Congenital-Nevus-Like Nevi, Nevi Spili, and Café-Au-Lait Spots in Patients with Malignant Melanoma

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ARTICLE

Abstract. The prevalence of congenital-nevus-like nevi (CNLN) in a group of 105 adults who had malignant melanoma (MM) was compared with that in a control group of 601 adults not afflicted by MM. Total cutaneous examinations were performed on both groups. The control group presented with complaints other than pigmented lesions. In this series, 10 (9.5%) of the group with MM had clinically diagnosed CNLN 1.5 cm or larger in diameter. These CNLN were not in contiguity with the MM sites. The 9.5% prevalence of CNLN in the group with MM was significantly higher ($p < 0.005$) than the 2.5% CNLN observed in the control population. None of the patients in either group had large congenital nevocytic nevi (≥20 cm).

In addition, in the group with MM, 5 patients (4.8%) had nevi spili (NS) and 13 (12.4%) had café-au-lait spots (CLS). The prevalence rates for these two types of pigmented lesions were not significantly different from those observed in the nonmelanoma control group (2.3% for NS; 13.8% for CLS).

The relative risk for developing MM is 4.1 in people with CNLN compared with those without CNLN, which indicates that these nevi may be markers for individuals prone to develop malignant melanoma.

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There is considerable controversy concerning congenital nevocytic nevi (CNN) in relation to their histologic features, natural history, and association with malignant melanoma (MM).

The adjective "congenital" denotes an entity dating from the time of birth.[1] In a previous paper,[2] we reported that, in a predominantly adult population, many lesions that had the clinical features of congenital nevocytic nevi were probably absent at birth. The conclusion of that study was that there was a significantly higher prevalence of congenital-nevus-like nevi (CNLN) in adults in the general population compared with the prevalence of CNN previously reported in newborns.[3,4] This led to the concept that many lesions that meet the clinical criteria of CNN are actually tardive in their onset (that is, they have clinical features of CNN but occur later in life). Thus, the lesions categorized in adults as CNLN include a spectrum of clinically similar lesions that differ in age of onset and possibly in their potential for giving rise to malignant melanoma.

Several authors have documented an increased risk for MM to arise in large CNN (≥20 cm),[5–10] and some believe that small (<1.5 cm) and medium-sized (1.5 to 19.9 cm) CNN may also present substantial risks for MM.[11–15]

Although the nevus spilus (NS) and café-au-lait spot (CLS) are not considered to be precursors of MM,[16,17] we also pondered whether these pigmented lesions display a different prevalence in patients with MM versus those without MM. The prevalence of NS and CLS was reported in our previous publication to be 2.3 and 13.8%, respectively.[2] In this study, we used the data from our prior report[2] as a control and compared it with the data from a group of patients who had MM.

MATERIALS AND METHODS

Total cutaneous examinations were performed on 105 white patients who had malignant melanoma and on 601 white control patients without MM. Both groups of patients were seen in the private practice of one of the authors. All patients in the control group presented with skin problems other than pigmented lesions. The study was limited to clinically diagnosed congenital-nevus-like nevi, nevi spili, and café-au-lait spots. For all three types of lesions only those with diameters of 1.5 cm or larger were included. The precise locations were marked on anatomic diagrams.

The characteristics of the MM group were as follows: 101 stage I, 3 stage II, and 1 stage III; all patients were white; the age range was 22 to 81 years (mean, 49.7 years); there were 55 males and 50 females. The lesions were classified as 46 superficial spreading MM, 8 lentigo maligna, 3 lentigo maligna MM, 2 nodular MM; 2 acral lentiginous MM, and 44 not otherwise classified MM.

The criteria for diagnosis of congenital-nevus-like nevi were: predominantly macular patch or raised plaque; pigment uniform or mottled and varying from light tan to tan to brown to dark brown to black; various degrees of hypertrichosis; surface pattern disturbed and varying from smooth to mammillated to papular to verrucous; and usually sharp margination at the perimeter. The lesions considered to be CNLN lacked the clinical features of dysplastic nevi, which have a wider range of colors, more irregular perimeters, macular tan margins that fade peripherally, and no hypertrichosis.

