Clinical Characteristics of Malignant Melanomas Developing in Persons With Dysplastic Nevi

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A total of 452 patients with dysplastic nevi (DN) were followed prospectively by repetitive, complete cutaneous examinations in order to determine the clinical features of early malignant melanomas (MM) arising in them. Sixteen patients (3.5%) developed 18 newly diagnosed MM during an average follow-up period of 27 months. Twelve of the 18 MM were *in situ* and all of the primary invasive MM diagnosed prospectively in this follow-up were less than 0.89 mm in Breslow thickness, implying an excellent prognosis. The principal clinical clue to the diagnosis of MM was change in a preexisting pigmented lesion. Total-body photographs were very useful in helping to identify the early MM in these patients.

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DYSPLASTIC NEVI (DN) are considered to be cutaneous markers which identify individuals who are at increased risk for developing malignant melanomas (MM) compared with individuals in the general population.[1-7] Several studies have estimated a substantial risk for MM in those relatives who have DN in the familial MM setting.[2,8] Based on a follow-up of 452 consecutive patients with DN, we have found that patients from all Groups of DN are at increased risk of developing MM in addition to patients in the familial MM setting.[9] Early detection and treatment of MM is particularly important in this high-risk subset of the population. This study determines if there were specific clinical features that could help identify MM in these patients to facilitate early identification and determine the reasons for lesion removal.

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Methods

A series of 452 consecutive white patients with clinical (Table 1) and histologic features[10] of DN are reported here. The clinical diagnosis of DN was based on the presence of at least two atypical moles. The key features for identifying patients with "classic" DN included the following: numerous nevocytic nevi (usually > 100); large diameter of some (≥ 8 mm); and dysmorphism (unusual clinical features including principally significant color variegation, irregular margins that fade imperceptibly into the surrounding skin, heterogeneity [lesions do not mimic their neighbors]).

The overall composition of the patients included in this study is summarized in Table 2. These patients were followed prospectively between January 1980 and October 1987. Before entry into the study, each patient had a biopsy performed of one or more atypical nevi which had the clinical and histologic features of DN. A standardized series of 24 color transparencies (35-mm) documenting the total-body surface was taken.[11] Each patient was followed at 3-month to 12-month intervals at which times a complete cutaneous examination was performed using the baseline photographs for comparison.

Any lesion which changed or arose *de novo* and was suggestive of MM was surgically removed *in toto*. Occasionally some lesions were removed because the patient requested it. The surgical specimen was blocked by cutting parallel steps at 2-mm intervals throughout. Sections were stained with hematoxylin-eosin and reviewed independently by two dermatopathologists (R.J.F., E.R.H.). Each specimen was examined for the presence of the histologic

TABLE 1. Clinical Characteristics of Classic Dysplastic Nevi

Feature	Clinical finding
Size	Vary; at least some 8 or more mm in diameter
Color	Variegate; multiple shades of tans, browns, black, red
Elevation	Usually raised centrally
Perimeter	Often irregular; usually fades imperceptibly into surrounding skin
Shoulder	Peripheral macular tan zone
Surface	Often mammillated ("pebbly," "cobblestoned")
Location	Usually trunk > limbs > face
Symptoms	None
Hypertrichosis	Absent
Erosion/ulceration	Absent

features of MM[12,13] and any associated histologic precursor (*e.g.*, dysplastic nevus) using previously published histologic criteria.[10]

The intraepidermal component of an *in situ* melanoma was differentiated from that of a dysplastic nevus on the basis that *in situ* melanomas are characterized by melanocytes arranged as solitary units above the dermoepidermal junction, melanocytes as solitary units that predominate in some foci over melanocytes arranged in nests, nests of melanocytes that vary in sizes and shapes, have irregular shapes, and tend to confluence, some nests of melanocytes above the dermoepidermal junction and similar changes as those just described within the epithelial structures of adnexa. The presence of pagetoid melanocytes was considered specific for *in situ* melanoma because, as a rule, junctional types of melanocytic nevi are not associated with pagetoid melanocytes.[13]

A malignant melanoma diagnosed at the initial visit to the physician was not considered as a "newly diagnosed MM" in this study. Only those MM which were newly diagnosed after the first examination were included in the results.

The medical records of all 452 patients were reviewed to determine the pertinent clinical and histologic characteristics of the 18 newly diagnosed MM which led to the diagnosis of MM in this study.

