Melanocytic Nevi in Histologic Association with Primary Cutaneous Melanoma of Superficial Spreading and Nodular Types: Effect of Tumor Thickness

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The histologic presence of benign dermal nevus cells in contiguity with primary cutaneous melanoma, as a distinct population separate from malignant melanocytes, was evaluated in a large referral data base. The melanomas were limited to superficial spreading melanoma (SSM) and nodular melanoma (NM). Overall, dermal melanocytic nevi were found associated with 1126 of 1954 primary SSM/NM (57.6%). When the melanomas were stratified by tumor thickness, an inverse relationship between the presence of benign nevus cells and tumor thickness was found: 64.9% of tumors less than 0.76 mm and 64.5% of those between 0.76 and 1.69 mm were associated with dermal nevi, whereas in the thickness range 1.70–3.60 mm, there were 45.6% associated nevi, and in melanomas greater than 3.60 mm, there were only 32.0% noted to have nevus cells. When melanomas were separated by nevus type, it was found that 41% were associated with an acquired pattern nevus, 38% with congenital pattern nevus, and 21% with dysplastic nevus. It may be concluded that 1) the histologic presence of nevus cells is a common event in SSM/NM; 2) the association of melanocytic nevus and melanoma is more easily demonstrated in thinner tumors; and 3) acquired pattern nevi, congenital pattern nevi, and dysplastic nevi are all potential precursors of melanoma. *J Invest Dermatol 100:322S–325S, 1993*

The association of melanocytic nevi and melanoma has been an area of recent interest, initiated largely by the description in 1978 of melanoma arising in ''heritable melanocytic lesions'' (now called dysplastic nevi) by Clark *et al* [1]. Earlier reports could be found of the association of melanoma and moles, especially in families [2,3]. This association had even been noted in the 1800s; however, the observation of dysplastic nevi and the description of the dysplastic nevus syndrome [4] focused attention on these lesions as potential precursors of melanoma and as markers of increased risk of developing melanoma. It was hoped that the ability to identify risk groups for the development of melanoma [5–10] – including those people with dysplastic, acquired, and/or congenital melanocytic nevi – would allow earlier diagnosis and improved survival, a hope only partially fulfilled.

Nevi are present in the majority of light-skinned people but are more common in patients with melanoma than in control subjects [7–10]. In a review of multiple reported series, Elder *et al* [11] found that patients with cutaneous melanoma gave a history of a pre-existing clinical pigmented lesion at a melanoma site in 18–85% of primary melanoma cases. Such a range is of little use to either the educated patient or the patient's physician in trying to determine which mole, if any, should be considered a potential precursor lesion. It is difficult to know whether the history from a patient of a pre-existing pigmented lesion represents early melanoma or a benign nevus. From the demonstrated difficulty of accurate clinical diagnosis of melanocytic lesions [12], it would seem that the appearance alone is not uniformly helpful. Some patients report a definite stable lesion undergoing a more or less recent change [13], and such an accurate history may well be related to malignant transformation in precursor nevi. The history of a pigmented lesion present since birth at the site of a melanoma seems somewhat more accurate, especially when confirmed by photographs or questioning of parents [14,15]. Now that dysplastic nevi have become a focus of attention for evaluating precursor lesions, a consensus of clinical and histologic definition is needed. Studies of combined clinical and histologic features seem to allow a more accurate diagnosis of dysplastic nevi [16]. In part because of the lack of uniformity of definition, however, the reports of histologic melanocytic dysplasia in association with melanoma range from 5 to 36% [11,17–20].

In addition to clinical judgment of either patient or physician, the histologic presence of benign nevus cells, whether dysplastic or not, as a distinct population separate from the melanoma cells can also be used to assess the association of melanocytic nevi and melanoma. The purpose of the present study was 1) to determine in a large referral melanoma clinic the incidence of various types of histologic melanocytic nevi in association with primary cutaneous melanoma, and 2) to test whether tumor thickness had any bearing on the ability to assess the presence of nevi.