Nevus spilus was recorded as a lesion that was a tan, "café-au-lait-like" macule with superimposed macular or slightly papular speckles of darker brown color.[18] Café-au-lait spot was defined as a completely macular lesion with a uniform "coffee-with-milk" color.

Patient histories of the durations of the lesions included in this study were unreliable and, thus, were not used as a criterion for diagnosis. It was not ethically possible to excise the CNLN for histologic examination. Photographs were taken of those lesions considered to be CNLN.

Differences between groups for continuous variables (such as age and diameter) were tested using the two-sample t-test.[19] Differences for discrete variables were tested using chi-square tests.[19] The relative risk of developing malignant melanoma for persons with CNLN compared to persons without CNLN was estimated by calculating the odds ratio for a fourfold table.[20]

RESULTS

Of the 105 patients with malignant melanoma, 10 (9.5%) had CNLN; 5 (4.8%) had NS; and 13 (12.4%) had CLS. These were compared with the 601 nonmelanoma control patients, of whom 15 (2.5%) had CNLN, 14 (2.3%) had NS, and 83 (13.8%) had CLS. These data are presented in Figure 1. The details of the data obtained for the control groups were out-

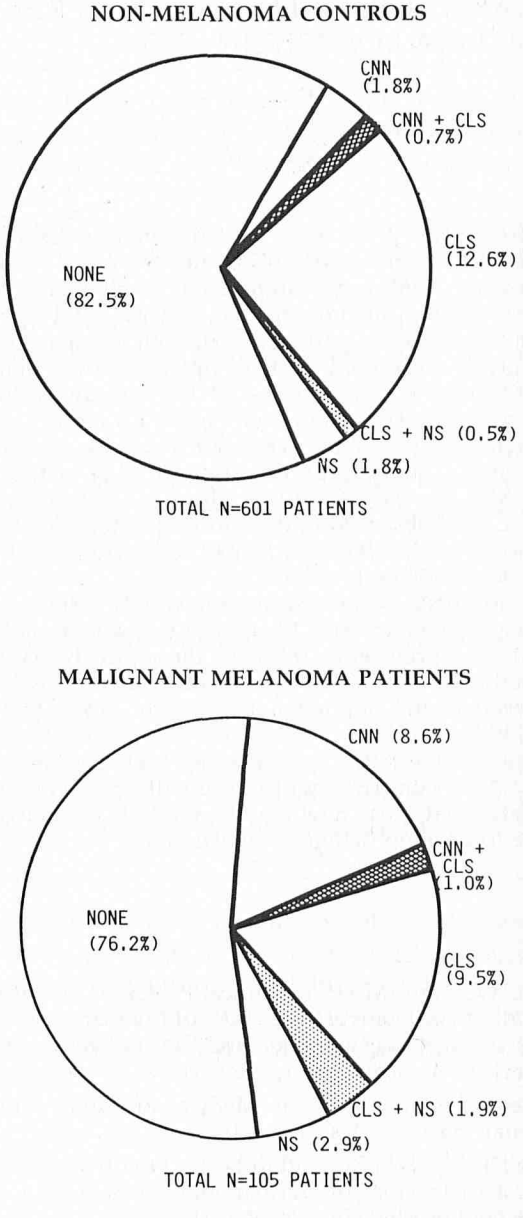

FIGURE 1. Prevalence of congenital-nevus-like nevi (CNLN), nevi spili (NS), and café-au-lait spots (CLS) in malignant melanoma patients and nonmelanoma controls. Overlap CNLN + CLS, crosshatched; CLS + NS, stippled. No subjects had NS + CNLN.

