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Amelanotic melanoma of the skin – detailed review of the problem

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RESEARCH

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ABSTRACT

Background
Malignant melanoma (MM) of the skin accounts for about one per cent of all malignancies in humans. Amelanotic melanoma is a rare tumour, diagnosed in eight per cent of all melanomas.

Aims
The study aimed to analyse our clinical experience with amelanotic MM of the skin and the statistical data from a retrospective five year analysis of pigmented and amelanotic types of skin melanoma. Furthermore, we compare our results to those from other teams' studies. To reach the corresponding in-depth conclusions.

Methods
The study included 151 patients with malignant melanoma of the skin, diagnosed and treated at Dr. Georgi Stranski University in Pleven, Bulgaria, between 2012 and 2016. All the patients signed informed consent forms.

Results
Of the 151 patients we studied, 14 (9.3 per cent) were diagnosed with amelanotic melanoma. The average Breslow thickness in patients with amelanotic MM was 4.2mm, while in pigmented MM patients it 2.1mm. Local recurrence rates (35.7 per cent) were higher in patients with amelanotic melanoma. Distant metastases were found in 39 of all tested patients with melanoma. Of the 14 patients with amelanotic MM, eight had such metastases.

Conclusion
Amelanotic melanoma was diagnosed too late. Local recurrences were six times as many as the ones diagnosed in pigment melanoma. Distant metastases were twice as many, and mortality rates were three times higher.

Key Words
Amelanotic melanoma, malignant melanoma, pigment melanoma

What this study adds:

1. What is known about this subject?
Amelanotic melanoma is a rare tumour, diagnosed in eight per cent of all melanomas and its progression is more malignant as compared to that of pigmented MM.

2. What new information is offered in this study?
Amelanotic melanoma has more often local recurrences, distant metastases and the mortality rate is three times as high as pigmented melanoma.

3. What are the implications for research, policy, or practice?
Amelanotic melanoma has to be treated more aggressively and monitored more actively than pigmented melanoma.

Background

Malignant melanoma (MM) of the skin accounts for around

one per cent of all malignancies in humans. Amelanotic skin MM lacks melanin or, when present, it is in minimal amounts. MM is a rare tumour found in approximately eight per cent of all diagnosed melanomas. The diagnostic procedures employed include local dermatoscopy and biopsy of the skin lesion. The final diagnosis is confirmed after standard histological and immunohistochemical testing.[1-6] Macroscopically, the tumour presents as a red or pink-pigmented lesion.[7,8] Histologically, the subtypes of amelanotic melanoma are identical with the pigment type of MM and include nodular superficial spreading of lentigo maligna and acral lentiginosis.[1,9] The diagnosis is difficult to make and is usually late, due to the lack of typical clinical presentation. The differential diagnosis includes a variety of skin diseases, such as eczema, psoriasis, rosacea, actinic and seborrheic keratosis, granuloma annulare, discoid lupus erythematosus, Bowen's disease, basal-cell carcinoma.[10] Amelanotic MM is more aggressive than pigment MM. Local recurrences, distant metastases are more common, and the mortality rate is higher.[11]

Method

The study included 151 with MM of the skin, who were diagnosed and treated at Dr. Georgi Stranski university hospital in Pleven, Bulgaria during the period 2012-2016. The average age of patients with pigmented melanoma was 66 years, age range 17–91 years. The average age of those with amelanotic melanoma was 65, varying between 31 and 81 years. Of all the patients studied, 14 (9.3 per cent) were diagnosed with amelanotic skin MM. All the patients signed informed consent forms. The study was reviewed and approved by the ethics committee for clinical research at the Medical University-Pleven.

Evaluation was based on the following criteria: gender, age, Breslow thickness, Clark level of invasion, sentinel biopsy of the regional lymph pool, presence of a positive sentinel lymph node, performed lymph dissection, presence of distant metastases, presence of local recurrences, number of months till recurrence, mortality rates, and survival in months. The statistical analysis is retrospective. The methods employed were as follows: summary of the processed data, cross tabulation, and chi-square test. The survivability was analysed by the Kaplan-Meier function for survivability. The statistical analysis was made with IBM SPSS Statistics 23.

Results

Of the 151 patients with MM, 14 (9.3 per cent) were diagnosed with its amelanotic type (Table 1).