MATERIALS AND METHODS

Data Base The computerized data base of the Melanoma Clinic at the University of California, San Francisco, was searched for patients with malignant melanoma, superficial spreading (SSM) and nodular (NM) types who also had information concerning the presence or absence of an associated benign melanocytic nevus. A subset of the data was searched for type of nevus.

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Abbreviations: NM, nodular melanoma; SSM, superficial spreading melanoma

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The Melanoma Clinic has entered clinical and histologic data prospectively since March 1971. A total of 3450 patients have been seen with all types of melanoma at all stages of the disease. After excluding unusual types, unknown primaries, and 206 patients whose pathology was inadequate for evaluation, there remained a population of 1954 patients with SSM and NM who also had adequate histologic material for evaluation of pre-existing nevi. In the data base, tumor thickness was measured by the Breslow technique [21].

Definitions

Tumor Type: Histogenetic types SSM/NM were classified in routine hematoxylin and eosin-stained sections using the original description of Clark *et al* in 1969 [22]. Other types, such as lentigo maligna, acral lentiginous melanoma, and unclassified or unusual types, were excluded from this analysis because preliminary studies indicated that types other than SSM/NM had such a low prevalence that no analysis of data could be made with regard to these types.

Associated Nevus: The dermal component of a melanocytic nevus had to appear as a cell type distinct from the melanoma cells to be recorded. To avoid confusion in differentiating *in situ* melanoma from junctional nevus, the junctional component was only considered in dysplastic nevi. The dermal nevus was recognized by smaller size, absent mitoses, orderly pattern of growth, and lack of lymphocytic or mesenchymal (vascular and/or stromal) host response. Melanomas in which larger tumor cells gradually diminished in size at the base were not included because the distinction between two cell types, as noted above, could not be made.

Nevus Type: Whenever possible, the associated nevus was classified as acquired pattern, congenital pattern, or dysplastic, using the following definitions [23]: 1) The *acquired pattern* is present within the epidermis and/or the expanded papillary dermis. It is orderly and confined laterally as well as at the deep margin along the papillary-reticular dermal junction. 2) The *congenital pattern* nevus extends between reticular dermal collagen bundles and is closely associated with appendages, especially pilosebaceous units. As used in this study, nevus cells do not need to descend into the lower third of the reticular dermis, as suggested by Mark *et al* [24], if they exhibit the above criteria. This is a histologic pattern, not necessarily correlated with the clinical definition of "apparent at birth," as discussed by Rhodes [13,14]. 3) The *dysplastic nevus,* although considered ill defined by many and nonexistent by a few [26], is nevertheless not difficult to define. The generally accepted published criteria were followed [9,16,18,20,23,27,28]. These include lateral extension of an intraepidermal melanocytic proliferation beyond a dermal nevus; disordered architecture of the epidermis; a cellular-mesenchymal host response, including angiogenesis, fibroplasia, and cross-bridging of adjacent rete ridges, and the presence of atypical individual melanocytes in the epidermis. Because of the characteristic pattern of epidermal ridge pattern and junctional nest cross-bridging in dysplastic nevi, the junctional changes were considered an integral part of the diagnosis.

RESULTS

Incidence of Associated Nevi In the overall population of 1954 cases of SSM/NM, 1126 showed histologic evidence of an associated benign melanocytic nevus (57.6%).

Table I. Numbers of Melanoma Cases Associated with Dermal Melanocytic Nevi as a Function of Tumor Thickness

Tumor Thickness (mm)[a]	Total Cases of Melanoma[b]	Cases Associated with Nevus (%)
<0.76	696	452 (64.9)
0.76–1.69	659	425 (64.5)
1.70–3.60	421	192 (45.6)
>3.60	178	57 (32.0)
Total	1954	1126 (57.6)

[a]Millimeters by ocular microscopic on slide.
[b]SSM and NM types only.