TABLE 1
Age Distribution by Decades for the Pigmented Lesion Studied: Melanoma Patients

Lesion type	Age groups 0–10	11–20	21–30	31–40	41–50	51–60	61–70	71–80	81–90	Row totals
CNLN	0	0	1	1	2	2	3	1	0	10
NS	0	0	0	2	0	1	2	0	0	5
CLS	0	0	0	3	4	2	3	1	0	13
Total patients[a]	0	0	8	24	21	25	21	4	2	105

[a]With and without lesions.

lined elsewhere.[2] A chi-square test revealed a significant difference ($p < 0.005$) in the 9.5% prevalence of CNLN in patients with MM compared with the 2.5% prevalence of CNLN in the controls. There was no significant difference in prevalence of NS ($p = 0.29$) or CLS ($p = 0.75$) compared to their respective control groups.

Congenital-Nevus-like Nevi

Of the 10 patients with MM and CNLN, 7 were men and 3 were women. In no case was the CNLN the patient's chief complaint. The 10 patients ranged from 25 to 76 years of age, with a mean of 54.3 ± 13.8 years (mean ± standard deviation) (Table 1). Only 1 CNLN was discovered on the head or neck, and none was found on the upper extremities (Fig. 2). This anatomic distribution is similar to that in the controls, in whom most of the CNLN were located on the trunk or lower extremities and spared the head, neck, and upper limbs.[2] None of the 10 CNLN was in contiguity with a MM site, and, conversely, none of the 10 MM was associated with a nevus (of any type) histologically.

The CNLN were found to have a mean diameter of 1.8 ± 0.4 cm in the MM group and a mean diameter of 2.0 ± 0.7 cm in the control group ($p = 0.40$).

The relative risk for developing MM was determined to be 4.1 (95% C.I. 1.90–8.87) in people with CNLN compared to those without CNLN.

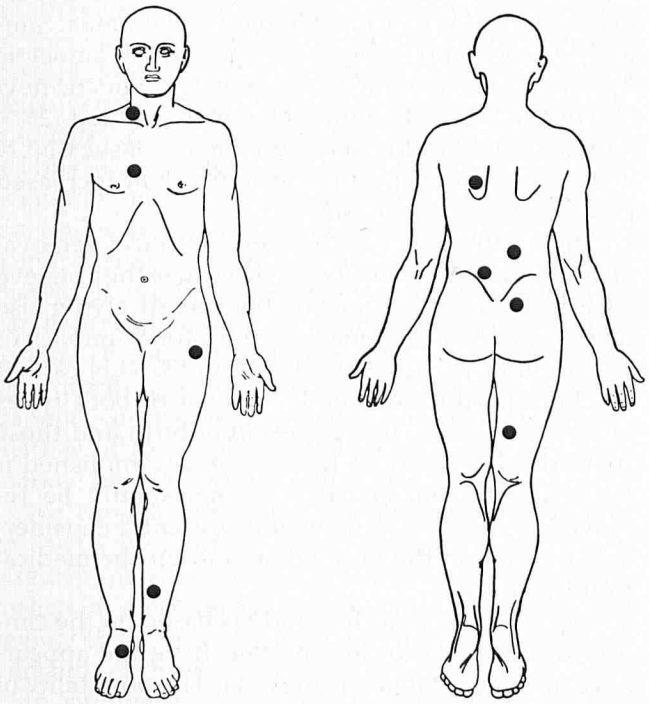

FIGURE 2. Anatomic distribution of the 10 congenital-nevus-like nevi.

Nevus Spilus

A total of seven NS were observed in 5 of 105 patients with MM, a figure comparable to the proportion observed in controls. The NS occurred in two men and three women. These five patients had a mean age of 48.8 ± 15.8 years (Table 1). In both the MM and control groups, NS were significantly larger than CNLN ($p < 0.001$ and $p < 0.025$, respectively) with the average size of NS 3.0 ± 0.8 cm in the patients with MM and 4.3 ± 3.5 cm in those without MM. In both groups, NS spared the head, neck, and upper extremities (Fig. 3).

