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ORIGINAL ARTICLES

Multiple Primary Melanoma

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Abstract *Introduction.* The risk of multiple melanoma is estimated to be between 1% and 8%, with the majority of studies being carried out on North American populations. Our objective was to determine the risk and the clinical-pathological features of multiple primary melanoma in a Spanish Mediterranean population.
Material and methods. We performed a retrospective study of the medical records and the database of the Melanoma Unit of Hospital de Bellvitge, Barcelona, Spain, between 1988 and 2005.
Results. We found 25 cases of multiple primary melanoma among 934 patients studied, representing a risk of 2.6% in our population of melanoma patients. In 50% of cases, the second melanoma appeared during the first year of follow-up. These subsequent lesions occurred at a different site from the initial lesion in 58% of cases. In the majority of cases, lesions in a single patient showed similar cytological and architectural features. However, we did observe marked interindividual variability in the histology of multiple primary melanomas.
Conclusion. Although the risk of a second melanoma in our population appears to be lower than in North American populations, it is not negligible. Melanoma patients must therefore be followed up for life, not only for the risk of metastases but also for the risk of a new primary tumor. Complete examination of the skin must be performed at each visit.

Key words: multiple, melanoma, Mediterranean, Spain.

MELANOMA PRIMARIO MÚLTIPLE

Resumen. *Introducción.* El riesgo de melanoma múltiple se cifra aproximadamente entre un 1 y un 8 %. La mayoría de los estudios se basan en población anglosajona. Nuestro objetivo es determinar el riesgo y las características clínicas e histológicas de los melanomas múltiples en una población mediterránea.
Material y métodos. Hemos realizado un estudio retrospectivo a partir de las historias clínicas y la base de datos de la Unidad de Melanoma del Hospital de Bellvitge (Barcelona) de los pacientes con melanoma diagnosticados entre 1988 y 2005.
Resultados. Hemos encontrado 25 pacientes con melanoma primario múltiple de entre los 934 pacientes estudiados, siendo el riesgo del 2,6 % para nuestra población de pacientes con melanoma. El 50 % de segundos melanomas aparecieron dentro del primer año de seguimiento. En el 58 % de los casos el siguiente melanoma apareció en un área distinta al anterior. En la mayoría de los casos las características histológicas se mantuvieron, por lo que se refiere a la citología y el tipo de distribución arquitectural en los distintos melanomas de un mismo paciente. No observamos similitud histológica y sí una gran variabilidad interindividual de los melanomas primarios múltiples de distintos pacientes.
Conclusión. Aunque en la población mediterránea el riesgo de padecer un segundo melanoma parece ser menor que en los anglosajones, éste no es despreciable. Por dicho motivo, los pacientes con melanoma deben ser seguidos de por vida no sólo por el riesgo de metástasis, sino por el de aparición de otros nuevos primarios, debiéndose de explorar todo el tegumento cutáneo en cada visita.

Palabras clave: múltiple, melanoma, mediterránea, España.

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Although Dr Abelardo Moreno passed away during the preparation of this manuscript, he was involved in the histologic evaluation of the multiple melanomas analyzed and in the drafting of the manuscript until the very last moment.

Introduction

In recent years, malignant cutaneous melanoma has become one of the cancers with the fastest growing incidence worldwide.[1-5] Because there is no cure for melanoma once it reaches an advanced stage, prevention[6] and early diagnosis[7] are the most important treatment stategies.[8-10] It is therefore particularly important to identify and monitor at-risk populations in order to detect lesions as early as possible. Patients who have

already had melanoma are among those at risk. While several population studies have evaluated the risk of second primary cutaneous melanomas in individuals with a history of melanoma,[1-13] few studies have evaluated the incidence and risk of multiple primary melanoma in Mediterranean populations.[4,14-16] The aim of this study was to analyze the incidence and clinicopathologic characteristics of multiple primary cutaneous melanoma in a Mediterranean population.

Materials and Methods

We analyzed all the patients diagnosed, treated, and monitored for cutaneous melanoma at Hospital Universitario de Bellvitge in Barcelona, Spain between 1988 and 2005. The hospital is a university hospital that provides tertiary health care to a population of approximately 1 million people.