Table II. Correlation of Melanocytic Nevus Type Associated with Histogenetic Types of Melanoma

Nevus Type	SSM (%)	NM (%)	Total (%)
Acquired	298 (42)	36 (38)	333 (41)
Congenital	248 (35)	56 (60)	304 (38)
Dysplastic	168 (24)	2 (2)	171 (21)
Total	714	94	808

Incidence by Tumor Thickness When the population was stratified by tumor thickness, the numbers of associated nevi decreased as the tumor thickness increased: 64.9% of tumors less than 0.76 mm and 64.5% of those between 0.76 and 1.69 mm contained associated nevi, whereas in the thickness range 1.70–3.60 mm, there were 45.6% associated nevi (Table I). In melanomas greater than 3.60 mm, only 32.0% were found to have associated dermal melanocytic nevus cells.

Incidence by Type of Nevus and Tumor A subset of 808 patients from the above population had data entered on both histogenetic type and, in more recent years, nevus subtype (Table II). There were 714 tumors of the SSM type, which were analyzed. By the preceding definitions of melanocytic nevus, 42% of the SSM type were associated with acquired pattern nevi, 35% were found to have a congenital pattern nevus, and 24% were associated with a nevus showing features of dysplasia.

Of the 94 NM tumors, 38% were associated with acquired pattern nevi, 60% with congenital pattern nevi, and only 2% with dysplastic nevi. Of the total 808 SSM and NM tumors classified in this way, 41% were found to have an associated acquired pattern nevus and 38% an associated congenital pattern nevus. Dysplastic nevi were found in 21% of this population.

DISCUSSION

Presence of Associated Nevi in SSM and NM The present study reports the association of melanocytic nevi found in contiguity with primary cutaneous malignant melanoma. It is based on a series of prospectively entered data on patients whose histologic attributes included an assessment of the presence or absence of an associated melanocytic nevus. Histologic dermal nevus associated with the melanoma was found in 57.6% of 1954 patients with primary cutaneous malignant melanomas. This figure is high when compared with the results of others (reviewed by Elder *et al* [11]). Several possible explanations could be cited:

1. The present study included only SSM/NM, and perhaps these have the highest association with precursor nevi. It is difficult to assume that the restriction of the present study to the SSM/NM types of melanoma could alone account for this difference because these histogenetic types account for 85–90% of most large series of malignant melanoma. Other types, such as acral lentiginous melanoma or those arising in lentigo maligna, were seldom found associated with nevi in a preliminary search of the data base, and they would only account for a maximum 10–15% dilution. Marks *et al* [29] also studied only SSM and NM tumors and found that 23.3% of cases had an associated melanocytic nevus. This study, however, utilized 12 pathologists in the Dorevitch Pathology Laboratory in Melbourne, Australia. The authors did not state specifically their criteria for the diagnosis of nevus or whether they included both junctional and dermal components.
2. The diagnostic criteria were not similar to those used in other studies. Friedman *et al* [30], who studied 557 patients with primary malignant melanoma, specifically excluded ''melanomas associated with histologic evidence of congenital as opposed to acquired melanocytic nevi''; they also found that 23% of their series had histologic evidence of an acquired melanocytic nevus in association with the melanoma. They cite similar criteria to those used in the present study.
3. The criteria were not applied consistently in these lesions. In an earlier study using the same criteria and the same pathologist [31], it was shown that 50% of *in situ* and 53% of thin melanomas less than 0.76 mm were associated with precursor nevi. This suggests that the populations and the pathologist are similar over time but does not explain the lower figures reported by others.
4. The population studied differed in some way from others reporting lower figures. It is possible that the study population comprises a higher proportion of patients with so-called low-risk or thin tumors than other series. It can be seen from Table I that more than one-third of the patients (696 of 954, or 35.6%) had tumors less than 0.76 mm thick and that more than two-thirds had tumors less than 1.70 mm thick. In thinner tumors it seems reasonable to as sume that the residua of associated nevi would be more apparent than in more deeply invasive tumors.

