Prospective Follow-Up for Malignant Melanoma in Patients with Atypical-Mole (Dysplastic-Nevus) Syndrome

AMY D. TIERSTEN, MD • CARON M. GRIN, MD
ALFRED W. KOPF, MD • GEOFFREY J. GOTTLIEB, MD
ROBERT S. BART, MD • DARRELL S. RIGEL, MD
ROBERT J. FRIEDMAN, MD • MARCIA J. LEVENSTEIN, DSC

A total of 357 white patients who had melanocytic nevi that fulfilled the clinical criteria for the "classic" atypical-mole (dysplastic-nevus) syndrome (100 or more melanocytic nevi; one or more melanocytic nevi 8 mm or larger in diameter; and, one or more melanocytic nevi with atypical features) were followed for the development of cutaneous malignant melanomas. Seventeen patients (4.8%) developed malignant melanomas during an average follow-up period of 49 months. One patient developed two malignant melanomas. Eight of the malignant melanomas detected were in situ and ten were invasive melanomas (< 0.86 mm in Breslow thickness), implying an excellent prognosis. The number of malignant melanomas detected in these patients exceeded significantly the number expected to occur in age- and sex-matched white controls. All groups were shown to have an increased risk for the development of malignant melanomas. Total-body photographs were helpful in detecting changes in size, shape, and color that led to the diagnosis of malignant melanoma. These data support the concept that patients with this readily regionalized clinical presentation of classic atypical-mole syndrome are at an increased risk for malignant melanomas and, therefore, should be examined regularly. J Dermatol Surg Oncol 1991;17:44–48.

It has been established that individuals with dysplastic nevi are at an increased risk for developing cutaneous malignant melanomas.[1–3] Since there is considerable controversy concerning the clinical and histologic diagnosis of dysplastic nevi, we decided to report on those patients with a readily recognizable clinical presentation of dysplastic nevi that we have previously defined as the *"classic" atypical-mole syndrome.*[4] The criteria for this clinical diagnosis are: 1) 100 or more melanocytic nevi; 2) one or more melanocytic nevi 8 mm or larger in greatest diameter; and 3) one or more melanocytic nevi with atypical features (Table 1). We present a study that evaluated the risk for developing malignant melanomas in a consecutive series of 357 patients with the classic atypical-mole syndrome.

Materials and Methods

The 357 white patients included in this study were all followed in a private dermatologic practice (AWK). Only those patients with total-body photographs (a standardized series of 24 color 35-mm transparencies documenting the melanocytic nevi)[5] were considered for this study. Without knowledge of which patients developed malignant melanomas, a review of the total body photographs was done. Those patients who met the pre-established clinical criteria for the classic atypical-mole syndrome (Table 1) were entered into the study. Following selection of the cases based on their total body photographs, each patient's medical record was reviewed to verify that he or she met the three criteria for the classic atypical-mole syndrome.

The date of entry into the study was established as the date of the patient's first office visit. The clinical characteristics of the patients in the study are summarized in Table 2. The age of the patient was that at entry into the study. The number of melanocytic neoplasms removed

From the Department of Dermatology, New York University School of Medicine and the Melanoma Cooperative Group, New York University Medical Center.

Supported by the Melanoma Funds of the NYU School of Medicine Departments of Dermatology and Surgery; the David A. Leinbach Memorial Fund and the Niarchos Fund of the Skin Cancer Foundation; NYU Kaplan Cancer Center (Core Support Grant no. P30 CA-16087); National Cancer Institute Grant no. 2 RIO CA 1366-05; National Institute of Occupational Safety and Health Grant no. ROI OH00915; the Department of Energy Grant no. EY-76-C-02-3077.

Address reprint requests to: Alfred W. Kopf, MD, Oncology Section, Skin and Cancer Unit, New York University Medical Center, 562 First Avenue, New York, NY 10016.

