; 1 patient was black and 233 were white, with an age range of 12 to 90 years (mean = 47.9 years). Histology was determined in 234 unselected melanoma specimens entered into the Harvard Melanoma Registry within 30 days of diagnosis during the period from September 1, 1972, to May 30, 1977. Tumor-associated nevi were examined to determine whether they were nevocellular nevi with congenital features based on the presence of nevus cells in the dermis.

Data on the third group of patients were obtained from a previous study by Walton et al. (1976) in order to determine the prevalence of congenital nevocellular nevi by histology in 841 white newborn neonates examined within 72 hours of birth.

Finally, the data from all the groups were used to calculate an odds ratio for primary cutaneous melanoma associated with SCN. This was done by dividing the exposure odds of SCN among patients with melanoma by the exposure odds of SCN among neonates.

Results of the Rhodes and Melski (1982) study were determined based on the sample groups. Of the 134 patients with melanoma in the first group, 20 (14.9%) gave a detailed history of the existence of a PPL at the tumor site present since birth. Out of these 20 cases, 5 were ascertained by direct interview with parents (2 of which cases had photographs during the first 6 months of life), whereas the other 15 were ascertained indirectly by parental statements in the past. Among these 20 patients, the estimated greatest diameter for the PPL ranged from 3 to 15 mm (mean = 9 mm +/- 4 mm). Out of the 234 melanoma specimens in the first group who did not report a detailed history of a PPL at the tumor site, 19 (8.1%) were designated tumor-associated nevocellular nevi with congenital features. Furthermore, out of these 19 cases, a total of 6 (2.6%) had nevus cells in the lower two thirds of the reticular dermis (a highly sensitive indicator of congenital nevi). Of the 30 patients who were included in both groups, 2 patients were among the 20 PPLs in the first group, and 2 different patients were among the 19 tumor-associated nevocellular nevi with congenital features specimens in the second group. Of the Walton et al. (1976) third study group, 7 patients...
(0.83%) had nevocellular nevi confirmed by biopsy, all of which were ≤3.0 cm in greatest diameter. Based on these results, the study determined an odds ratio for cutaneous melanoma in persons with SCN to be 20.9 based on history (95% confidence interval 11.0 to 39.9) and 10.5 based on histology (95% confidence interval 5.1 to 21.6). The odds ratio was 3.1 for the 6 specimens taken from the 19 nevocellular nevi with congenital features. The authors concluded that congenital nevi of any size may be precursors to cutaneous melanoma.

The Rhodes and Melski (1982) study was among the first studies to address the risk of malignant melanoma in patients with SCN. The study methodology of distinguishing three different subject groups further aided in minimizing confounding effects of various other parameters that were not controlled. In addition, by separating patients based on history versus tissue diagnosis, the authors were able to note a difference in the odds ratio, possibly raising the issue that PPL history alone may overestimate the odds ratio of melanoma.

Although the authors’ conclusion may ultimately be supported by their data, the methodology in calculating the odds ratio is inherently flawed. Information from the patients in the first subject group was in some cases not obtained directly from the patients or families. Among those cases in which information was directly obtained, only two had photographic evidence of the PPL. Thus, great subjectivity in the form of recall bias during patient interviews is likely to confound the estimation of PPL size. In the second subject group, nearly two times more patients were present than in the first group. Though more subjects contribute to the power of the study results, it is optimal to have close to an equal number of subjects in both groups in order to minimize the effects of statistical outliers. Among the 30 patients in the third subject group, 2 reported a history of PPL (6.66%) and 2 others had positive histology (6.66%), raising the issue of the accuracy of the study results.

Finally, the authors chose to use the study by Walton et al. (1976) to estimate the prevalence rate of SCN. This is also represents a flaw in study design because the authors make the assumption that prevalence of SCN in newborn infants is constant and that the prevalence of SCN in adults is comparable to that in neonates.

The second report considered here, “Risk of melanoma...
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...and the power of the study results. However, certain flaws in the study design did exist. First, the authors determined whether the nevus was congenital by clinical characteristics. These are inherently subjective inclusion criteria, as nevi are known to evolve with respect to clinical appearance. Second, among the 227 patients ultimately enrolled in the study, only 174 received follow-up; while those patients lost to follow-up were not known to have developed melanoma, the loss of this potentially valuable data from the study is considerable. Furthermore, the average length of follow-up was merely 6.7 years from an average patient age of 19 years, an interval that may not be adequate to observe transformation of medium CMN to melanoma. Finally, among the patients with follow-up, the authors mentioned that they were asked “whether an MM [malignant melanoma] had developed within the CMN or elsewhere.” Once again, without tissue diagnosis, this introduced subjectivity...
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TABLE 2. MALIGNANT TRANSFORMATION (Adapted with permission from Ruiz-Maldonado et al., 1992)

<table>
<thead>
<tr>
<th>Histopathologic Diagnosis</th>
<th>Age of Patient</th>
<th>Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignant Melanoma</td>
<td>8 months</td>
<td>Deceased</td>
</tr>
<tr>
<td>Malignant Melanoma</td>
<td>2 years, 4 months</td>
<td>Deceased</td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>7 months</td>
<td>Deceased</td>
</tr>
<tr>
<td>Minimal Deviation Melanoma</td>
<td>14 years</td>
<td>Alive &amp; Well after 1 Year</td>
</tr>
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</table>

lation (p <0.001). About 80% of nevi were observed to be black in color, and 86% of nevi were pigmented and hairy. Predominant locations of nevi included the trunk (47%), limbs (30%), and head (22%). Histopathological features of the 62 of 80 (78%) patients thus examined with giant pigmented nevi were: 64% predominantly intradermal, 12% predominantly compound, and 22% cellular blue nevi. Finally, four malignancies were found among the 80 patients. Two of the patients diagnosed with malignant melanoma at the ages of 8 months and 28 months died of metastasis despite chemotherapy and surgery. One patient diagnosed with neuroblastoma at the age of 7 months died as well. Another patient was diagnosed with minimal deviation melanoma at the same position; the nevus was previously treated by chemical peel, and the patient was alive and well one year after the diagnosis (Table 2). The authors concluded that there is a “high risk of malignant transformation of GPN [giant pigmented nevi].”

