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ORIGINAL ARTICLE

Retrospective Analysis of Clinicopathological Characteristics of Pregnancy Associated Melanoma

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Abstract Pregnancy associated melanoma (PAM) by definition appears during pregnancy or within 1 year after delivery. In this retrospective study we analysed the pathological characteristics and survival rate of PAM and matched the data with non-pregnant age- and stage-matched control patients. Between 2003 and 2014, 34 pregnant women (aged 32.5±5.6 years) were diagnosed with melanoma at the Department of Dermatology, Venereology and Dermatooncology of the Semmelweis University. During the pathological process histologic subtype, Breslow thickness and Clark level, tumor cell type, mitotic rate, peritumoral inflammation, as well as ulceration, regression, necrosis, vascular invasion and presence of satellite were analyzed and related to clinical data. Primary tumor location and clinical staging, disease course, local recurrence and metastases, 5-year survival rate, other tumor development before or after the diagnosis of melanoma have also been documented. We found no difference in all parameters between pregnant and non-pregnant melanoma cases except peritumoral inflammation which was higher in PAM group, moreover the presence of mild inflammation was significantly higher in PAM group compared to non-pregnancy associated melanoma (NPAM) women group.

Keywords Melanoma · Pregnancy · Postpartum · Young women

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Introduction

The incidence of melanoma is rising worldwide representing a major oncological problem. Stage III–IV melanoma is one of the most aggressive and therapy resistant human malignancies with poor prognosis and unpredictable progression. Beside skin type, positive family history, genetic background, immunosuppression, also hormonal factors may contribute to development and progression of melanoma [1]. Recently, melanoma was also recognized as an estrogen dependent tumor similarly to breast and ovarian cancer, as higher estrogen levels under pregnancy or fertility drug use may also contribute to malignant transformation of naevi or to melanoma progression [2].

According to the medical terminology tumors in pregnancy are considered if they diagnosed during pregnancy or within 1 year from delivery [3, 4]. With that definition the incidence of PAM is 1: 1000–10,000 (per number of gestations) according to the data of the European Society for Medical Oncology [5]. Others define the postpartum diagnosis from 6 months to 2 years from delivery [6, 7]. Norwegian, Danish and Swedish studies indicate melanoma as the most common malignancy diagnosed during pregnancy followed by ovarian and breast cancers [8–10].

Although there are several data about the clinicopathological features of melanoma, only few deal with melanoma during pregnancy or lactation. In this study the data of 34 women with PAM are presented.

Patients and Methods

Patients

We reviewed the database of Dermatology, Venereology and Dermatooncology Department of the Semmelweis University and evaluated the features of all malignant melanoma cases in

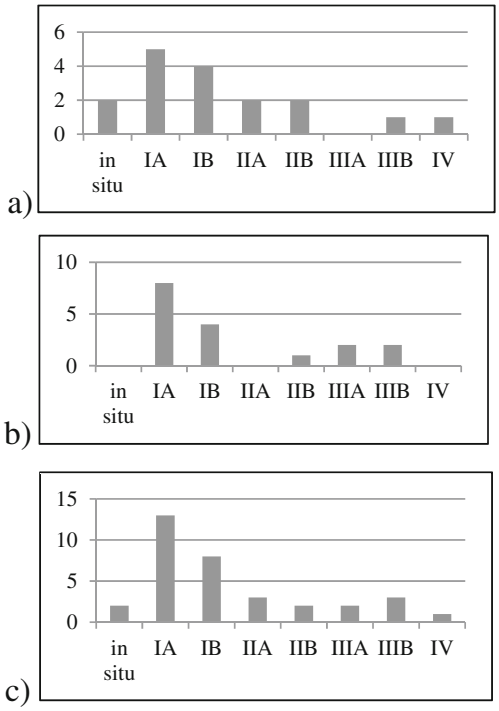

Fig. 1 Stage distribution of PAM diagnosed **a** under pregnancy **b** within 1 year after delivery. **c** Under pregnancy + within 1 year after delivery (in most PAM cases 21/34 (61.7 %) stage I was observable