Table 1: Distribution of patients diagnosed with pigmented and amelanotic melanoma

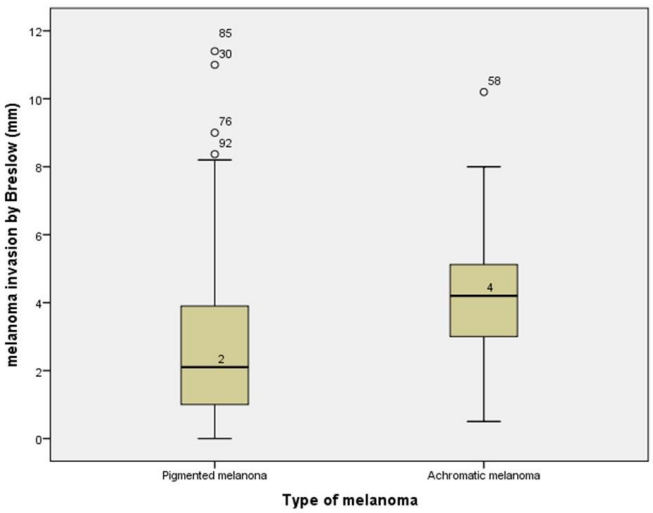
Indicator	Pigmented MM	Amelanotic MM	Total
Number	137	14	151
Percent	90.70%	9.30%	100%

Pigmented melanoma was slightly prevalent in the male patients: 51.8 per cent *vs.* 48.2 per cent in the females. However, the number of males with amelanotic MM was equal to that of the females: seven cases for each group (p=0.896) (Table 2).

Pigmented melanoma was generally localized in the back area (33 patients), on the lower extremity (31 patients), in the head area (29 patients) and the upper extremity (19 patients). Amelanotic melanoma was located mostly in the lower extremity (four cases), in the head area (three cases), back area (three cases). It rarely affected the neck area (one case), the chest (one case), lumbar area (one case) and the upper extremity (one case) (Table 3).

The mean thickness of Breslow melanoma was more significant in patients with an amelanotic MM (4.2mm) than those with a pigment (2.1mm), and the difference between the groups was significant (U=0.584; p=0.016) (Table 4 and Figure 1).

Figure 1: Distribution of melanoma by Breslow thickness



Evaluation of invasion after Clark revealed invasion into the reticular dermis in the majority of the patients: in 58 patients with pigmented MM, and in eight patients with amelanotic MM. Invasion into the papillary or reticular

dermis was found in 41 patients with pigmented MM, and in three with amelanotic MM (Table 5).

According to the TNM system for classification of malignant tumours, approximately 25 per cent of the patients had the IV stage of the disease: 32 with pigmented melanoma, six with amelanotic (Table 6).

Sentinel lymph node biopsy (SLNB) was performed relatively more often in patients with pigmented melanoma (Table 7).

Table 7: Sentinel lymph biopsy performed in cases of pigmented and amelanotic MM

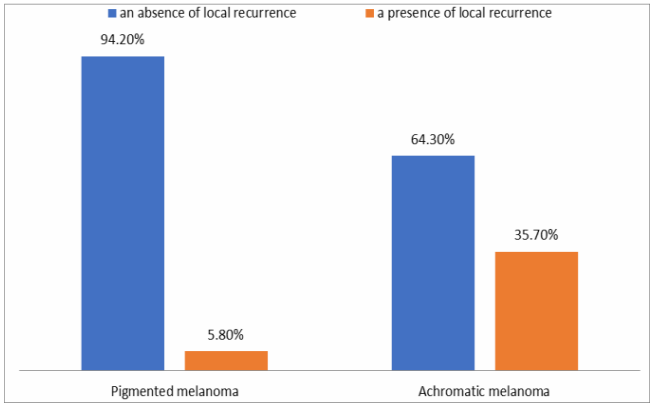
SLNB	Pigmented melanoma	Amelanotic melanoma	Total (n)
Not performed	81 (59%)	12 (85.7%)	93
Performed	56 (41%)	2 (14.3%)	58
Total (n, %)	137 (100%)	14 (100%)	151

* Sentinel lymph node biopsy

In 34 of the patients with pigmented melanoma and seven with amelanotic melanoma, the lymph dissection was performed in cases of pathologically confirmed metastases in lymph nodes (Table 8).

The frequency of local recurrence was six times higher in patients with amelanotic melanoma (35.7 per cent) compared to those with pigmented MM (5.8 per cent), and the differences in the groups are statistically significant ($\chi 2=14.408$; p=0.001) (Figure 2).

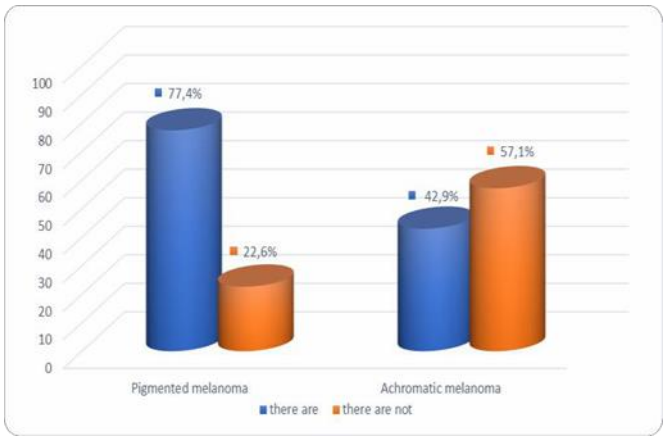
Figure 2: Distribution of melanoma by stages of disease



The average time for local recurrence was 11 months for patients with pigmented and 12 months for patients with amelanotic melanoma, and the differences in the groups were not significant (U=15.000; p=0.459).

