Regression in malignant melanoma

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A multiple stepwise logistic regression analysis shows that histologic regression is more likely to be found in a malignant melanoma that is level III or less, more than 10 mm in diameter, associated with solar elastosis, located on an anatomic area other than the head or neck, and when there are areas of whiteness clinically. Although patients with malignant melanomas displaying signs of regression histologically have a slightly better 5-year disease-free survival, this may be attributed to a difference in tumor thickness. (J AM ACAD DERMATOL **8**:363-368, 1983.)

Partial regression is a common feature in primary malignant melanomas. Although it probably represents an immunologic response of the host directed against the malignant cells, the exact mechanism for such regression is not understood. In order to gather information about the biologic significance of regression, we correlated its presence or absence with several other factors available to us in our computerized data base. Furthermore, we tried to determine if partial regression relates to the 5-year disease-free survival of patients with malignant melanomas.

MATERIALS AND METHODS

A total of 1,015 consecutive patients with primary cutaneous malignant melanoma were entered prospectively into the New York University Melanoma Cooperative Group data base from 1972 through 1980. In 549 of these 1,015 records, step sections were done throughout the specimen of the primary lesion so that a pathologist could accurately measure the greatest thickness of the lesions. Due to the previously demonstrated importance of using step sections in determining greatest thickness,[3] this study was initially limited to these 549 cases.

Histologic regression was defined in this study as a dense, lichenoid, lymphohistiocytic infiltrate in the early phase, and dermal fibrosis associated with a variable number of melanophages, dilated blood vessels, and thickened collagen bundles as the inflammatory process subsides.[1-3]

Because histologic features of regression were never observed in our series of nodular melanomas, because lentigo maligna melanoma may represent a different disease entity from superficial spreading melanoma,[4] and because of the paucity of cases classified as acral-lentiginous melanoma, the subsequent analyses were limited to superficial spreading melanoma.

Five-year disease-free survival, using a life-table analysis method,[5] was computed for stage I (primary lesion only) superficial spreading melanomas that had evidence of regression histologically versus those that did not. The differences were compared using the Lee-Desu statistic.[6] To determine if regression has prognostic value by itself, independently of thickness, a Cox

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Table I. Prevalence of regression in the various types of malignant melanoma

	All melanomas	SSM*	LMM*	NM*	Other†
Regression	135 (24.6%)	123 (27.1%)	4 (17.4%)	0 (0%)	8 (18.6%)
No regression	414 (75.4%)	331 (62.9%)	19 (82.6%)	29 (100%)	35 (81.4%)
Total	549 (100%)	454 (100%)	23 (100%)	29 (100%)	43 (100%)

*SSM: Superficial spreading melanoma; LMM: lentigo maligna melanoma; NM: nodular melanoma.

†Includes lentigo maligna, acral lentiginous melanoma, unclassified melanoma with radial growth pattern, and type unknown.

Table II. Five-year disease-free survival for superficial spreading melanoma, stage I with step sections (N-416)

	Cases	Five-year* disease-free survival
Lesions with regression	119 (26.2%)	92.4%
Lesions without regression	297 (73.8%)	84.2%

*p = 0.057, Lee-Desu Comparison.

Table III. Prognostic value of lesion thickness and evidence of regression in superficial spreading melanoma*

Variable	P value†
Thickness ≥1.7 mm	<0.00001
Thickness 0.76-1.69 mm	0.004
Presence of regression	0.068

*Cox Proportional Hazards Model. Overall Model Chi Square = 96.4 with 3 df; $p < 0.00001$.

†p value associated with Standardized Regression Coefficient.

proportional hazards model analysis was performed.[7]

A total of nineteen separate variables concerning the patients and their lesions were then reviewed in order to find their relationship, if any, to the presence or absence of regression in superficial spreading melanomas. Chi-square analysis or, when appropriate, Student's t test was performed to determine the significance of the relationship of each of these variables to regression. In order to determine the relative importance of these factors shown by chi-square analysis to be related to regression, a stepwise logistic regression analysis was performed.[8] To minimize the influence of irrelevant factors, only those with a p value of <0.20 in the previous analysis were included in the logistic analysis. By this method the significant factors that permitted separation of superficial spreading melanomas into those with and those without histologic regression were derived.

RESULTS

Histologic regression was present in 135 (24.6%) of 549 step-sectioned melanomas (Table I). It was found in 123 (27.1%) of 454 superficial spreading melanomas, 4 (17.4%) of 23 lentigo maligna melanomas, none of 29 nodular melanomas, and 8 (18.6%) of 43 melanomas of other types.