Patients with in situ melanoma were followed for 2 years, after which they were referred to their local dermatologist for annual check-ups. Those with invasive melanoma were followed for 10 years (every 4 months for the first 2 years, every 6 months from year 2 to year 5, and every year from year 5 to year 10). After this period, they were referred to their local dermatologist for annual screening. Patients with invasive melanoma were also scheduled for regular evaluations such as lactate dehydrogenase testing and plain chest radiographs for the first 2 years, in addition to any tests deemed necessary to explore clinical manifestations.

The mean (SD) follow-up time for the series was 4.36 (11.37) years, with a median of 3 years.

For patients diagnosed with multiple primary melanoma, we analyzed age, sex, time between the diagnosis of the first and subsequent melanomas, history of melanoma in first-degree relatives, skin phototype, Breslow depth, Clark level, site of occurrence of initial and subsequent melanomas, and clinicopathologic features. When 2 melanomas were diagnosed at the same time, the lesion that had prompted referral was classified as the initial melanoma (Table).

We reviewed the histologic slides from all the patients with multiple melanoma to compare the histologic features of different tumors from the same patient and to determine whether multiple melanomas shared distinctive morphologic features.

Two patients from the same family with multiple primary melanoma and xeroderma pigmentosum were not included in the study.

Results

Between 1988 and 2005, our hospital diagnosed, treated, and followed 934 patients with primary melanoma. Twenty-five of these patients had multiple melanoma, which corresponds to an incidence of 2.6% for this period. Thirteen of the patients were men (52%) and 12 were women (48%), and the mean (SD) age at which the first tumor was diagnosed was 52.96 (15.72) years (range, 25-78 years). We detected 2 primary melanomas in 20 patients (80%), 3 in 4 patients (16%), and 4 in just 1 patient (4%).

The mean (SD) time between diagnosis of the first and second melanoma was 35.84 (37.95) months (range, 0-9.3 years). In 8 of the 25 patients, the 2 melanomas were diagnosed simultaneously. In the remaining patients, the second melanoma was diagnosed within a year of the first in 5 patients, between year 1 and 2 in 2 patients, between year 2 and 5 in 3 patients, and between year 5 and 10 in 7 patients.

Two of the initial melanomas were in situ and the rest were invasive; 14 had a Breslow depth of less than 1 mm, 4 extended to a depth of 1 mm to 2 mm, and 2 exceeded a depth of 4 mm.

Of the subsequent melanomas detected, 13 were in situ, 16 had a Breslow depth of less than 1 mm, 2 penetrated to a depth of 1 mm to 2 mm, and none exceeded 2 mm.

The mean maximum depth of the invasive melanomas was 1.41 mm for the first melanoma and 0.34 mm for successive melanomas.

The most common Clark level of invasion in the group of initial melanomas was level III, found in 14 of the 25 lesions. Clark level III was also the most common level of invasion in subsequent lesions (15/31 lesions).

As with Breslow depth, the Clark level was lower in successive than in initial lesions in the majority of patients (13/25). The level was the same in 10 cases and higher in 2.

The most common skin phototypes (Fitzpatrick system) in the group of patients with multiple primary melanomas were type II (15/25) and type III (10/25). All of the patients were white Mediterraneans. We detected no cases of multiple melanoma in patients with other phototypes.

Only 2 of the 25 patients with multiple melanomas had a first-degree relative with a history of melanoma and none of the patients had been diagnosed with histologically confirmed atypical moles.

On analyzing the clinicopathologic features of the melanomas detected, we found that most (50/56) were superficial spreading melanomas; there were 4 cases of nodular melanoma, and 2 cases of acral lentiginous melanoma.