© 1991 by Elsevier Science Publishing Co., Inc. • 0148-0812/91/$3.50

Table 1. Clinical Characteristics of Melanocytic Nevi in Patients with Classic Atypical-Mole Syndrome

Feature	Clinical Finding
General Clinical Characteristics of MN	
Number	100 or more
Uniformity	Heterogenous (neighboring nevi differ)
Clinical Characteristics of MN	
Size	At least one, 8 mm or more in diameter
Color	Variegate: Multiple shades of tans, browns, black, reds
Elevation	For its large diameter, the lesion is only slightly elevated throughout most of its area
Perimeter	May be irregular; usually fades imperceptibly into surrounding skin
"Shoulder"	Peripheral macular tan zone
Surface	Often mamillated ("pebbly," "cobblestoned")
Symptoms	None
Hypertrichosis	Absent
Erosion/ulceration	Absent

MN = melanocytic nevi.

after entry into the study reflects the lesion(s) removed for diagnostic and/or for cosmetic purposes. Throughout the study at least one lesion was usually removed in the workup of the patient.

A personal and/or family history for malignant melanoma was obtained in the modified nuclear pedigree (parents, offspring, siblings, grandparents, aunts, and uncles). Each patient was categorized into one of four groups[6] on the basis of this information. In this classification no point is given if there is no personal and/or family history of malignant melanoma; one point is given if the patient has had malignant melanoma before entry into the study; two points are given for each family member who has had malignant melanoma or developed malignant melanoma at any time throughout the study. Based on the total points, we classified each patient into one of four groups as follows: Group 0 = 0 points; Group 1 = 1 point; Group 2 = 2 points; Group 3 = 3 or more points.

The records of the patients were reviewed from their first visit to the time of the most recent follow-up examinations to identify those patients who developed malignant melanoma. A malignant melanoma diagnosed at the initial visit was not considered as a newly diagnosed malignant melanoma in this study. Only those malignant melanomas that were diagnosed after the initial office visits were included in the results. All biopsy specimens considered to be malignant melanoma or possible malignant melanoma were reviewed by a dermatopathologist

Table 2. Clinical Characteristics of Patients in the Study

Characteristic	N(%)*
Study population	357
Sex	
Male	197 (55%)
Female	160 (45%)
Average age (y)	35.9
Mean Follow-up (mo)	49
Group†	
0	157 (44.0%)
1	95 (26.6%)
2	89 (24.9%)
3	16 (4.5%)
Median number of biopsies‡	1.0

* *Total study population, N = 357.*
† *Based on classification of Rigel et al.*[6]
‡ *Median number of melanocytic neoplasms biopsied after entry into study.*

(GJG) to confirm the diagnosis of malignant melanoma. Of the 22 lesions diagnosed histologically as malignant melanoma or possible malignant melanoma, four were diagnosed as unusual melanocytic nevi and were therefore excluded. The remaining 18 tumors were diagnosed as malignant melanomas (10 invasive and 8 in situ).

The estimated occurrence of invasive malignant melanoma, based on age- and sex-specific incidence rates from the 1980–1985 Surveillance Epidemiology and End Results data base (SEER)[7] was calculated for a cohort of the general white population of the same size, age, and sex distribution as each of the four groups, adjusting for months of follow-up.

Results

Of 357 patients with the classic atypical-mole syndrome, followed prospectively for an average of 49 months, 17 (4.8%) developed newly-diagnosed cutaneous malignant melanoma; one patient developed two such malignant melanomas. The 18 malignant melanomas were diagnosed at a median of 32 months after entry into the study. Eight of the malignant melanomas were in situ lesions and ten were invasive, ranging from 0.2–0.85 mm in Breslow thickness. An associated melanocytic nevus was found on histologic examination in seven of the 18 malignant melanomas.

The characteristics of the patients who developed malignant melanomas during the study period compared with those who did not are summarized in Table 3. The average age of the patients with malignant melanoma was 43.4 years. Twelve of the 17 patients had a personal history of a previous cutaneous malignant melanoma. Of these 12 patients, one had a family history of malignant melanoma as well. Two other patients had only a family history of malignant melanoma.

