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Disease Progression in Cases of Multiple Primary Melanoma

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ABSTRACT Multiple primary melanoma (MPM) is a well-known phenomenon, but outcome studies regarding patients with MPM are rare. Aim of our study was to analyze whether MPM are less likely to metastasize than single primary melanomas (SPM). In our study disease progression (defined by the occurrence of regional lymph node or distant metastases) in cases of MPM was compared to cases of SPM on a sample of 1698 melanomas. Statistically significant difference in the occurrence of disease progression was found between the analyzed groups, progression being significantly less frequent in patients with MPM (P=0.009). Also, MPM occurred significantly more frequently in male patients (P=0.001).

We attribute these results not only to early detection of subsequent MPM, but to a variety of possible reasons, including different genetics and biology of tumors and, possibly, the immune response of the host. Further studies are required to elucidate these interesting findings.

KEY WORDS: melanoma, multiple primary melanoma, disease progression

INTRODUCTION

There have been a number of studies on the phenomenon of multiple primary melanomas (MPM), especially over the last decades. According to various studies, the risk of developing an additional primary tumor in patients who have already been diagnosed with primary melanoma ranges from 0.6% to 12.7% (1-9). Many aspects of MPM have been investigated, including their epidemiological and clinical properties, clinicopathologic differences between first and subsequent melanomas in people with MPM, as well as dermoscopic features of MPM (10-12). However, outcome and prognosis studies regarding MPM are rare.

An association has been found between MPM and other malignant diseases, leading to a proposition of common genetic or environmental factors (10). However, the most relevant findings in that study are the disease-free survival curves of MPM and single primary melanoma (SPM) patients, which did not differ significantly, and survival curves, which inexplicably favored patients with MPM (10). The latest multicenter study reported an increased risk of death with increasing tumor thickness in patients with SPM compared with patients with MPM (13). To unravel some more details about this fact, we analyzed individual melanoma cases in patients with both MPM and SPM

and compared the frequency of disease progression between those two groups. The aim of this study was to determine whether the tumors in patients with MPM are less likely to metastasize than those in patients with SPM.

PATIENTS AND METHODS

In this study, we focused on melanoma cases *per se*, rather than on the number of patients with melanoma, as it provided us with an opportunity to assess the frequency of disease progression for each individual tumor. The cases of melanoma were taken from the database of the Croatian Referral Melanoma Centre (Department of Dermatovenereology, Sestre milosrdnice University Hospital Centre, Zagreb, Croatia), and melanoma cases (of consecutively diagnosed patients) evidenced in the Referral Melanoma Centre during a 11-year-period (2002-2012) were analyzed. Histopathological data about tumors was obtained from the histopathological reports, and clinical data (age, sex, follow-up, and the occurrence of disease progression) was obtained from the department charts. The study was carried out in compliance with the Helsinki Declaration and approved by the institution's ethics committee.

After exclusion criteria (incomplete data, melanoma of unknown primary origin, primary melanoma of the eye, patients who received adjuvant therapy after the diagnosis of the first primary melanoma) were met, 1698 cases of melanoma remained, of which 164 (9.65%) appeared alongside other primary melanomas in 72 patients with MPM. To avoid early detection bias, we added to exclusion criteria the early stages of melanoma (melanoma *in situ* (MIS) and Breslow I tumors of <0.75 mm thickness) when they would have been unlikely to produce metastases. Most of the patients with MPM had 2 melanomas (56 patients, 77.77%). There were 10 (13.88%) patients with 3 MPM, 2 (2.77%) patients with 4 MPM, and 4 (5.54%) patients with 5 or more MPM. The highest number of primary tumors in one patient was 16.

Cases of melanoma were divided in two groups, with cases of melanoma in patients with multiple primaries in the first group, and single primary melanomas as controls in the second group. We compared the disease progression in cases of MPM with the cases in patients with SPM. The disease progression was defined by the detection of regional lymph node or distant cutaneous, subcutaneous or visceral metastases. The follow up protocol was the same for both groups, with the frequency of examinations (clinical examination, laboratory examinations, ultrasound of the regional lymph nodes and abdomen, chest X-ray, and CT or PET/CT scans) depending on the primary tumor thickness/the thickest primary melanoma thickness and stage of the disease. The mean follow up of this cohort was 58.16 months, and the median follow-up was 60 months. The shortest follow-up was 6 months, and the longest follow-up was 194 months.