Results

A total of 16 (3.5%) of the 452 DN patients followed for an average of 27 months (range, 1–83 months) developed a total of 18 newly diagnosed cutaneous MM on prospective follow-up. Twelve of the 18 MM were Level I (MM *in situ*) lesions, whereas the remaining six lesions were invasive MM that ranged between 0.1 and 0.88 mm in Breslow thickness. Four of the six invasive MM developed in individuals with a preceding family history of MM (Patients 11, 13–15). No patient has developed recurrence or metastasis during subsequent follow-up (range, 6–47 months; average, 25 months).

The average age for the 16 DN patients who developed newly diagnosed MM on prospective follow-up was 40 years compared with a median age of 45 years for Stage I MM in the general population[14] and to 49 years for Stage I MM less than 0.89 mm thick in the New York University (NYU) Melanoma Cooperative Group data base of 315 such patients.

The clinical and histologic features of all 18 of the newly diagnosed MM appear in Tables 3 and 4. Various combinations of colors were present in these newly diagnosed MM including tans, browns, reds, and black. Only four of the 18 MM had a component of black color. Fourteen of the 18 MM were irregularly shaped, three were oval, and one was round. The diameters of the MM ranged from 3 to 12 mm, with an average diameter of 7.1 mm. Ten of the MM were macular, four were elevated up to 1 mm above the surface of the skin, whereas the remaining four MM were between 1 and 3 mm in elevation. Ten of the lesions had clinical "shoulders" (macular, tan regions extending beyond the raised central portion of the MM). Intact skin markings were present in all of the MM and three of these were noted to have increased markings. One of the 18 MM was a clinically *de novo* (previously nonexistent) lesion documented by its absence on baseline total-body photographs.

Histologically, 12 of the MM diagnosed prospectively were *in situ* lesions. The six remaining MM were 0.1 mm, 0.26 mm, 0.4 mm, 0.5 mm, 0.7 mm, and 0.88 mm in Breslow thickness, respectively. Also of note was that eight of the 18 MM had contiguous DN associated with them on histologic examination of the step-sectioned specimens.

The changes and clinical characteristics of the cutaneous lesions which led to the removal and subsequent diagnosis of MM are noted in Table 5. Fifteen of the MM were noted on physical examination by the physician to undergo change in size, 12 change in shape, 11 change in color, and two change in surface characteristics (some lesions changed in more than one aspect). However, 13 of the 16 patients were unaware of any change in their MM (Table 3). Two of the patients were suspicious of changes in their lesions, but ignored them. One patient was very aware of the change in her MM and requested that the physician remove it. Both patients who developed a sec-

TABLE 2. Distribution of Dysplastic Nevus Patients Included in Study

No. of patients	452
Men	206 (46%)
Women	246 (54%)
Average age ± SD (yr)	36.1 ± 13.1
Range	7 to 81
Total patient-mo of follow-up	12,227
Range (mo)	1 to 83
Average mo of follow-up per patient ± SD	27 ± 16

TABLE 3. Clinical Characteristics of Newly Diagnosed Malignant Melanomas

Patient	Sex/ age	Color	Shape	Shoulder (Y or N)	Diameter (mm)	Elevation*	Helioder- matosis†	Skin markings‡	Exaggeration of skin markings (Y or N)	Site	Patient comment
1	M/58	T/LB/DB	I	Y	12	+	++	++	Y	Calf	Unaware
2	M/48	T/R	I	Y	9	+	++	++	N	Subscapular	Unaware
3	F/33	LB/DB	O	Y	5	+	0	++	Y	Thigh	Patient suspicious
4	F/34	DB	I	N	3	0	+	++	N	Shin	Unaware
		LB/DB	I	N	5	0	+	++	N	Temple	Noted change
5	F/24	T/LB/DB	I	Y	6	++	++	++	N	Presternal	Unaware
6	M/23	T/R	R	N	10	0	+	++	N	Scapula	Unaware
7	F/29	BL	I	N	4	0	0	++	N	Calf	Noted change
8	F/25	T/LB/DB	I	Y	5	0	+++	++	N	Forearm	Unaware
		LB/DB	I	Y	5	0	0	++	N	Thigh	Noted change
9	F/30	LB	O	N	8	0	0	++	N	Calf	Unaware
10	M/70	T/LB/DB	I	Y	6	0	++	++	N	Ear	Unaware
11	F/37	LB/DB	I	N	8	0	+	++	N	Midback	Unaware
12	M/45	T/LB/DB/BL	I	Y	7	++	+++	+	Y	Forearm	Unaware
13	M/51	T/LB/DB/BL/R	I	N	10	+	+++	++	N	Posterior shoulder	Unaware
14	M/64	LB/DB	I	N	9	0	+++	++	N	Forearm§	Unaware
15	M/35	T/DB/BL/R	I	Y	6	++	0	+	N	Scalp	Unaware
16	F/39	LB/DB/R	O	Y	9	++	++	+	N	Knee	Ignored change

T: tan; LB: light brown; DB: dark brown; BL: black; R: red; BU: blue; O: oval; R: round; I: irregular; Y: yes; N: no; heliodermatosis: contiguous sun-damaged skin.