The Ruiz-Maldonado et al. (1992) study has several strong points. The inclusion criteria were clearly defined and relatively simple, thus improving generalization of results. The mean age of patients was 20 months, which is closer to the ideal age of birth in assessing lifetime risk of malignant melanoma. Additionally, this study made an attempt to further quantify the prevalence of giant pigmented nevi according to patient gender and family history. Nonetheless, imperfections in the study design did exist. The authors reported the average length of follow-up time to be 4.7 years, leaving readers to question whether long-term risk is properly addressed in such a short period of time. Moreover, the authors briefly mention that 21% of patients enlisted were lost to follow-up. Not only does this limit the power of the study results, but it also lends greater weight to outlier effects and miscalculation of melanoma risk since those lost to follow-up may have developed malignancy.

DISCUSSION

Both worldwide and in the United States, the incidence of melanoma is increasing more rapidly than that of any other cancer (Lens and Dawes, 2004; Tsao et al., 2004). On average, one person dies every hour from metastatic melanoma in the United States (Lens and Dawes, 2004; Tsao et al., 2004). Among these deaths, melanomas arising from CMN compose a portion, but the rate of this risk remains a matter of controversy.

Several studies have suggested a vast array of risks associated with CMN, but the level and nature of the risks uncovered often varies among individual studies. These disparities may well be due to a lack of standardization in defining CMN, as several differing criteria have been employed, such as greatest size in diameter (Kopf et al., 1979), the amount of body surface area covered by the nevus (Lanier et al., 1976), and ease of excision and primary closure without deformity (Kaplan, 1974). The adoption of a standard definition is particularly important for primary-care physicians, as they are most likely to be the first medical professionals to interact with patients with CMN. Therefore, we chose the Kopf model to define CMN in our literature review due to its wide acceptance among clinicians and its relative ease of use in practice. Subsequently, our literature review focused primarily on ascertaining what size of CMN increases the risk of malignant melanoma in the affected patients.

The study conducted by Rhodes and Melski (1982) determined an odds ratio for cutaneous melanoma in persons with SCN of 20.9 based on history and 10.5 based on histology, leading the authors to conclude that congenital nevi of any size may be precursors to cutaneous melanoma. The calculation of the odds ratio was inherently flawed due to faulty assumptions made by the authors, along with poor evidence in determining a history of PPL in patients with cutaneous melanoma. Sahin et al. (1998) reported no incidence of malignant melanoma in 227 patients arising from medium CMN, and concluded that medium-sized CMN did not reveal an increased risk for melanoma. Their study, however, is limited by subjective inclusion data, loss of many patients to follow-up, and an inadequate follow-up interval to observe transformation of medium CMN to melanoma were it to occur. Finally, Ruiz-Maldonado et al. (1992) studied giant CMN in 80 patients and concluded that there exists a high risk of malignant transformation for this type of CMN. Although the statistical power of the study was weakened by a substantial loss of patients to follow-up, the diagnosis of melanoma in four patients is remarkable in view of the diminished sample size. Moreover, the death of three patients younger than four years of
age in this study highlights the potential catastrophic harm that CMN possess in the event of malignant transformation.

CONCLUSIONS

Considering the results of this literature review, we have come to the following conclusions. First, the odds ratio calculated by Rhodes and Melski (1982) constitutes an important initial attempt to quantify the risk of small CMN transforming into melanoma, but more evidence is needed to properly evaluate the risk. Second, several shortcomings present in the Sahin et al. (1998) study likely limit the authors’ claim that medium-sized CMN do not impart an increased risk for melanoma. Third, despite the suboptimal methodology present in the Ruiz-Maldonado et al. (1992) study, the evidence presented therein is substantial and corroborates the risk of melanoma from giant CMN.

Based on this analysis, clinicians may consider several points in treating a patient with CMN. The consensus remains that each patient should receive a total body skin and mucosal surface exam for skin lesions upon initial presentation. Those patients with small CMN measuring <1.5 cm in largest diameter and medium CMN measuring ≥1.5 cm to 19.9 cm in largest diameter should be photographed and observed for any changes throughout the patient’s lifetime, or given the option for specialist referral upon initial presentation. This flexibility may be beneficial in the absence of unequivocal indications of melanoma, particularly because patients should be given the autonomy to make their own decisions in the context of possible melanoma transformation. Lastly, patients with large CMN measuring ≥20 cm should be referred to specialists upon initial presentation in view of the strong evidence supporting the increased risk of malignant transformation (Figure 1). This plan of treatment does not take into account resectability, cosmesis, or age, since these factors are beyond the scope of this article.

Further research is needed to enhance our understanding of this critical issue. Most importantly, efforts should be made to establish evidence-based standard guidelines for primary-care physicians to confidently address the issue of CMN in their patients. The adoption of such guidelines is imperative in underserved areas because the consequences of CMN are preventable and ultimately lifesaving. Thus, we have attempted to address this issue and provide clinical recommendations in an effort to establish standard guidelines for primary-care physicians when dealing with CMN. In the future, more-specific evidence-based clinical recommendations should be possible pending more original data and epidemiological studies.

REFERENCES


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Corresponding Author: Address correspondence to Jeremy Nikfarjam, MD (jenikfar@montefiore.org).

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