Statistical analysis

Differences in the frequency of disease progression in both case and control groups (MPM and SPM) were assessed using the χ^2 test. The underlying characteristics of both the case and control group and the differences between categorical variables were analyzed using the Student t-test. The level of significance was set at $P<0.05$ in all cases. All analyses were performed with MedCalc for Windows, version 11.3 (www.medcalc.be).

RESULTS

The clinicopathologic data of all patients with MPM and SPM are shown in Table 1. Analysis of all melanoma cases (N=1698) showed that there was no significant difference in tumor thickness ($P=0.188$) and follow-up period ($P=0.501$) between MPM and SPM. A significant difference was noticed in the age of patients with melanoma, with patients with MPM being older than those with SPM ($P=0.028$) (Table 1).

The mean tumor thickness of the first melanoma

Table 1. Clinicopathologic characteristics of all patients with multiple primary melanomas (MPM) and single primary melanoma (SPM) (N=1698)

	Cases (MPM)	Controls (SPM)	*P*-value
Number of cases	164	1534	
Patient age mean (years)	58.08 ± 14.79	54.42±15.29	0.028
Women/Men	25 (34.72%)/47(65.28%)	837 (54.56%)/697 (45.44%)	0.001
Thickness mean (mm)	1.87 ± 3.82	2.22±2.79	0.188
Number of disseminated melanomas	5 (3.04%)	189 (12.32%)	0.001
Follow-up mean (months)	59.53	56.80	0.501

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diagnosed in the MPM group was 2.68±5.29 mm, whereas the mean tumor thickness in the SPM group was 2.22±2.79 mm, *P*=0.521. The mean tumor thickness of all subsequently diagnosed melanomas in the MPM group was 1.29 mm.

Furthermore, the analysis of all melanoma cases in the study (N=1698) showed that in the control group (SPM) disease progression occurred in 189 out of 1534 cases (12.32%), whereas in the case group (MPM), disease progression occurred in 5 out of 164 cases (3.04%). The difference in the occurrence of disease progression between these two groups was statistically significant (*P*<0.0001) (Table 1).

To avoid early detection bias, we added to exclusion criteria the early stages of melanoma (melanoma *in situ* (MIS) and Breslow I tumors) when they would have been unlikely to produce metastases. After the exclusion of all MIS and Breslow I tumours, 75 melanoma cases in the case group and 963 cases in the control group remained (Table 2).

After exclusion of all MIS and Breslow I melanomas, the results also showed no significant difference in tumor thickness (*P*=0.776) and follow-up period (*P*=0.882) between MPM and SPM, as well as no significant difference in the age of patients (*P*=0.077) (Table 2). In addition, disease progression in the control group (SPM) occurred in 189 out of 963 cases (19.62%), whereas in the case group (MPM), disease progression occurred in 5 out of 75 cases (6.67%). The difference in the occurrence of disease progression between these two groups was still statistically significant (*P*=0.003) (Table 2).

The difference in the occurrence of MPM according to gender distribution was statistically significant before and after excluding early stage melanomas (*P*=0.001 and P=0.012, respectively), with MPM occurring significantly more often in male than in female patients (Table 1, Table 2).

DISCUSSION

Patients who have already been diagnosed with one primary melanoma have a substantially increased risk of developing further primary melanomas, ranging from 0.6% to 12.7% in different studies (1,3,4,8,10,14,15). The most important risk factors associated with the development of MPM seem to be positive family history of melanoma and the presence of atypical nevi (7,16-18). Generally, people with numerous atypical moles and a family or personal history of melanoma are at the greatest risk for developing cutaneous melanoma. Patients from this population tend to develop melanoma approximately 10 years earlier than the general population and have an increased risk for developing MPM (19). It has been shown that the risk of subsequent melanoma is the highest within the first two years after the first melanoma being diagnosed (8,10).

Even though the occurrence of MPM is a well-documented phenomenon, studies on the prognostic implications in such patients are rare (13,20). Only a few studies exist analyzing a large number of cases, all of which observed that patients with MPM have the same, or even better prognosis compared to their SPM counterparts (10,13). This has always been very confounding, as it would be reasonable to expect that two independent malignant diseases would be more prone to progression and poor outcome than a single one.This was attributed mainly to the assumption that, after being diagnosed with the first primary melanoma, patients remain under regular dermatological follow-up and self-examination, and generally behave more photoprotectively. Therefore, subsequent melanomas in such patients would be discovered at early stage of the disease, when chances for disease progression would be accordingly smaller (21-23).