J Dermatol Surg Oncol
1991;17:44-48

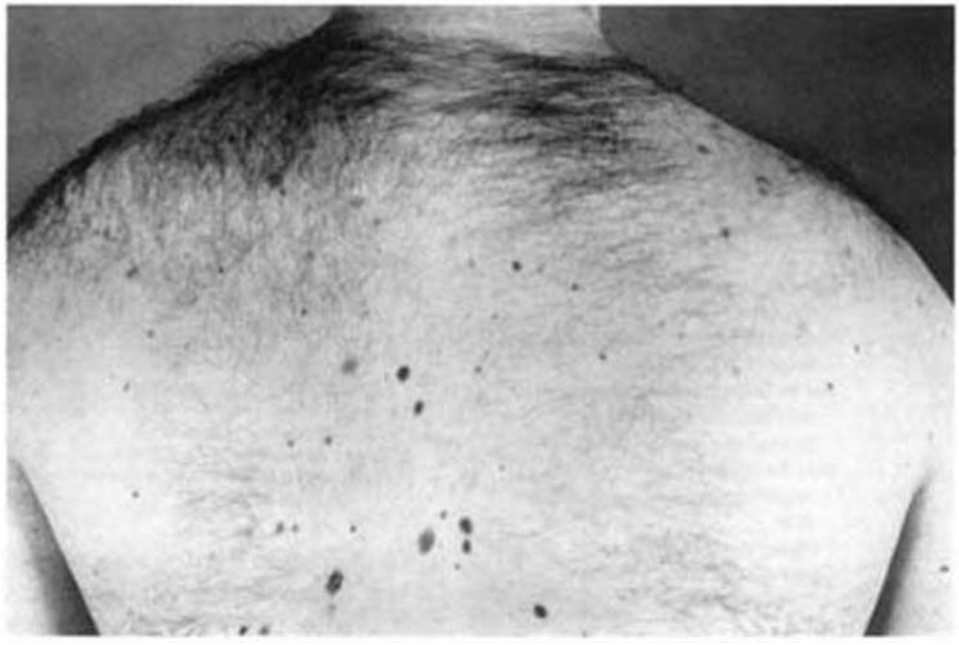

Figure 1. The back of a patient with "classic" dysplastic nevi.

Table 4 compares the number of invasive malignant melanomas in our study to that expected in a white population of the same size, age, and sex calculated from the SEER data base.[7] Our patients were observed to develop 10 newly diagnosed invasive malignant melanomas. In the matched controls from the general population the expected risk was only 0.167 during a comparable time span. None of the patients had developed local recurrences or in-transit/distant metastases of their malignant melanomas at the time of the completion of the study.

Discussion

Dysplastic nevi were first studied in depth in 1978 by Clark et al,[8] who published data suggesting that people with certain atypical moles who had blood relatives with malignant melanomas were themselves at very high risk for developing malignant melanoma. The recognition of such atypical moles in individuals without a family history of malignant melanoma was reported subsequently.[2,9-13] In 1985, Greene et al[1] reported that individuals from families with malignant melanoma who have dysplastic nevi are significantly more likely to develop malignant melanoma than members in the same families without such melanocytic nevi. They estimated that in these families the probability of a dysplastic nevi-affected individual of developing malignant melanoma between the ages of 20 and 59 is 56%. During an average follow-up of 6 years, four (5.7%) of 77 people with dysplastic nevi in these families developed their first new primary malignant melanoma. Compared with the estimated lifetime risk of approximately 1% for whites,[14] this is very high. Kraemer et al[3] followed dysplastic-nevi patients from families with familial malignant melanoma and reported that individuals classified as Type D-2 (ie, two or more family members with a history of malignant melanoma) are 395 times more likely to develop malignant

Table 3. Comparison of Patients with Classic Atypical-Mole Syndrome Who Developed Malignant Melanoma Versus Those Who Did Not

Characteristic	*Melanoma* N(%)	*No Melanoma* N(%)
Sex		
Male	16 (94.1%)	181 (53.2%)
Female	1 (5.9%)	159 (46.8%)
Group*		
0	3 (17.6)	154 (45.3%)
1	11 (64.7%)	84 (24.7%)
2	2 (11.8%)	87 (25.6%)
3	1 (5.9%)	15 (4.4%)
Mean age (y)	43.4	35.6
Median follow-up (mo)	63	34
Median mo to MM detection	32	
Median number of biopsies†	4	1

MM = malignant melanoma
** Based on classification of Rigel et al.[6]*
† Median number of melanocytic neoplasms biopsied after entry into study.