Life-table analysis of 416 patients with superficial spreading melanoma and adequate follow-up data revealed that patients with stage I superficial spreading melanomas displaying histologic signs of regression had a better 5-year disease-free survival (92%) than patients without regression (84%). This difference almost reached the 0.05 level of statistical significance (Table II; p = 0.057). However, when adding thicknesses of the melanomas to the presence of histologic regression in a Cox proportional hazards model analysis, only thicknesses remained significant (Table III). The following variables were then tested for their relationship to regression: age at primary diagnosis; sex; duration of the melanoma, by history; previous sun exposure, by history; previous sunburns, by history; skin color (pale, medium, or dark); presence or absence of freckles; history of bleeding or ulceration; anatomic location (head and neck, upper limbs, lower limbs, trunk); presence or absence of white, red, or blue color; largest diameter; evidence of sun damage at lesion site; level; thickness; presence or absence of nevus histologically; and solar elastosis. Of the nineteen variables tested, ten had a value of $p \leq 0.20$ and were, therefore, included in the stepwise logistic regression analysis (Table IV). These variables were: thickness; level; whiteness clinically; solar elastosis; largest diameter; presence versus absence of a nevus; location; skin color; history of bleeding; and red color. The significantly associated

Table IV. Variables related to histologic regression of step-sectioned, stage I, superficial spreading melanomas (univariate analysis)

Variable	Groupings	Percentage of lesions with regression	p value
Thickness	0.01-0.75 mm	36%	0.0001*
	0.76-1.69 mm	27%	
	1.70 mm or more	19%	
Level	II-III	33%	0.0004
	IV-V	18%	
Solar elastosis	Present	34%	0.0111
	Absent	23%	
White color	Present	39%	0.0354
	Absent	25%	
Largest diameter	1-10 mm	19%	0.0700*
	11 mm or more	32%	
Skin color	Pale	29%	0.0809
	Medium	25%	
	Dark	0%	
Previous nevus (histologically)	Present	34%	0.0916
	Absent	25%	
Location	Head and neck	13%	0.1033
	Upper limbs	29%	
	Trunk	31%	
	Lower limbs	25%	
History of bleeding	Present	21%	0.1433
	Absent	29%	
Red dominant color	Yes	14%	0.1706
	No	28%	

*p value from t test comparison of means.

variables were found to be (Table V): level (less regression when level IV or V); diameter (more regression when >10 mm); solar elastosis (more regression when solar elastosis was present); anatomic location (less regression when melanoma present on head or neck); and clinical whiteness (more regression when white color present).

DISCUSSION

Spontaneous regression has been defined as the partial or complete disappearance of a malignant tumor in the absence of treatment. Everson and Cole[9] documented 176 cases of complete spontaneous regression of all types of cancer from 1900 to 1966, of which nineteen were malignant melanomas. Although malignant melanomas make up only 1.8% of all cancers,[10] 11% of the cases of complete spontaneous regression reported by these authors were melanomas. Thus, the incidence of spontaneous regression of malignant melanoma is six times the expected incidence, suggesting that the phenomenon is relatively more common in this cancer and perhaps has a more significant role in its natural history than in other malignancies.[11] Evidence of partial regression of melanoma is even more commonly reported by pathologists. Although the incidence of partial regression was previously considered to be approximately 10%,[1,12,13] according to McGovern et al[14] it may be as high as 35%. In our series, regression was present in 24.6% of all step-sectioned melanomas.[3] These apparent increases may be due to the fact that pathologists now more readily recognize the subtle features of histologic regression and that step sections through the entire block are more often being done. In addition, the relative frequency of thin melanomas, in which histologic regression is more common,[2,3,15] is increasing.[16]

Table V. Model for variables associated with presence of histologic regression*

Variable	P value†
Level II-III	0.0006
Lesion diameter >10 mm	0.0026
Solar elastosis	0.0229
Site other than head or neck	0.0364
Presence of white color	0.0495

*Logistic Regression Model. Overall Model Chi-Square = 37.86 with 5 df; $p < 0.00001$.

†p value associated with Standardized Regression Coefficient.

Among the 549 melanomas of all thicknesses (Table I), regression was present in 27.1% of the superficial spreading melanomas and in 17.4% of the lentigo maligna melanomas. It was not found in the twenty-nine nodular melanomas. This supports the impression that regression occurs primarily in melanomas with adjacent intraepidermal horizontal growth components.[1,2] It is also possible that no regression was seen in nodular melanomas because they are generally thicker than superficial spreading melanomas (in our series, mean thickness was 1.70 mm for superficial

spreading melanomas and 4.45 mm for nodular melanomas) and regression is more frequently seen in thin lesions.[2,3,14]

Although the 5-year disease-free survival for patients with histologic evidence of regression was better than for patients without regression (92% versus 84%) and this difference was nearly statistically significant ($p = 0.057$), by adding thickness to regression in the Cox model analysis, only thickness proved to be a significant prognostic variable. Regression failed to appear in the model as an additive significant prognostic factor. This is similar to what was found in Australia by McGovern et al.[14] These authors studied 634 patients with localized cutaneous malignant melanoma and examined the influence of histologic regression on prognosis for four thickness ranges. They found that the slightly superior prognosis for lesions showing partial regression was attributable to the fact that thin lesions (with a good prognosis) had a much higher prevalence of regression than thick lesions. They concluded, therefore, that regression had no effect by itself on survival rate but derived its purported prognostic significance because of its close correlation with tumor thickness, the most important prognostic determinant. In the report of Balch et al,[13] only a small percentage ($17/170 = 10\%$) of their patients had histologic evidence of regression, and this factor had no significant influence on survival ($p = 0.13$). In none of the multivariate analyses, for different categories of malignant melanoma done by Day et al[17–24] and that included regression as a cofactor, has this histologic feature proved to be an independent risk factor for recurrent disease or for death from melanoma.