In the current study, we analyzed the frequency of disease progression (defined by the detection of regional lymph nodes or distant cutaneous, subcutaneous, or visceral metastases) in a large, relatively homologous cohort of MPM and SPM specimens with defined histological features, clinical data, and follow up.

In our research, we tried to circumvent the potential bias of early melanoma detection by exclud-

Table 2. Clinicopathologic characteristics of patients with multiple primary melanomas (MPM) and single primary melanoma (SPM) after the exclusion of all melanoma *in situ* and Breslow I tumours (N=1038)

	Cases (MPM)	Controls (SPM)	*P*-value
Number of cases	75	963	
Patient age mean (years)	58.64±13.48	55.02±15.33	0.077
Women/Men	20 (33.90%)/39 (66.10%)	497 (51.60%)/466 (48.40%)	0.012
Tumor thickness mean (mm)	2.92	3.03	0.776
Number of disseminated melanomas	5 (6.66%)	189 (19.62%)	0.009
Follow-up mean (months)	60.36	59.76	0.882

ing all the melanoma cases in early stages, leaving melanoma cases of similar mean thickness and Breslow stage in both the case (MPM) and control (SPM) groups. Additionally, we focused on melanoma cases *per se* rather than on the number of patients with melanoma, as it provided us with an opportunity to assess the frequency of propagation for each individual tumor. This enabled us to investigate the curious finding that there is no difference in disease-free survival between patients with a single malignant tumor and those with two or more. Clearly, this is surprising, as every subsequent tumor that the patient acquires should deteriorate the chance of long-term disease-free survival. The results of our study suggest that melanomas which occur in people with MPM metastasize statistically significantly less frequently than tumors in people with SPM.

The latest multicenter study which explored survival in a large population-based sample of patients with SPM and MPM of any stage reported an increased risk of death with increasing tumor thickness (which was the main determinant of fatality in the analysis) which was higher in patients with SPM than in patients with MPM (13). Although overall fatalities due to SPM and MPM were similar, relative fatality for thicker SPM was greater than for thicker MPM. This finding may indicate that the difference in the outcome between patients with SPM and MPM might be related to factors other than closer surveillance and earlier diagnosis (13). However, in our study, no statistically significant difference in tumor thickness between SPM and MPM cases was found (which could have influenced the difference in the occurrence of metastases), however, the incidence of disease progression was significantly higher in the cases of SPM than in MPM. On the other hand, other clinicopathologic parameters, such as anatomical localization of the primary tumors, mitotic rate, and ulceration were not included in the current study and might play a role in the differences seen between the analyzed groups.

Additionally, the results of our study showed that MPM occur significantly more often in male than in female patients. This was not deemed a potential source of bias when assessing the differences in disease progression, as male sex was found to be a risk factor leading to worse outcome of the disease (20), and in our research we saw a tendency towards better outcomes in the group with a higher percentage of male patients. It is also uncertain why there would be a higher occurrence of MPM in male patients, and other studies have not duplicated this finding (10,11). It is unlikely that this is a result of higher disease awareness in females or better follow-up after first melanoma, as this has no effect on the development of the next melanoma, influencing rather its discovery in the early stage. It is possible that the significant difference in gender distribution of MPM frequency is a result of better sun protection and self-examinations in female patients after being diagnosed with their first melanoma.

CONCLUSION

The reason as to why two tumors, otherwise considered to be equally aggressive, would behave differently in people that have only one of them than in people with two or more tumors of the same type, is uncertain. Possibly, the genetic error in the cascade that leads to melanoma development is different, in one variety leading to one more malignant tumor and to multiple less aggressive tumors in another. Another explanation might be that the immune system learns from the first melanoma, which enables it to react more efficiently to the next one. A possibility has been suggested that patients with rapidly progressing single primary melanoma die before they have had enough time to develop subsequent melanomas, skewing the statistics towards poor outcome in SPM (10). Either way, further research is needed to clarify this intriguing prognostic finding in patients with MPM, as well as the fact that MPM seems to be occurring more often in male than in female patients.