women of childbearing age (18–45 years) between 1st of January 2003 and 31st of December 2014. A total of 336 young women were diagnosed with melanoma of whom 34 (10.1 %; aged 32.5±5.6 years; including two patients with in situ melanoma and one patient with duplex melanoma) were defined as PAM [9]. We also analyzed the data of age- and tumor stage-matched NPAM women (n=32, aged 32.7±7.11 years) and men (n=32, aged 33.8±4.9 years). These control patients were diagnosed or followed with melanoma at the same Department during the same time period as the PAM patients.

Clinicopathological Data

Overall 34 PAM (also a patient with duplex melanoma), 64 NPAM melanoma tissue samples underwent pathological analysis by two experienced pathologists (H. J. and K. E.) according to the AJCC/UICC TNM, 7th edition [11].

For clinicopathological comparison the following parameters were analyzed:

1) histologic subtype; 2) Breslow thickness and Clark level; 3) tumor cell type; 4) mitotic rate; 5) peritumoral inflammation; 6) vascular invasion; 7) presence of tumor ulceration, necrosis or regression; 8) presence of satellite; 9) serum level of S-100 protein.

Histologic subtypes of melanoma were classified as superficial spreading melanoma (SSM), nodular melanoma (NM), lentigo maligna melanoma (LMM), acral lentiginous melanoma (ALM), non-classified melanoma (NCM) and others (in our case spitzoid variant melanoma). Beside pathological data, age at time of diagnosis, location of primary melanoma, medical report on de novo or naevus associated melanoma, clinical staging at the time of diagnosis, disease course, follow-up for local recurrence and metastases, 5-year survival rate, presence of other, non-melanoma tumors before or after the diagnosis of PAM were also evaluated.

Serum S-100 protein level of 25 PAM patients was measured by electrochemiluminescence immunoassay (Roche Diagnostics GmbH, Mannheim, Germany) according to the manufacturer instruction.

Statistical Analysis

SPSS version 22.0 (Armonk, NY: IBM Corp) was applied. For continuous variables, PAM and NPAM groups were compared by independent sample t-tests (age at diagnosis) and Mann–Whitney U test (Breslow thickness and mitotic rate). Between-group differences in discrete variables (e.g., Clark level, peritumoral inflammation, tumor cell types, histologic subtype) Chi-square test or Fisher's exact test were used. A Kaplan-Meier survival analysis was carried out using Log-rank test. All the statistical tests were two-sided and $p<0.05$ was considered statistically significant.

Table 1 Histologic subtypes of PAMs and NPAMs

Histologic subtype	PAM (n=33)[a]	NPAM, women (n=32)	p value	Men (n=32)	p value
SSM	22 (68.8 %)	26 (81.3 %)	0.248	27 (84.4 %)	0.140
NM	5 (17.6 %)	2 (6.3 %)	0.426	2 (6.3 %)	0.426
NCM	4 (12.5 %)	2 (6.3 %)	0.672	3 (9.4 %)	1.000
SSM with secunder nodular component	0 (0 %)	2 (6.3 %)	0.492	0 (0 %)	–
ALM	1 (3.1 %)	0 (0 %)	1.000	0 (0 %)	1.000
Spitzoid variant	1 (3.1 %)	0 (0 %)	1.000	0 (0 %)	1.000

SSM superficial spreading melanoma, *NM* nodular melanoma, *NCM* non-classified melanoma, *ALM* acral lentiginous melanoma

[a] One PAM patient had duplex melanoma (1 SSM and 1 NCM) and therefore total of the first column is 33