Incidence by Tumor Thickness The results indicate a clear decrease in the numbers of associated dermal nevi in contiguity with primary melanoma of increasing tumor thickness. As indicated above, there were a large number of thin tumors in the overall data base, and 65% of those tumors less than 1.70 mm showed associated nevi. In the study by Marks *et al* [29], the frequency of melanoma-associated nevi was found to decrease with level of invasion from 31.3% of level I tumors to 21.3% of level IV tumors. Thickness was only analyzed as less than or greater than 1.0 mm, but in this division the percent of associated nevi was 27.0 and 14.8%, respectively. Although the trend toward fewer nevi demonstrable in thicker or deeper tumors can be seen in the study by Marks *et al,* the absolute numbers are lower, as noted above. In fact, Marks *et al* concluded that most melanomas do not arise in pre-existing nevi, whereas the present study supports the suggestion that most thin melanomas do in fact arise in association with pre-existing nevi. Whether the thicker tumors develop with a similar proportion of nevi and the tumor growth over-rides the nevus, or whether thicker tumors develop less frequently in nevi and attain a greater thickness because of some other mechanism, is not known.

The contribution of Friedman *et al* [30] suggests a more favorable prognosis in those melanomas associated with acquired melanocytic nevi. Confirmation of this study by another group is lacking, and the present study did not address this issue.

Incidence of Nevus Type and Histogenetic Type In SSM associated with nevi, 42% are of the acquired type; 35% are congenital nevi, and 24% show features of dysplasia. It must be remembered that these data include all tumor thicknesses, so that the congenital pattern nevus may be somewhat over-represented in thicker tumors because its nevus cells extend deeper, and it would take a thicker tumor to obscure the nevus. The finding of dysplastic nevi in almost one-quarter of SSM is also high compared with other published studies but can perhaps be explained on the basis of the referral pattern of patients who have unusual mole patterns and the increased likelihood of detecting thin tumors in this subgroup. The findings of Hastrup *et al* [18], showing approximately 7% of melanoma arising in a prior dysplastic nevus, are based on a population-based study and are probably closer to the actual incidence.

In the case of NM, 38% were associated with acquired pattern nevi and 60% were associated with congenital pattern nevi. It must be remembered that thickness is not included in this analysis, so that NM developing in contiguity with acquired nevi could quickly obscure or destroy the precursor nevus. Because the acquired pattern was defined as confined to the papillary dermis, one might not expect many NM tumors to remain confined to this anatomic site because the vertical growth of such tumors fills the papillary dermis even in thin NM tumors. A deeper nevus, as defined by the congenital pattern, could be seen more easily in association with the deeper NM tumors. An alternative hypothesis might be that congenital pattern nevi are truly more prone to develop NM than other types.

Only two cases (2%) of NM were found to be associated with dysplastic nevi. This might be expected, considering the fact that the dysplastic changes are noted at the periphery of the precursor nevus and that NM is confined to the vertical growth without adjacent spread. Lateral features would be expected more commonly in melanomas with a radial growth phase. An alternative explanation for the low prevalence of dysplastic nevi in association with NM could be misclassification of dysplastic changes adjacent to the vertical growth as radial growth of SSM rather than dysplasia in association with NM.

Cook and Robertson [32] examined melanocytic dysplasia and melanoma, distinguishing between lentiginous and epithelioid dysplasia. They concluded that these processes were similar components of a spectrum of melanocytic dysplasia. They reported that 27.4% of 226 melanomas showed such changes, a figure similar to the present study. The present study did not address the issue of separating lentiginous from epithelioid dysplasia.

Finally, the study of Black [17] examined 500 SSM excisions and found residual remnants of dysplastic nevi in 32.4% of tumors. Although this is somewhat higher than the present study, which found 24% of SSM excisions associated with dysplastic nevi, Black also found only 9.8% of nevi in SSM excisions without dysplasia (compared with 42% of SSM in the present study).

In conclusion, the present study has shown that melanocytic nevi are a common association in routine histologic sections of primary cutaneous malignant melanoma of the SSM and NM types. The overall frequency of 57.6% of these tumors associated with nevi may be somewhat elevated by the proportion of thin tumors in this series, but the frequency of almost two-thirds of melanoma with thicknesses less than 1.70 mm associated with dermal nevi indicates that the majority of melanomas may be associated with precursor nevi. These findings support the hypothesis of tumor progression in the melanocytic system, as discussed by Clark [33].

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