A comparison of the histologic features of different tumors from same patient revealed that most had the same clinicopathologic and cellular features (superficial spreading melanoma and pagetoid spread). Only 3 of the 25 patients had histologically dissimilar lesions (different clinicopathologic type). One of these patients

Table 1. Characteristics of Patients and Multiple Primary Melanoma Lesions

Patient	*Sex/Age, y*	*Phototype*	*Family History*	*Location (Lesion 1)*	*Breslow Depth, mm (Lesion 1)*	*Clark Level (Lesion 1)*	*Type (Lesion 1)*	*Time Between Lesion 1 and 1, mo*	*Location (Lesion 2)*	Breslow Depth, mm (Lesion 2)
1	F/41	3	No	Lumbar region	0.84	III	SSM	21	Thigh	0.72
2	F/35	2	No	Calf	0.84	III	SSM	68	Pretibial region	0.23
3	M/65	2	No	Lumbar region	1.16	II	SSM	0	Scapula	0
4	M/69	2		Head	2.1	III	SSM	48	Cheek	0.57
5	M/65	2	No	Deltoids	0.62	III	Nodular	6	Scapula	1.04
6	M/55	2	No	Deltoids	0.51	III	SSM	41	Foot	0.37
7	F/77	3	No	Neck	4.71	IV	SSM	78	Scapula	0.47
8	M/69	4	No	Leg	9.5	V	Nodular	0	Chest	0
9	M/57	2	No	Pectoral region	2	III	SSM	84	Back	0
10	F/68	2	Father	Postauricular region	0.86	IV	SSM	10	Postauricular region	1.15
11	F/31	2	No	Face	0.5	II	SSM	73	Knee	0
12	M/25	2	No	Pectoral region	1.21	II	SSM	81	Forearm	0
13	M/45	3	No	Leg	1.24	III	SSM	59	Abdomen	0.32
14	F/34	2	No	Foot	0	I	ALM	0	Thigh	0
15	M/43	3	No	Arm	2.33	III	SSM		Leg	0
16	F/45	3	No	Scapula	0.37	III	SSM	23	Thigh	0
17	M/69	3	No	Pectoral region	0.47	II	SSM	0	Breast	0
18	F/28	2	No	Scapula	0.45	III	SSM	0	Lumbar region	0.7
19	F/64	3	No	Back	0.34	III	SSM	5	Back	0
20	M/47	2	No	Back	0.9	III	SSM	0	Back	0.76
21	M/49	3	No	Back	0.5	III	SSM	81	Lumbar region	0.63
22	F/68	2	No	Face	1.31	IV	SSM	0	Face	0
23	M/44	3	No	Back	0.53	III	SSM	0	Leg	0
24	F/53	2	Uncle	Leg	0.46	II	SSM	10	Leg	0.68
25	F/78	2	No	Back	0	I	SSM	10	Back	0.39

Abbreviations: ALM, acral lentiginous melanoma; F, female; M, male; SSM, superficial spreading melanoma.

had developed a superficial spreading melanoma followed by an acral lentiginous melanoma of the foot. The second patient, in whom we detected histologic differences in terms of infiltration pattern, cell size, and architectural pattern, had developed a nodular melanoma followed by a superficial spreading melanoma. Finally, the third patient had developed an acral lentiginous melanoma followed by a nodular melanoma.

Clark Level (Lesion 2)	Type (Lesion 2)	Location (Lesion 3)	Breslow Depth, mm (Lesion 3)	Clark Level (Lesion 3)	Time Between Lesion 2 and 3, mo	Type (Lesion 3)	Location (Lesion 4)	Breslow Depth, mm (Lesion 4)	Clark Level (Lesion 4)	Type (Lesion 4)	Time Between Lesion 3 and 4, mo
III	SSM										
III	SSM										
I	SSM										
III	SSM										
III	Nodular										
III	ALM										
III	SSM										
I	SSM										
I	SSM	Back	0.35	III	0	SSM					
IV	SSM	Postauricular region	0.7	IV	2	SSM					
I	SSM										
I	SSM										
III	SSM										
I	Nodular										
I	SSM										
I	SSM										
I	SSM										
III	SSM	Popliteal fossa	0	I	15	SSM					
I	SSM										
II	SSM	Leg	0.19	III	36	SSM	Abdomen	0.26	III	SSM	41
III	SSM										
I	SSM	Back	0.84	III	12	SSM					
I	SSM										
III	SSM										
III	SSM										