Table 2 Distribution of PAM and NPAM by Clark classification

	PAM (n=33)[a]	NPAM (women) (n=32)	p value	Men (n=32)	p value
Clark II	7 (21.2 %)	9 (28.1 %)	0.574	10 (31.3 %)	0.357
Clark II-III	2 (6.1 %)	3 (9.4 %)	0.672	0 (0 %)	0.492
Clark III	10 (30.3 %)	7 (21.9 %)	0.440	8 (25 %)	0.633
Clark III-IV	1 (3.0 %)	1 (3.1 %)	1.000	4 (12.5 %)	0.197
Clark IV	12 (36.4 %)	12 (37.5 %)	0.924	10 (31.3 %)	0.663
Clark V	1 (3.0 %)	0 (0 %)	1.000	0 (0 %)	1.000

Clark I: in situ melanoma, tumor cells in epidermis

I: tumor cells appear in papillary dermis

II-III: papillary dermis not totally invaded by tumor cells

III: papillary dermis entirely invaded by tumor cells

III-IV: reticular dermis not fully invaded by tumor cells

IV: reticular dermis invaded by tumor cells totally

V: subcutis invaded by tumor cells (Clark level according to the AJCC/UICC TNM, 7th edition [11])

[a] One PAM patient had duplex melanoma; therefore the total of the first column is 33; in situ melanoma (Clark I) was not compared with the other groups

Results

Temporal Relation and Clinical Staging of Melanoma to Pregnancy

In 17/34 cases (50.0 %) melanoma was diagnosed under pregnancy (in 10 cases during the first trimester, in 5 cases during the second and in further 2 cases in the third trimester of pregnancy) and in 17 patients (50.0 %) within 1 year after delivery (Fig. 1). The mean age of women at melanoma diagnosis was 32.5± 5.6 years (min.-max. 22–40). Most PAMs (23/34, 67.6 %) were diagnosed at very early stages (2/34 (5.9 %) in situ melanoma, 21/34 (61.7 %) stage I melanoma). In 3 PAM cases (stage IB and IIB after a 4 year, stage IIIB after a half year symptom-free period) progression was seen, therefore their final stages were IV.

The most progressive stages (III–IV) during pregnancy or after delivery were identified only in 5/34 patients (14.7 %). Remarkably, the only stage IV case was diagnosed under pregnancy.

PAM Development

In 8/35 cases (22.8 %) PAM was naevus associated, as confirmed by pathology, while in further 15/35 females (42.8 %) only the medical documentation (without pathological confirmation) reported melanoma development from a preexisting naevus. In 11/35 PAM patients (31.4 %) melanoma definitely arose de novo.

Histologic Subtype

The most common histologic subtype of PAM was SSM (22/35, 62.8 %). Nodular melanoma (NM) was found in 5/35 samples (14.3 %), while 1 spitzoid variant, 1 ALM (2.8–2.8 %) and 4 NCM (11.4 %) occurred. In NPAM women group the most common histologic subtype was also SSM. These data did not show significant difference by using Chi square or Fisher exact tests when compared with the two NPAM control groups (Table 1).

Table 3 Breslow thickness and mitotic rate in PAM and NPAM samples

	PAM (n=32)[a, b]		NPAM women (n=32)		p value	Men (n=32)		p value
	Mean (SD)	Median	Mean (SD)	Median		Mean (SD)	Median	
Breslow thickness	1.58 (1.38)	1.00	1.57 (1.34)	1, 23	0.969	1.55 (1.31)	1, 25	0.834
Mitotic rate	4.41 (5.71)	2.50	3.81 (3.82)	3.00	0.968	4.50 (6.61)	3.00	0.462

The Man-Whitney U test did not reveal significant differences in Breslow thickness or mitotic rate between the groups

[a] In one PAM case the mitotic rate was missing

[b] One patient had duplex melanoma

Clark Level

In a remarkable proportion of the PAM cases Clark IV level were verified (36.3 %). Comparing with the two control groups we have not found any significant difference in Clark level (Table 2).