Distant metastases were found in 39 of all tested patients with melanoma, and they were more than twice as many in patients with amelanotic melanoma (57.1 per cent) as compared to patients with pigmented melanoma (22.6 per cent) with p=0.005 (Figure 3).

Figure 3: Distribution of melanoma by distant metastases



In 21 of the patients with pigmented melanoma and five of those with amelanotic melanoma the distant metastases affected one organ, and in eight of the patients with pigmented melanoma two organs were affected (Table 9).

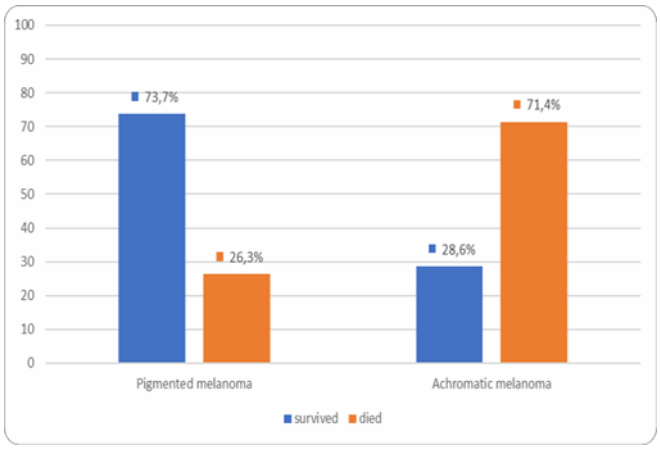
Table 9: Organs affected in patients with pigmented MM and amelanotic MM

Distant metastasis melanoma	1 organ	2 organs	3 organs	Total
Pigmented melanoma	21	8	2	31
Amelanotic melanoma	5	1	2	8
Total	26	9	4	39

Distant metastases were found mostly in the skin: in 18 patients with pigmented MM and in four patients with amelanotic MM. In two of the patients with amelanotic MM, distant metastases were found in the small intestine (1 patient) and the lungs (1 patient), and in two patients with amelanotic MM, the tumour metastasized in the skin, lungs, and liver.

The mortality was three times higher in the patients with amelanotic melanoma (71.4 per cent), as compared to the mortality of patients with pigmented melanoma (26.3 per cent), and the differences in the two groups were significant ($\chi 2=12.224$; p=0.001) (Figure 4).

Figure 4: Distribution of melanoma by mortality



The median survival was higher in the patients with pigmented MM (Mdn=28 months, 4÷72) as compared to the patients with amelanotic MM (Mdn=24.5 months, 10÷120) with p=0.653).

Discussion

In our study, amelanotic MM accounted for 9.3 per cent of all the MM cases. This ratio was a little higher than the eight per cent incidence reported in the literature.[2,4,6,11] Our data showed that amelanotic melanoma affected the men and women equally, while the pigmented MM affected more males than females. Similar studies by other teams have reported contradicting data. Some have found a higher frequency of amelanotic melanoma in men[11-13] and others - in women.[1,2] An equal number of affected males and females was reported in one study.[14]

Both types of melanomas in our sample affected older patients. This finding corresponded to results from similar studies.[11,12]

The most common localization MM was in the lower extremities (28.6 per cent of the cases). For pigmented MM, the back localization accounted for 24.1 per cent. Some authors have reported a higher incidence of involvement of the back and the chest for both types of melanoma.[11]

The average Breslow thickness we found was significantly higher (U=0.584, p=0.01) in amelanotic MM (4.2mm) as compared with the thickness in pigmented MM (2.1mm). This finding coincides with the results established by other authors.[5,11,12,15] However, our results for average thickness from investigating both pigmented and amelanotic MM were about twice as high. According to our data, the deep invasion in both types of melanoma was mostly found in the reticular dermis, which corresponds to Clark IV. Unfortunately, our results showed, that the largest percentage of patients with both types of melanoma was in the IV clinical stage, while patients included in other studies were in I and II stages.[11]

Sentinel lymph node biopsy was performed in 41 per cent of patients with pigmented MM, and in 14.3 per cent of those with amelanotic MM. Approximately one-third of pigmented MM patients and half of those with amelanotic MM, underwent regional lymph node dissection after a lymph node had been proved clinically positive. This implies a more malignant progression of amelanotic MM.