* 0: macular; +: slight (up to 1 mm); ++: moderate (1–3 mm).

† : 0: none; +: mild; ++: moderate; +++: marked.

‡ 0: absent; +: present (interrupted); ++: present (throughout).

§ *De novo* lesion (*i.e.*, appeared on previously normal skin per comparison with baseline photographs).

ond MM on prospective follow-up were unaware of their first MM, but did notice changes occurring in their second MM. It is important to notice that ten of the 18 MM were diagnosed by the physician who detected *changes* in the pigmented lesion by comparison with the baseline total-body photographs.

Discussion

It has been shown that early diagnosis and complete surgical excision of MM less than 0.76 mm, and even less than 0.86 mm, in Breslow thickness is associated with an excellent prognosis.[15–18] It is quite important, therefore, to recognize the clinical characteristics of early (thin) MM. Of the 18 MM detected thus far in the 452 patients with DN reported here, 12 were *in situ* lesions and six were < 0.89 mm thick. Based on Stage I MM patients entered into the NYU Melanoma Cooperative Group data base between 1972 and 1982, the cumulative 10-year survival rate for the 246 Stage I patients who had MM less than 0.89 mm thick is 97.7%. No patient in the current study of 452 DN patients has developed a recurrence or metastasis of their newly diagnosed MM.

In agreement with others,[19] eight of the 18 MM (44%) arose in histologic contiguity to a DN. Some authors[20,21] have reported that this type of association confers to the patient a more favorable prognosis than is seen in those patients in whom their MM arose *de novo,* even after matching for tumor thickness. The reason for this association is uncertain.

Table 3 lists the clinical characteristics of the 18 newly diagnosed MM in this study. Most of the MM exhibited a color combination of tans, browns, reds, and black.

TABLE 4. Histologic Characteristics of Newly Diagnosed Malignant Melanomas

Patient	Thickness of MM (*in situ,* or in mm)	Contiguous DN (Y or N)
1	*in situ*	N
2	*in situ*	Y
3	*in situ*	Y
4	*in situ*	N
	in situ (lentigo maligna)	N
5	*in situ*	Y
6	*in situ*	N
7	*in situ*	N
8	*in situ*	N
	in situ	Y
9	*in situ*	Y
10	*in situ* (lentigo maligna)	N
11	0.10 mm	N
12	0.26 mm	Y
13	0.40 mm	N
14	0.50 mm	N
15	0.70 mm	Y
16	0.88 mm	Y

MM: malignant melanoma; DN: dysplastic nevus; Y: yes; N: no.

TABLE 5. Reasons for Removal of Cutaneous Lesion

Patient	Change in				Lesion	Reason
	Color	Shape	Size	Surface	Black component	MD's comment
1	Y	Y	Y	N	N	Reason not given
2	N	Y	Y	N	N	Dx: superficial BCE with contiguous DN
3	Y	N	Y	N	N	Change per photo
4	N	Y	Y	N	N	Change per photo (doubled in size)
	Y	Y	Y	N	N	Dx: MM
5	N	Y	Y	N	N	Change per photo
6	N	Y	N	N	N	Change per photo
7	Y	Y	Y	N	Y	Reason not given
8	Y	Y	Y	N	N	Change per photo (enlarged, lightened)
	Y	Y	Y	N	N	Change per photo (enlarged)
9	N	N	Y		N	Change per photo
10	Y	Y	Y	N	N	Change per photo
11	Y	Y	Y	N	N	Change per photo
12	—	—	—	—	Y	Dx: DN
13	Y	N	Y	N	Y	Dx: MM
14	Y	Y	Y		N	Change per photo (new lesion on skin)
15	—	—	—	—	Y	Dx: MM
16	Y	N	Y	Y	N	Bled after cat scratch

Y: yes; N: no; MD: Medical Doctor; Dx: diagnosis; BCE: basal-cell carcinoma; DN: dysplastic nevi; MM: malignant melanoma.