Breslow Thickness and Mitotic Rate

The mean value of Breslow thickness of PAM patients was 1.58±1.38 mm (1.66±1.31 under pregnancy and 1.50±1.47 when melanoma was diagnosed after delivery). In half of PAM cases it was ≤ 1 cm (17 cases, 51.5 %) of which in seven cases it was ≤ 0.5 mm. Also a higher proportion of melanomas were between 1.1 and 2 cm (8 cases, 24.2 %). Between 2.1 and 3 mm six cases were detected (18.2 %). Only two cases were above 5.1 mm (6.1 %). The mean mitotic rate was 4.74± 6.04 (Table 3).

Tumor Cell Type

The most common tumor cell type was naevoid in all three groups (in PAM group in 14 cases, in NPAM, women group in 15 cases and in men group in 18 cases), while the second most common type was epitheloid, the third was spindle. Spitzoid, naevoid-epitheloid, naevoid-spindle, spindle-epitheloid, polygonal, dendritic, and cuboid like was also detected. The Chi square or Fisher exact tests did not indicate significant differences in tumor cell types between PAM and NPAM groups.

Peritumoral Inflammation

Peritumoral inflammation was also analyzed in PAM and NPAM groups. It was higher in PAM group than in NPAM groups and the 'mild inflammation' was significantly higher in PAM tissue samples than in NPAM (women) (p=0.032) (Table 4). Comparing PAM and NPAM groups (women and men together, n=64) the presence of significantly higher peritumoral inflammation in PAM group was still observable (p=0.029). Although in PAM group the 'severe' inflammation was not higher than in NPAM groups, but peritumoral inflammation was more frequent in PAM than in the two control groups.

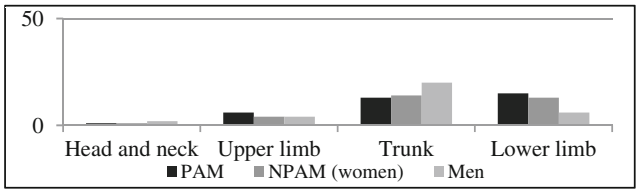

Fig. 2 The location of melanomas in PAM and NPAM groups

Ulceration, Regression, Vascular Invasion, Necrosis and Presence of Satellite

These features were rarely detected in the PAM and control groups. Satellites were not present in the examined groups. Vascular invasion and necrosis were found in 1–1 case in PAM and in NPAM (men) groups. Ulceration was detected in two cases in PAM group, in one case in NPAM (women) and in five cases in NPAM (men). Regression occurred in four PAM patients, in two NPAM (women) cases and in three NPAM (men) cases. We did not find significant difference in the mentioned parameters between the age- and stage-matched groups.

S-100 Protein Level

In all PAM patients (25) the values were within the normal range at the time of diagnosis. The mean value of S-100 protein was 0.052±0.02.

Location of Melanomas

In PAM group the most common predilection site was the sun exposed lower limb (42.8 %). In NPAM (women) the trunk (43.7 %) and the lower limb (40.6 %), in men group the trunk (62.5 %) was the most common location site. In PAM group in 6/35 (17.1 %) cases the upper limb and in one patient the head-neck region (2.8 %) were involved. In the location of melanomas significant difference was not found between the groups (Fig. 2).

Table 4 Chi square test showed a significant difference in, 'mild' peritumoral inflammation between PAM and NPAM (women) (p=0.032), indicated with bold in the table

Peritumoral inflammation	PAM (n=32)[a,b]	NPAM (women) (n=32)	p value	Men (n=32)	p value
Absent	5 (16.1 %)	9 (28.1 %)	0.252	10 (31.3 %)	0.159
Mild	11 (35.5 %)	4 (12.5 %)	**0.032**	6 (18.8 %)	0.135
Moderate	10 (32.3 %)	9 (28.1 %)	0.721	5 (15.6 %)	0.121
Severe	6 (19.4 %)	10 (31.3 %)	0.278	11 (34.4 %)	0.179