The rate of local recurrences in the cases of amelanotic MM was significantly higher - about six times, ($\chi 2$=14.408; p=0.001) as compared to those with pigmented melanoma. The time before a relapse in cases of amelanotic MM and pigmented MM was 12 and 11 months, respectively. Distant metastases in the amelanotic type are also significantly (p=0.005) higher (about two times), as compared with the pigmented type. In amelanotic MM, distant metastases were detected in one organ, usually the skin. The data on the more common local recurrences and distant metastases in the cases of amelanotic melanoma we found explain the worse prognosis in amelanotic MM. Our data on recurrences and distant metastases coincide with the data reported by other researchers.[11]

Lethality in cases with amelanotic MM was significantly higher ($\chi 2$=12.224; p=0.001) than in those of patients with pigmented MM, and the median survival was 24.5 and 28 months, respectively. Our results coincide with the data from other similar studies.[2,11]

Conclusion

The diagnosis of amelanotic melanoma was made later than that of pigmented melanoma when the thickness of the tumour was significantly bigger. The progression of the amelanotic MM is more malignant as compared to that of pigmented MM. In the amelanotic type, local recurrences are 6 times more common, and distant metastases were twice more frequent. The mortality rate in patients with amelanotic melanoma was three times as high, as compared to the patient with pigmented MM, and the median survival was lower.

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PEER REVIEW

Not commissioned. Externally peer reviewed.

CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

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ETHICS COMMITTEE APPROVAL

N/A

Table 2: Distribution of patients with MM by gender

Gender distribution	Indicator	Pigmented MM	Amelanotic MM	Total
Men	Number	71	7	78
	Percentage of total	91%	9%	100%
	Percentage in the groups	51.8%	50%	
Women	Number	66	7	73
	Percentage of total	90.4%	9.6%	100%
	Percentage in the groups	48.2%	50%	

Table 3: Localisation of pigmented MM and amelanotic MM

Localization	Indicator	Pigmented MM	Amelanotic MM	Total
Head	Number	29	3	32
	Percentage	21.20%	21.40%	21.20%
Neck	Number	0	1	1
	Percentage	0.00%	7.10%	0.70%
Chest	Number	10	1	11
	Percentage	7.30%	7.10%	7.30%
Abdomen	Number	10	0	10
	Percentage	7.30%	0.00%	6.60%
Back	Number	33	3	36
	Percentage	24.10%	21.40%	23.80%
Lumbar area	Number	5	1	6
	Percentage	3.60%	7.10%	4.00%
Upper extremity	Number	19	1	20
	Percentage	13.90%	7.10%	13.20%
Lower	Number	31	4	35
extremity	Percentage	22.60%	28.60%	23.20%

Table 4: Breslow thickness in pigmented and amelanotic MM

Breslow thickness Melanoma	*In situ*	Invasion <75mm	Invasion 0.76-1 mm	Invasion 1.1-2mm	Invasion 2.1-4mm	Invasion >4.1mm	Total
Pigmented melanoma (n)	10	18	9	31	38	31	137
Amelanotic melanoma (n)	0	1	1	1	4	7	14
Total	10	19	10	32	42	38	151

Table 5: Distribution of patients with pigmented and amelanotic MM by Clark level of invasion

Clark level of invasion	(I)[1]	(II)[2]	(III)[3]	(IV)[4]	(V)[5]	Total
Type of melanoma	Intraepidermal	Partial invasion of the papillary dermis	Fill and/or expand the papillary dermis	Invasion of reticular dermis	Invading the subcutaneous fat or deeper	
Pigmented melanoma (n)	15	13	41	58	10	137
Amelanotic melanoma (n)	1	1	3	8	1	14
Total	16	14	44	66	11	151

[1]level I - Intraepidermal

[2]level II - Partial invasion of the papillary dermis

[3]level III - Fill and/or expand the papillary dermis

[4]level IV - Invasion of reticular dermis

[5]level V - Invading the subcutaneous fat or deeper

Table 6: Distribution of patients by TNM stage

Stage melanoma	0	Ia	Ib	IIa	IIb	IIc	III	IV	Total
Pigmented melanoma (n)	9	21	25	13	12	17	8	32	137
Amelanotic melanoma (n)	0	0	1	0	1	2	4	6	14
Total (n)	9	21	26	13	13	19	12	38	151

Table 8: Distribution of patients by lymph dissection

	Not done	Done after SLBN	Done after positive lymph nodes	Done after SLBN and positive lymph nodes	Total
Pigmented melanoma	96	6	34	1	137
Amelanotic melanoma	7	0	7	0	14
Total	103	6	41	1	151

* Sentinel lymph node biopsy