Café-au-lait Spots

Of the 13 MM patients with one or more CLS, 7 were men and 6 were women. These patients had a mean age of 50.7 ± 13.4 years (Table 1). CLS were more common on the trunk and lower extremities, accounting for the location of 81% of lesions in patients with MM and 91% in those patients without MM (Fig. 4). The mean diameter of CLS in the MM and control groups was 3.3 ± 2.1 and 4.6 ± 3.8

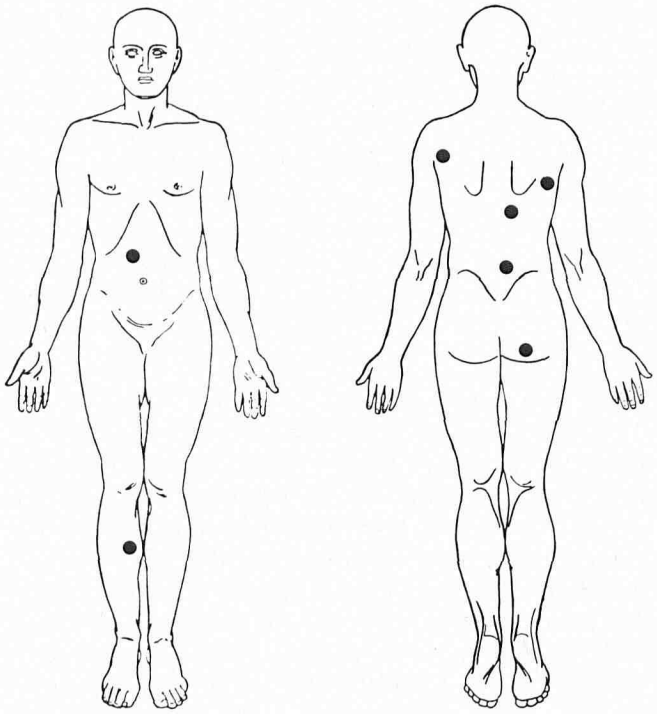

FIGURE 3. Anatomic distribution of the seven nevi spili.

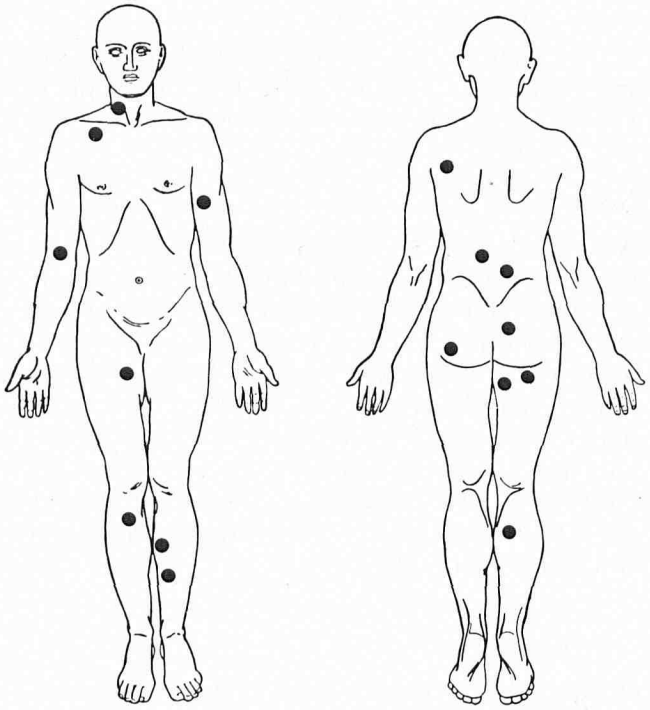

FIGURE 4. Anatomic distribution of the 16 café-au-lait spots.

cm, respectively. In both groups the mean diameter of CLS proved to be significantly greater than the mean diameter of CNLN ($p < 0.025$, MM group; $p < 0.01$, control group).

COMMENTS

In this study, a significantly greater prevalence of congenital-nevus-like nevi was found in patients who had malignant melanoma compared with the non-melanoma controls. Perhaps CNLN, like dysplastic nevi, are markers as well as precursors for malignant melanoma. The precursor aspects of congenital nevocytic nevi (CNN) are not addressed here but have been the subject of considerable controversy.[11–14,21,22] The concept of CNLN as a marker is new. The data presented here indicate that the relative risk for developing MM is 4.1 in individuals with CNLN compared with those who do not have CNLN. The implication is that such lesions may identify a group of individuals who are at increased risk for developing MM on anatomic areas not necessarily contiguous to the CNLN.