Similarly, McLean et al,[25] looking upon white depressed areas in the primary lesions of superficial spreading melanomas, could not find any prognostic importance for this clinical counterpart of regression. Contrary to the findings of Gromet et al,[26] who reported a statistically significant worse prognosis in thin (<0.76 mm) malignant melanomas presenting signs of partial regression histologically, we[3] found that, when step-sectioned material is studied, metastases are exceptional events in thin melanomas even in the presence of partial regression.

From the multiple stepwise logistic regression analysis it appears that regression is more common when a melanoma is level III or less, when it is more than 10 mm in diameter, when associated solar elastosis is present, when the melanoma is located on an anatomic area other than the head or neck, and when clinically there are areas of whiteness.

It is postulated that regression represents a morphologic correlate of the immunologic reaction of the host against the neoplasm. Superficial spreading melanoma starts in the epidermis and enlarges first by horizontal extension (horizontal growth phase); it may be that at this stage little or no immunologic response of the host is mounted against the malignant melanocytes. It is in the later vertical growth phase, when the melanoma cells are present in the papillary dermis, that the host recognizes the malignant cells as "not-self" and mounts an immunologic response against them. This hypothesis correlates well with the observation by many pathologists that an in situ melanoma (i.e., one totally confined to the epidermis) is only rarely associated with a dense inflammatory cell infiltrate in contrast to the common finding of such an infiltrate when a melanoma has invaded the superficial dermis.

Although determination of level is generally of less prognostic significance than measurement of thickness, it may still have more value than thickness in estimating the immunologic stance. Regression is more commonly seen in level II and level III lesions, when the melanoma is confined to the papillary dermis. As the tumor reaches the reticular dermis (level IV), new clones of cells may appear, which are too weakly antigenic to be recognized and destroyed by the host's immune system.

The fact that regression is seen more often in superficial spreading melanomas that have evidence of solar elastosis histologically is consistent with the higher prevalence of regression (35%) of malignant melanomas in Australia[14] where sun exposure is heavy in comparison with the lower prevalence of regression (24.6%) in our series, observed in the less sunny New York area. It may be that the higher prevalence of regression in Australia is related to the fact that melanomas there tend

to be thinner than those in our series. However, in our series, partial regression histologically is less common in malignant melanomas located on the head and neck than in those located on other anatomic sites; one would expect to find more solar elastosis on the head and neck areas than on other sites.

The last variable that appears to be correlated with histologic regression is clinical whiteness. Regression usually begins as a focal phenomenon that involves only a small portion of the primary lesion. At first the most probable clinical correlate of regression is erythema. It is only when regression evolves further that leukoderma becomes apparent. Thus, there is a spectrum of colors; red, white, and blue (due to melanin-laden macrophages deep in the dermis), which can be appreciated as clinical expressions of the phenomenon of regression.

In conclusion, in our series, histologic regression played only a marginal role as a prognostic factor in superficial spreading melanoma, deriving its significance mainly from its close relationship to the thickness of the melanoma.

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Factitious cheilitis

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Six patients (four male and two female) with factitious cheilitis are described. All had personality disturbances as well as crusted lip lesions that varied in severity from thin serous crusts to thick hemorrhagic crusts. This entity must be distinguished from infectious cheilitis, contact cheilitis, actinic cheilitis, photosensitivity dermatoses, exfoliative cheilitis, and cheilitis glandularis on the basis of the history and laboratory evaluation. (J AM ACAD DERMATOL **8:**368-372, 1983.)

Factitious cheilitis is described as dryness, scaling, cracking, or fissuring of the lips due to various habits, including biting or continual licking.[1] In 1921, Brocq[2] suggested that some inflammatory disorders of the lips might be due to nervous instability. The French have described a condition that is referred to as *le tic des lèvres,* in which manipulation of the lips produces a cheilitis or exacerbates an already existing one.[3]

Six cases of factitious lip crusting have been reported.[4,5] This condition often is diagnosed by exclusion of other entities, but patients usually have a history of psychiatric problems and on rare occasions will admit to producing the lesions. Patients present with hemorrhagic or serous crusts involving the lips and rarely the perioral area.

Patients with crusted lip lesions can present a difficult diagnostic problem. After infectious, actinic, contact, and photosensitive factors have been ruled out, exfoliative cheilitis, cheilitis glandularis, and factitious cheilitis remain as possibilities.

Previous reports of exfoliative cheilitis and cheilitis glandularis have not clarified the distinction between these conditions and factitious cheilitis. Tyldesley[6] described a patient with exfoliative cheilitis who ultimately responded to tranquilization and removal of stressful stimuli.

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