Table 4. Number of Invasive Melanomas Detected in Patients with Classic Atypical-Mole Syndrome Versus Number Estimated in Reference Population During the Same Observation Period

	Group*				
	0	1	2	3	Total
N	157	95	89	16	357
Total follow-up (mo)	8,173	4,415	4,132	602	17,322
DN patients who developed MM (N)	4	4	1	1	10
People in reference population expected to develop MM (N)†	0.0760	0.0539	0.0302	0.0073	0.1674

N = *number, DN = dsyplastic nevi; MM = malignant melanoma.*
* *Based on the classification of Rigel et al.*[6]
History of malignant melanoma:
group 0, in neither patient nor family member;
group 1, in patient;
group 2, in one family member; and
group 3, in either patient and at least one family member or in two or more family members.
† *The chance of finding the number of malignant melanomas detected in the dysplastic nevi group (as determined by a binomial distribution,*[22] *given the estimated values in the Surveillance Epidemiology and End Results reference population*[7]*) is* $P < .001$ *for each group and for the aggregate.*

melanoma than are individuals in the general population. They estimated the relative risk of malignant melanoma in all other types of dysplastic nevi combined to be approximately 7–26 times that of the general population based on the SEER data. Holly et al[2] demonstrated an increased relative risk for development of malignant melanoma in patients with dysplastic nevi compared with controls. They established that, compared with controls, individuals with 1–5 dysplastic nevi have a relative risk of developing malignant melanoma of 3.8 ($P = .001$) and that individuals with 6 or more dysplastic nevi have a relative risk of 6.3 ($P = .003$). In our previous study[15] of 452 patients with dysplastic nevi, 16 (3.5%) of them developed a malignant melanoma during an average of 27 months of follow-up.

Because there is considerable controversy concerning the clinical diagnosis of dysplastic nevi, we chose to study patients with a readily recognizable clinical presentation, which we have named the classic atypical-mole syndrome. This study indicates that this cohort is at a significantly increased risk of developing malignant melanoma when compared with a general white population of the same size, age, and sex distribution using the SEER data base as reference.

It is noteworthy that the invasive malignant melanomas were all thin melanomas (<0.86 mm in Breslow thickness) associated with an excellent prognosis.[16] This is similar to the finding by Vasen et al[17] who diagnosed thin malignant melanomas in their prospective follow-up of patients with dysplastic nevi.[17]

There are several questions raised by our results. The disproportionate number of males in those patients who developed malignant melanoma (16 men, 1 woman) may in part reflect the fact that these patients were older on average (43.4 years) than those who did not develop malignant melanoma (35.6 years). In the general population, men and women have equal incidence rate of melanoma until the older-age decades when the incidence rate of malignant melanoma in men exceeds that in women.[7] The discrepancy may also be in part because more men than women have outdoor occupations and recreational activities, which may lead to greater sun exposure. However, these explanations are insufficient to explain the degree of difference noted in this study. Of interest is that Greene et al[1] also reported a predominance of men in their group of patients with malignant melanoma (Men: N = 41, Women: N = 28).

It is noteworthy that 64.7% of the dysplastic-nevi patients who develop malignant melanoma had a previous personal history of malignant melanoma compared with only 24.7% of those who did not develop malignant melanoma. It has been established that a previous personal history of malignant melanoma is an independent risk factor for malignant melanoma.[18–21] However, because the small sample size of patients with both the clinical picture of the classic atypical-mole syndrome and a personal history of malignant melanoma, it is difficult to separate these risk factors as independent. Nonetheless, even those patients in our study with the classic atypical-mole syndrome without a personal history of malignant melanoma had a higher risk of developing malignant melanoma compared with the reference population (Table 4). The large number of people in both subsets with a personal and/or family history of malignant melanoma may reflect the nature of the particular dermatologic practice, which is composed largely of referrals of patients with melanocytic neoplasms.

The fact that the patients who were found to have malignant melanoma on follow-up examination had a longer median length of follow-up (63 months) than the patients who did not develop malignant melanoma (34 months) might lead to the conclusion that the longer fol-

low-up is the reason for the increased number of malignant melanomas observed. However, the median months until detection of the malignant melanomas was only 32 months.

The number of melanocytic neoplasms biopsied after entry into the study reflects lesions removed for diagnostic as well as cosmetic purposes. The greater number of biopsies performed in the dysplastic-nevi patients who eventually developed malignant melanoma may reflect greater atypicality of melanocytic neoplasms in this subset.