[a] One missing data from PAM patients

[b] One patient had duplex melanoma

Table 5 Local recurrence and metastases in PAM patients

Patients	Sentinel lymph node	Regional lymph node	Liver	Lung	Peritoneum	Brain	Bone	Ovarium	Cutan
1	+	+							
2	+								
3	+								
4	+	+	+		+		+		
5	+	+	+				+		
6	+	+	+	+		+	+	+	
7	+	+		+					+

Positive Sentinel lymph node was detected in seven cases

BRAF Mutation Analysis in Stage III and Stage IV Melanoma

Four out of the six studied PAM cases (3 in stage III, 3 in stage IV) and 3–3 cases (one stage III, other 5 stage IV) from both NPAM groups were positive for the BRAF V600E mutation (sequence specific PCR and Sanger DNA sequencing).

Other, Non-melanoma Tumors in PAM Patients

Five patients (5/34; 14.7 %) developed one further tumor after (intraductal breast cancer, cervix cancer, isolated rectal polyp (adenoma tubulo-villosum), myoma in two cases) but none before the PAM diagnosis. One PAM patient presented simultaneously with two independent melanomas during pregnancy, one SSM and one NCM. Altogether 6/34 duplex tumors occurred in PAM group.

Local Recurrence and Metastases

Local recurrence or metastases of PAM patients were found in seven cases (in three cases only local, in four cases distant metastases). Distant metastases were detected in liver, lung, peritoneum, ovarium, brain and bone (Table 5).

Five-Year Survival

The mean follow-up time in the three groups was 3.5 years (SD 3.2). Because of the rather short follow up duration, the 5-year survival rate were evaluated only for 16 PAM cases. Fifteen patients survived 5 years after the diagnosis, and one woman with simultaneous duplex melanoma in stage IV died 6 months after the diagnosis. Comparing the survival rate in the PAM and in the NPAM groups by Kaplan-Meier analysis no significant differences were found (Fig. 3). Mean survival in months in PAM group was 122.29 (SD 6.60), in NPAM (women) 116.23 (SD 6.61) and in NPAM (men) 91.70 (SD 4.19).

Discussion

The first case report in PubMed about PAM dates back to 1946 [12]. According to the data of the England Cancer Registration which involved 16,528 melanomas, for cutaneous melanoma a two-fold death rate was found for those women who gave birth within 1 year before the tumor diagnosis [13]. The published literature is controversial about the characteristics of PAM which led us to study the clinicopathological characteristics of the mentioned study group, that represents a distinct clinical population. The delayed maternal age could

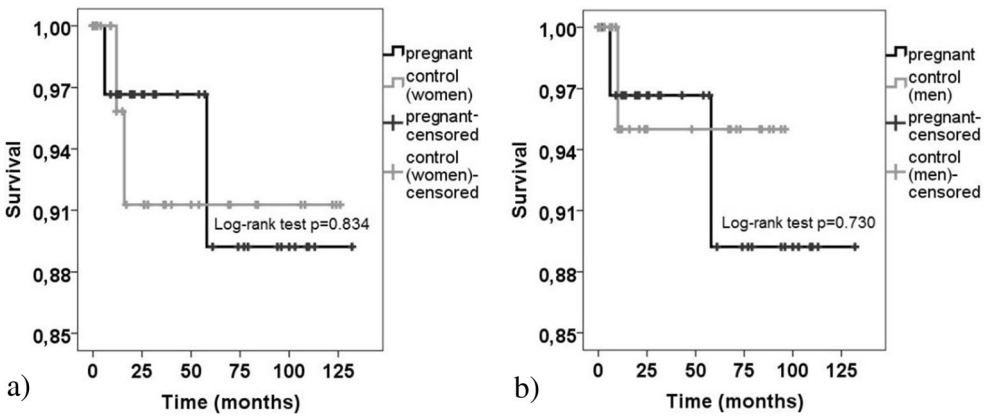

Fig. 3 **a** Overall survival of PAM (n=32) and NPAM (women, n=32) control patients (p=0.834); **b** Overall survival of PAM and men (n=32) control patients (p=0.730)

also contribute to the growing incidence of pregnancy associated cancers [9].