Greene *et al.*[2] stated that "the appearance of new black pigmentation in a dysplastic nevus was the best predictor of the presence of early melanoma." Only four of the 18 MM in our study had a black component. In another study in progress of 100 consecutive histologically examined DN, 24% had a black component.[22] From these observations, it appears that the presence of black color is neither a specific clinical sign of MM nor a feature that is absent in DN. Yet, it may serve as one clue to the suspicion that a lesion may be a MM.

Most of the 18 MM were irregular in shape. They varied in size from 3 to 12 mm in largest diameter. A third of the MM were less than 6 mm in diameter indicating that MM should not be ruled out clinically on the basis of small size. Over 50% of the MM were macular and the remainder were no higher than 3 mm in elevation. All of the lesions had intact skin markings; only three had exaggerated markings. None of the lesions was hypertrichotic. Thus, there does not appear to be any particular clinical characteristic that is pathognomonic for an early MM in our DN patients. The principal clinical clue to the diagnosis of MM in this series was change in size, shape, and color.

Table 5 summarizes what prompted the removal of the MM in each of the 18 newly diagnosed lesions. Most of these lesions did not clinically look like typical MM (only three were removed because the lesions had these classic attributes). It was the change in the clinical characteristics noted in comparison to the total-body photos and to the patient's other nevocytic nevi that prompted the removal of these early MM. The most important conclusion that can be drawn from this experience is that cutaneous lesions should be removed if they have the classic clinical attributes of MM, or if they are noted to undergo significant change relative to the patient's other nevocytic nevi.

Previous authors have also noted the importance of changing lesions in DN and non-DN patients in regard to the diagnosis of early MM.[19,23,24] Along these lines, we, as others, have found the use of total-body photographs very helpful as an aid to the diagnosis of thin, and thus, curable MM in these DN patients.[11,25–32] In addition it is important to emphasize that it was the clinician, not the patient, who noted the clinical features that led to the diagnosis of MM. This is despite our attempts to educate the patients in the art of diagnosing MM, including the provision of brochures depicting the clinical features of such lesions. Thus, any change in a pigmented lesion could be a sign of evolving MM, especially when a particular pigmented lesion is changing disproportionately to other similar nevocytic nevi.

The average age of the patients in this prospective study who developed newly diagnosed primary cutaneous MM on follow-up was 40 years (four were in their twenties) compared with the average age of 50 years for the patients entered into the general NYU Melanoma Cooperative Group data base. It has been previously reported that patients with familial MM have their MM diagnosed at a significantly earlier age than patients who have nonfamilial MM.[33] Our data show that people with DN have their MM diagnosed at a relatively young age, even in the nonfamilial setting.[9] Thus, we recommend that people who have DN be followed regularly beginning at least in the third decade of life.

In conclusion, there was no specific clinical characteristic that was pathognomonic for the diagnosis of early melanoma in our series of DN patients. Rather, it was the change in the clinical features of size, shape, and color, best noted by comparison to total-body photographs, which alerted us to make the diagnosis of most of the early malignant melanomas in these patients.

REFERENCES

1. Kraemer KH. Dysplastic nevi as precursors to hereditary melanoma. *J Dermatol Surg Oncol* 1983; 9:619–622.

2. Greene MH, Clark WH, Tucker MA *et al.* High risk of malignant melanoma in melanoma-prone families with dysplastic nevi. *Ann Intern Med* 1985; 102:458–465.

3. Sagebiel RW. Diagnosis and management of premalignant melanocytic proliferations. *Pathology* 1985; 17:285–290.

4. Roush GC, Barnhill RL, Duray PH *et al.* Diagnosis of the dysplastic nevus in different populations. *J Am Acad Dermatol* 1986; 14:419–425.

5. Kraemer KH, Tucker M, Tarone R, Elder DE, Clark WH. Risk of cutaneous melanoma in dysplastic nevus syndrome types A and B. *N Engl J Med* 1986; 2:1615–1616.

6. Holly EA, Kelly JW, Shpall SN, Chiu S-H. Number of melanocytic nevi as a major risk factor for malignant melanoma. *J Am Acad Dermatol* 1987; 17:459–468.

7. Consensus conference on precursors to malignant melanoma. *J Dermatol Surg Oncol* 1985; 11:537–540.

8. Kraemer KH, Greene MH, Tarone R *et al.* Dysplastic naevi and cutaneous melanoma risk. *Lancet* 1983; 2:1076–1077.

9. Rigel DS, Rivers JK, Kopf AW *et al.* Dysplastic nevi: Markers for increased risk for melanoma. *Cancer* 1989; 63:386–389.