Discussion

Of the 934 patients diagnosed with melanoma by the melanoma unit at our hospital between 1988 and 2005, 25 had multiple primary melanoma, which corresponds to an incidence of 2.6%. Based on data from the literature, between 1% and 8% of patients with malignant cutaneous melanoma develop 2 or more primary melanomas.[12,16,17]

The majority of these studies, however, have been conducted in the United States of America (USA). Using a similar method to ours, Johnson et al[12] identified 60 cases of multiple melanoma in 1482 patients with melanoma followed for a mean of 96 months in the USA; this corresponds to an incidence of 4%. Although the incidence identified in our series is lower than that reported for other countries, we believe that it is still considerable and justifies the practice of indefinite follow-up aimed at detecting the appearance of new primary melanomas as early as possible. Furthermore, patients with melanoma in situ require follow-up not only because they have a slight risk of metastasis but also because they are susceptible to developing another melanoma.

Only 2 of the 25 patients with multiple primary melanoma in our series had a family history of melanoma. This figure contrasts with rates of up to approximately 18% reported by other studies.[14] Although only 2 patients in our series had a first-degree relative with melanoma, several studies have suggested that there may be a genetic predisposition to this disorder and have highlighted a possible role for the genes *CDKN2A* and *CDK4*.[14,18] One particularly noteworthy study of patients with multiple primary melanoma performed by Hospital Clínico de Barcelona, in Barcelona, Spain, found a greater frequency of the *CDKN2A* mutation in patients with a family history of melanoma (35.5%) than in those without (8.2%).[14] We also detected differences between our series and those in other countries in terms of the prevalence of atypical moles. None of the 25 patients with multiple primary melanoma in our series had histologically confirmed atypical moles or a family history of atypical moles, contrasting with other countries, where such an association has been detected in 38% to 48% of cases.[12]

There are similarities between our study and others in terms of the age at which the first melanoma was diagnosed and the site of the lesions.[12,14,16,17,19-21] The mean age at the time of diagnosis of the first lesion in our series was 54 years in men and 52 years in women, and the most common lesion site was the back in the case of men (12/29) and the back (12/27) and the legs (12/27) in the case of women. According to the literature, subsequent melanomas do not necessarily develop in the same anatomic region as the initial lesion. Indeed, in our series they were located in a different part of the body in 14 of 25 patients, highlighting the importance of examining the entire skin surface during screening visits of patients with cutaneous melanoma. In agreement with findings from other studies,[14,16,17,19,20] in our series the mean depth of second and subsequent melanomas was less than that of initial melanomas, indicating that following patients helps to detect lesions earlier. (Two of the first melanomas diagnosed were in situ compared to 10 of the subsequent ones). New methods for the monitoring and diagnosis of pigmented lesions, such as dermatoscopy and confocal microscopy will help to detect second melanomas even earlier.[22,23]

Although most second primary melanomas are diagnosed within 2 years of the first, we detected cases in which new melanomas appeared up to 10 years later and believe that the risk of further melanoma persists for longer. Indeed, in a recent study, Manganoni et al[16] detected second melanomas as late as 28 years after the diagnosis of the first lesion.

The cytologic and architectural features of different melanomas in the same patient were very similar in 22 of our 25 patients, and we did not detect any distinguishing histologic features that would help to distinguish between multiple melanomas and other melanomas, and consequently help to identify patients at risk of developing new primary lesions.

Although the risk of developing second melanomas seems to be less in Mediterranean populations than that reported for populations in English-speaking countries, it is still considerable. Consequently, patients with a history of melanoma should be followed, not only to screen for recurrence or metastasis but also to detect the appearance of new primary melanomas. Because these melanomas do not necessarily appear in the same anatomic region as the first melanoma, it is important to examine the entire skin surface at each screening visit. Although the lifetime follow-up of patients with melanoma in a specialized unit is not always possible due to the increasing prevalence of this disorder, we believe that these patients should be referred to a dermatologist for indefinite follow-up.

Conflicts of Interest
The authors declare no conflicts of interest.

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