References:

1. Pack GT, Scharnagel IM, Hillyer RA. Multiple primary melanoma. Cancer 1952;5:1110-5.
2. Allen AC, Spitz S. Malignant melanoma; a clinicopathological analysis of the criteria for diagnosis and prognosis. Cancer 1953;6:1-45.
3. Beardmore GL, Davis NC. Multiple primary cutaneous melanomas. Arch Dermatol 1975;111:603-9.
4. Beardmore GL. The Queensland melanoma project. Int J Dermatol 1977;16:831-5.
5. Moseley HS, Giuliano AE, Storm FK 3rd, Clark WH, Robinson DS, Morton DL. Multiple primary melanoma. Cancer 1979;43:939-44.
6. Savoia P, Quaglino P, Verrone A, Bernengo MG. Multiple primary melanomas: analysis of 49 cases. Melanoma Res 1998;8:361-6.
7. Ferrone CR, Ben Porat L, Panageas KS, Berwick M, Halpern AC, Patel A, *et al.* Clinicopathological features of and risk factors for multiple primary melanomas. JAMA 2005;294:1647-54.
8. Buljan M, Situm M, Bolanca Z, Zivkovic MV, Mihic

LL. Multiple primary melanoma: epidemiological and prognostic implications; analysis of 36 cases. Coll Antropol 2010;Suppl 2:131-4.

9. Frank W, Rogers GS. Melanoma update. Second primary melanoma. J Dermatol Surg Oncol 1993;19:427-30.
10. Slingluff CL, Jr., Vollmer RT, Seigler HF. Multiple primary melanoma: incidence and risk factors in 283 patients. Surgery 1993;113:330-9.
11. Murali R, Goumas C, Kricker A, From L, Busam KJ, Begg CB, *et al.* Clinicopathologic features of incident and subsequent tumors in patients with multiple primary cutaneous melanomas. Ann Surg Oncol 2012;19:1024-33.
12. Moscarella E, Rabinovitz H, Puig S, Zalaudek I, Oliviero MC, Brown L, *et al.* Multiple primary melanomas: do they look the same? Br J Dermatol 2013;168:1267-72.
13. Kricker A, Armstrong BK, Goumas C, Thomas NE, From L, Busam K, *et al.* Survival for patients with single and multiple primary melanomas: the genes, environment, and melanoma study. JAMA Dermatol 2013;149:921-7.
14. Blackwood MA, Holmes R, Synnestvedt M, Young M, George C, Yang H, *et al.* Multiple primary melanoma revisited. Cancer 2002;94:2248-55.
15. Doubrovsky A, Menzies SW. Enhanced survival in patients with multiple primary melanoma. Arch Dermatol 2003;139:1013-8.
16. Titus-Ernstoff L, Perry AE, Spencer SK, Gibson J, Ding J, Cole B, *et al.* Multiple primary melanoma: two-year results from a population-based study. Arch Dermatol 2006;142:433-8.
17. Burden AD, Newell J, Andrew N, Kavanagh G, Connor JM, MacKie RM. Genetic and environmental influences in the development of multiple primary melanoma. Arch Dermatol 1999;135:261-5.
18. McMeniman E, De'Ambrosis K, De'Ambrosis B. Risk factors in a cohort of patients with multiple primary melanoma. Australas J Dermatol 2010;51:254-7.
19. Conrad N, Leis P, Orengo I, Medrano EE, Hayes TG, Baer S, *et al.* Multiple primary melanoma. Dermatol Surg 1999;25:576-81.
20. Burden AD, Vestey JP, Sirel JM, Aitchison TC, Hunter JA, MacKie RM. Multiple primary melanoma: risk factors and prognostic implications. BMJ 1994;309:375.
21. DiFronzo LA, Wanek LA, Morton DL. Earlier diagnosis of second primary melanoma confirms the benefits of patient education and routine postoperative follow-up. Cancer 2001;91:1520-4.
22. de Giorgi V, Rossari S, Papi F, Gori A, Alfaioli B, Grazzini M, *et al.* Multiple primary melanoma: the impact of atypical naevi and follow up. Br J Dermatol 2010;163:1319-22.
23. Manganoni AM, Farisoglio C, Tucci G, Facchetti F, Calzavara Pinton PG. The importance of self-examination in the earliest diagnosis of multiple primary cutaneous melanomas: a report of 47 cases. J Eur Acad Dermatol Venereol 2007;21:1333-6.