In a prospective follow-up of 357 patients with the classic atypical-mole syndrome, ten (2.8%) developed invasive malignant melanoma during a mean interval of 49 months. Thus, in approximately 4 years these patients had almost three times the estimated lifetime risk for developing malignant melanoma in whites (approximately 1% in 75 years).[14] Our study demonstrates that all groups[6] of patients with this syndrome are at a significantly increased risk for developing malignant melanoma. This finding confirms the need for targeting these types of patients for close follow-up, thereby allowing for early diagnosis of their malignant melanomas, when they are easily curable.

References

1. Green MH, Clark WH, Tucker MA, et al. High risk of malignant melanoma in melanoma-prone families with dysplastic nevi. Ann Intern Med 1985;102:458–65.
2. Holly EA, Kelly JW, Shpall SN, et al. Number of melanocytic nevi as a major risk factor for malignant melanoma. J Am Acad Dermatol 1987;17:459–68.
3. Kraemer KH, Greene MH, Tarone R, et al. Dysplastic naevi and cutaneous melanoma risk. Lancet 1983;ii:1076–7.
4. Kopf AW, Friedman RJ, Rigel DS. Atypical mole syndrome. J Am Acad Dermatol 1990;22:117–8.
5. Slue W, Kopf AW, Rivers JK. Total-body photographs of dysplastic nevi. Arch Dermatol 1988;124:1239–43.
6. Rigel DS, Rivers JK, Friedman RJ, et al. Risk gradient for malignant melanoma in individuals with dysplastic naevi. Lancet 1988;i:352–3.
7. Harlan LC. Age-specific incidence rates for malignant melanoma: Surveillance Epidemiology and End Results (SEER) data. NCI Surveillance and Operations Research Branch, May 1988.
8. Clark WH, Reimer RR, Greene M, et al. Origin of familial malignant melanomas from heritable melanocytic lesions. 'The B-K Mole Syndrome'. Arch Dermatol 1978;114: 732–8.
9. Elder DE, Goldman LI, Goldman SC, et al. Dysplastic nevus syndrome: A phenotypic association of sporadic cutaneous melanoma. Cancer 1980;46:1787–94.
10. Mackie RM, English J, Aitchison TC, et al. The number and distribution of benign pigmented moles (melanocytic naevi) in a healthy British population. Br J Dermatol 1985;113:167–74.
11. Piepkorn M, Meyer LJ, Goldgar D, et al. The dysplastic melanocytic nevus: A prevalent lesion that correlates poorly with clinical phenotype. J Am Acad Dermatol 1989;20:407–15.
12. Rhodes AR. Acquired dysplastic melanocytic nevi and cutaneous melanomas: Precursors and prevention. Ann Intern Med 1985;102:546–7.
13. Titus-Ernstoff L, Duray PH, Ernstoff MS. Dysplastic nevi in association with multiple primary melanoma. Cancer Res 1988;48:1016–8.
14. Seidman H, Mushinski MH, Gelb SK, et al. Probabilities of eventually developing or dying of cancer—United States, 1985. CA 1985;35:36–56.
15. Rigel DS, Rivers JK, Kopf AW, et al. Dysplastic nevi: Markers for increased risk for melanoma. Cancer 1989;63:386–9.
16. Kopf AW, Welkovitch B, Frankel RE, et al. Thickness of malignant melanoma: Global analysis of related factors. J Derm Surg Oncol 1987;13:345–420.
17. Vasen HF, Bergman W, Van Haeringen A, et al. The familial dysplastic nevus syndrome. Natural history and the impact of screening on prognosis. A study of nine families in the Netherlands. Eur J Cancer Clin Oncol 1989;25:337–41.
18. Beardmore GL, Davis NC. Multiple primary cutaneous melanomas. Arch Dermatol 1975;111:603–9.
19. Bellet RE, Vaisman I, Mastrangelo MJ, et al. Multiple primary malignancies in patients with cutaneous melanoma. Cancer 1977;40:1974–81.
20. Booher RJ. Recognition and treatment of melanoma. Surg Clin North Am 1969;49:389–405.
21. Cascinelli N, Fontana V, Cataldo I, et al. Multiple primary melanoma. Tumori 1975;61:481–6.
22. Rothman KJ. Modern Epidemiology. Boston: Little Brown, 1986:154.