In accordance with the literature, the progression of melanoma in women shows a slightly better prognosis than in men. Meanwhile, it has also been shown that men have worse disease free and overall survival and gender has an independent predictor of survival in melanoma [14–16]. Different hormone levels, UV exposed habits could also play a role in the gender-specific difference [17]. Women have better melanoma outcome and diagnosed with earlier tumor stages than men [18]. Estrogen inhibits the growth of human melanoma cell lines by reducing the expression of IL8 [19]. Previous assumptions suggested that PAM had worse prognosis, however several publications have refuted this [20–22]. Nonetheless, a newly published meta-analysis reported increased mortality in PAM [23].

Similarly to our findings, the prognosis of early stage PAM depends on tumor thickness and ulceration, and pregnancy usually does not accelerate the tumor progression and there is no significant difference in tumor location and histologic subtype between pregnant and non pregnant, age- and stage-matched patients [21]. Neither the Breslow thickness nor the survival rate showed significant differences between age- and stage-matched PAM and NPAM groups [20] in line with some recent literature, but contradicts to the previous publication [24].

In this report the most common predilection site for melanoma in PAM group was the lower limb and the trunk, the most frequent histologic subtype was SSM which the same as in the previous publications [10, 21]. Favorable fact, that most of the diagnosed PAMs at our clinic were classified as AJCC stage I.

According to our knowledge this was the first observation which compared the histologic characteristics of PAM in detail (including tumor cell type, mitotic rate, peritumoral inflammation, presence of satellite, regression, necrosis and vascular invasion also) with NPAM women and men. We could not find any significant difference in the tumor cell types between the pregnant and non-pregnant female and male groups.

Our data revealed that the presence of peritumoral inflammation was higher in PAM group and the 'mild' peritumoral inflammation was more frequent in PAM group than in NPAM women group (p=0.032). This is confirmed by the comparison of PAM group with the NPAM (men and women altogether, n=64) (p=0.029). It was observed, that inflammatory cell infiltration around melanoma predicts better survival and serve as an independant prognostic marker in thin melanoma [25]. The increased rate of CD25 and CD164 positive peritumoral lymphocytes indicate a favorable survival rate and fewer metastases in primary cutaneous melanoma cases [26]. Higher amount of the tumor infiltrating lymphocytes (TIL) also predicts better melanoma survival and the high levels of TIL is associated with lower melanoma mortality rate [27]. The survival rate of our PAM and NPAM patients was not significantly different which corresponds to previous publications [8, 10].

The incidence of PAM (34/336, 10.1 %) at our department was high among melanomas of women in reproductive age (18–45 years), but found a generally good prognosis which can be explained by the early diagnosis and the favorable stage distribution (67.6 % of PAM was diagnosed in a very early stage; in situ and stage I). The stage distribution of PAM patients (stage I in 61.7 % and stage IV in 2.9 %) was almost the same as a previous study from our Department, which showed that the majority of the diagnosed melanomas were stage I (60.4 %) and just in 0.4 % of melanomas were detected in stage IV [28].

In conclusion, in the analyzed PAM group compared with stage- and age-matched control NPAM patients we could not find any significant difference (except peritumoral inflammation) in clinicopathological characteristics such as histologic subtype, Breslow thickness, Clark level, tumor cell types, mitotic rate, ulceration, vascular invasion, necrosis, regression and tumor location. In summary, the high incidence of PAM observed at our department among women in childbearing age (34/336) confirmes the suspected hormone dependency of melanoma and suggests the role of estrogens in melanoma development. The literature is still poor and there is no clear standpoint about the relation between sex hormones and melanoma while our data underline the importance of thorough and frequent onco-dermatological screening of females in childbearing age.

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Conflict to Interest The authors declare that they have no conflicts of interest.

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