It would be useful to determine additional variables that identify those patients with CNLN who will develop MM versus those who will not be afflicted. These factors might include: (1) phenotypic features (such as eye, hair, and skin color); (2) coexistent dysplastic nevi; (3) familial history of MM; (4) cumulative sun exposure; (5) geographic factors; and (6) histologic features. Further research is needed to focus on the interaction of these MM risk factors. For example, there may be "dysplastic" CNLN. In this regard, Rhodes and coworkers[11] report the combination of malignant melanoma, congenital nevocytic nevus, and atypical melanocytic hyperplasia in 8 of 234 (3.4%) malignant melanomas. Similarly, Clark and colleagues[23] found melanocytic dysplasia associated with congenital nevocytic nevi in 5 of the 250 malignant melanomas studied (2%). Perhaps identification of a subset of dysplastic CNLN will help to predict which lesions are at increased risk for giving rise to MM.

Some authors[13–15] recommend surgical removal of all congenital nevocytic nevi because they believe such lesions carry a substantial risk of giving rise to malignant melanoma. An additional impact of our findings is that, since CNN and CNLN cannot be clinically differentiated, removal of both types of lesions (that is, those present at birth and those that arise later) would have to be accomplished if the mandate that *all* such lesions should be removed is adopted. This would present a considerable burden on the population and on the medical profession.[2,24]

One caveat is that this study is based on the clinical identification of lesions that have the appearance of congenital nevocytic nevi. The possibility of a misclassification bias was considered in relation to dysplastic nevus. Dysplastic nevi can also achieve

diameters of 1.5 cm or larger, but such lesions usually have a much greater play of colors, irregular margins and tan, macular borders that gradually fade peripherally, and are not hypertrichotic. Indeed, in this series of 105 consecutive patients with malignant melanoma, there were 2 who had dysplastic nevi larger than 1.49 cm in diameter. Furthermore, it has been shown by Greene and coworkers[25] that members of families with dysplastic nevi and malignant melanoma are more likely to have "congenital-nevus-like" lesions, indicating that these investigators were also able to distinguish dysplastic nevi from CNLN.

Another caveat in this study that must be taken into consideration is the finding of Rhodes and colleagues[26] that siblings of patients with CNN have a higher probability (12.5%) of having CNN than the general population (1.1%). Since some of the patients seen in this study were referred by relatives of patients who did have pigmented lesions of various types as their main complaints, it is possible that this may have caused some bias in this survey because of familial clustering of CNN and/or CNLN.

Concerning the two other pigmented lesions we studied, neither nevi spili nor café-au-lait spots are considered to be at significant risk for giving rise to MM.[27] However, Cohen and colleagues[16] reasoned that, since NS can have junctional nevus cells on histologic examination, they ought to be considered a variety of nevocytic nevi and, as such, may carry an increased risk for malignant change. In support of this view, it is noted that in the single reported case of MM arising in a café-au-lait spot,[28] nevus cells were seen on histologic examination of a second café-au-lait spot, possibly indicating that both lesions were in fact NS, not CLS. Also, we have seen one patient who developed a MM in a NS. As the understanding of NS is insufficient at this time, a more precise definition of the different clinicohistologic types of nevi spili is needed before we can accurately assess the precursor aspects of such lesions. In our data, unlike CNLN, there was no significantly greater prevalence of NS or CLS in MM patients compared with that in controls. Therefore, neither of these pigmented lesions seems to be a marker for MM-prone individuals.

We consider these data preliminary and intend to verify the findings by extending the study to a larger population of patients who have cutaneous malignant melanomas. We hope that others will also review their patient material to determine the universality of these observations.

In summary, these new findings identify congenital-nevus-like nevi as markers for individuals prone to develop malignant melanoma, however nevi spili and café-au-lait spots were not significantly more prevalent in the MM sample than in the controls.

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