10. Friedman RJ, Heilman ER, Rigel DS, Kopf AW. The dysplastic nevus: Clinical and pathologic features. *Dermatol Clin* 1985; 3:239–249.

11. Slue W, Kopf AW, Rivers JK. Total body photographs of dysplastic nevi. *Arch Dermatol* 1988; 124:1239–1243.

12. Ackerman AB. Pathology of Malignant Melanoma. New York: Masson, 1981; 59–91.

13. Ackerman AB. The concept of malignant melanoma *in situ*. In: Elder D, ed. Pathobiology of Malignant Melanoma. Basel: Karger, 1987; 205–210.

14. Balch CM, Shaw HM, Soong S-J, Milton GW. Changing trends in the clinical and pathologic features of melanoma. In: Balch CM, Milton GW, eds. Cutaneous Melanoma: Clinical Management and Treatment Results Worldwide. Philadelphia: JB Lippincott, 1985; 313–319.

15. Breslow A. Thickness, cross-sectional areas, and depth of invasion in the prognosis of cutaneous melanoma. *Ann Surg* 1970; 172:902–908.

16. Breslow A. Prognostic factors in the treatment of cutaneous malignant melanoma. *J Cutan Pathol* 1979; 6:208–212.

17. Day CL, Lew RA, Mihm M *et al.* The natural break points for primary tumor thickness in clinical Stage I melanoma. *N Engl J Med* 1981; 305:1155.

18. Kopf AW, Welkovich B, Frankel RE *et al.* Thickness of malignant melanoma: Global analysis of related factors. *J Dermatol Surg Oncol* 1987; 13:345–420.

19. Duray PH, Ernstoff MS. Dysplastic nevus in histologic contiguity with acquired nonfamilial melanoma: Clinicopathologic experience in a 100-bed hospital. *Arch Dermatol* 1987; 123:80-84.

20. Friedman RJ, Rigel DS, Kopf AW *et al.* Favorable prognosis for malignant melanomas associated with acquired melanocytic nevi. *Arch Dermatol* 1983; 119:455–462.

21. Sober AJ, Day CL, Fitzpatrick TB, Lew RA, Kopf AW, Mihm MC. Early death from clinical Stage I melanoma. *J Invest Dermatol* 1983; (Suppl 6) 80:50–52.

22. McBride A, Rivers JK, Kopf AW, Cockerell CJ, Bart RS. Quantification of clinical features of dysplastic nevi (in preparation).

23. Elder DE, Greene MH, Bondi EE *et al.* Acquired melanocytic nevi and melanoma: The dysplastic nevus syndrome. In: Ackerman AB, ed. Pathology of Malignant Melanoma. New York: Masson Publishing, 1981; 185–215.

24. Wick MM, Sober AJ, Fitzpatrick TB *et al.* Clinical characteristics of early cutaneous melanoma. *Cancer* 1980; 45:2684–2686.

25. Crutcher WA, Sagebiel RW. Prevalence of dysplastic naevi in a community practice. *Lancet* 1984; 1:729.

26. Greene MH, Clark WH, Tucker MA *et al.* Managing the dysplastic naevus syndrome. *Lancet* 1984; 1:166–167.

27. Greene MH, Clark WH, Tucker MA *et al.* Acquired precursors of cutaneous malignant melanoma: The familial dysplastic nevus syndrome. *N Engl J Med* 1985; 312:91–97.

28. Rhodes AR: Acquired dysplastic melanocytic nevi and cutaneous melanoma: Precursors and prevention. *Ann Intern Med* 1985; 102:546–548.

29. Kelly JW, Crutcher WA, Sagebiel RW. Clinical diagnosis of dysplastic melanocytic nevi. *J Am Acad Dermatol* 1986; 14:1044–1052.

30. Koh HK. The patient with a pigmented lesion. *Hosp Pract* 1986; 21:47–54.

31. Mysliborski JA. The dysplastic nevus syndrome. *Compr Ther* 1986; 12:17–22.

32. Kopf AW, Rivers JK, Slue W, Rigel DS, Friedman RJ. Photographs are useful for detection of malignant melanoma in patients who have dysplastic nevi. *J Am Acad Dermatol* 1988; 19:1132–1134.

33. Kopf AW, Hellman LJ, Rogers GS *et al.* Familial malignant melanoma. *JAMA* 1986; 256:1915–1919.