Clinicopathologic, misdiagnosis, and survival differences between clinically amelanotic melanomas and pigmented melanomas

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Background: Amelanotic malignant melanoma (AMM) is challenging to diagnose. Clinical risk factors for AMM are not well defined.

Objective: To investigate clinicopathologic, misdiagnosis, and survival differences between patients with AMM and those with pigmented malignant melanoma (PMM).

Methods: A cross-sectional retrospective medical record review at a tertiary academic medical center.

Results: A total of 933 patients with melanoma with known presenting tumor color were identified (342 with AMM vs 591 with PMM). AMM was associated with older age, history of nonmelanoma skin cancer, and red hair, whereas AMM was inversely associated with a family history of melanoma, more than 50 nevi, and a history of dysplastic nevi. Compared with PMM, AMM was more likely to be located on the head and/or neck, had more aggressive pathologic features (greater Breslow depth and/or mitoses, ulceration, nodular subtype), and was less likely to be associated with a precursor nevus or regression. Finally, patients with AMM were more likely to be misdiagnosed than were patients with PMM (25% vs 12% clinically and 12% vs 7% pathologically), and they had poorer melanoma-specific survival (5-year overall survival rate, 0.77 [95% confidence interval, 0.72-0.82] vs 0.84 [95% confidence interval, 0.80-0.87]).

Limitations: Retrospective study design, single-institutional study.

Conclusion: Greater clinician awareness, lower biopsy thresholds, and increased patient education may be useful to enhance AMM detection in patients with certain characteristics. (J Am Acad Dermatol 2019;80:1292-8.)

Key words: amelanotic; *MC1R*; melanoma; red hair; risk factors.

Amelanotic malignant melanoma (AMM) is challenging to diagnose and contributes to melanoma mortality as AMMs tend to be diagnosed at more advanced stages, with poorer overall survival than with pigmented malignant melanomas (PMMs).[1-3] Although epidemiologic studies over the past few decades have revealed general risk factors for melanoma, specific risk

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factors for AMM have not been well studied.[4-7] The Genes, Environment, and Melanoma study from 2014 found that AMMs were predominant in females, thicker, more likely nodular, lacking a coexisting nevus, and with more mitoses and severe adjacent solar elastosis.[3] AMMs have also been found to be associated with a self-reported absence of back nevi and a sun-sensitive skin type than have PMMs.[8] We sought to further investigate patients who are at risk of AMM. To our knowledge, our study is the first to comprehensively investigate patient characteristics and histologic features associated with clinically diagnosed AMM, misdiagnosis, and differences in melanoma-specific survival between clinically diagnosed AMM and PMM.

CAPSULE SUMMARY

- Risk factors for amelanotic melanoma are poorly understood.
- Patients with amelanotic melanomas may be more likely to be older and have nonmelanoma skin cancer and red hair and less likely to have many nevi or a family history of melanoma. Clinicians should be alert to amelanotic lesions in patients with these factors.

METHODS

With approval from the Harvard Cancer Center Institutional Review Board (protocol No. 14-187), we performed a cross-sectional retrospective review of the medical records of all patients with melanoma seen at the specialty Pigmented Lesion Clinic and Cutaneous Oncology Program in Boston, Massachusetts, between 2009 and 2015, with data updated through July 2016. The Pigmented Lesion Clinic is a high-risk dermatology clinic consisting of patients regionally referred for total body photography and/or follow-up given a diagnosis of an atypical mole phenotype and/or melanoma. The Cutaneous Oncology Program is a multidisciplinary clinic caring for patients with later-stage melanoma. All patients were examined at their visits, with total-body skin examinations and dermoscopy performed by 1 staff physician (C.C.K.) together with rotating residents, with or without total body digital photography. Information was collected from patient records, including clinical notes and pathology records (see Tables I-III for parameters). Only patients with the clinical color of their melanoma documented were included in the study. Amelanotic was defined clinically as skin-colored, pink, red, violaceous, or purple pigmentation, whereas pigmented included light or medium brown, dark brown or black, or variegated pigmentation. Patient eye color and hair color were recorded by the clinician, with hair grouped into the categories of red, red highlights, blonde, brown, or black. For patients with more than 1 melanoma, the thickest tumor was used.

Information on clinical or pathologic misdiagnosis and death from melanoma versus from other causes was extracted both from clinical records and from the public Social Security Death Index. A clinical misdiagnosis was defined as a clinician having examined the lesion before the diagnosis date and rendering a benign diagnosis. A pathologic misdiagnosis was defined as an initial diagnosis other than melanoma that was later diagnosed as melanoma after re-review of previous slides or a rebiopsy specimen.

Statistical analyses were conducted to compare patient characteristics and outcomes of patients with AMM versus those of patients with PMM. The *t* test was used for continuous variables and the chi-square test was for discrete variables. For analyses involving small sample sizes, corresponding nonparametric tests, the Wilcoxon-Mann-Whitney[9] or Fisher exact test[10] were used. Univariate and multivariate logistic regression models were developed. A backward selection method was used to build the multivariate model, in which significant ($P < .05$) or marginally significant ($P < .1$) variables in the univariate model were included. Survival outcome was defined as death due to melanoma. Deaths due to other or unknown reasons were removed. Survival time was measured from time from initial diagnosis to death. Alive patients were censored at last known visit date. The Kaplan-Meier method[11] was used to describe the survival distribution. Kaplan-Meier plot was generated by using R software (version 3.4.0), and all statistical analyses were performed using SAS software (version 9.4, SAS Inc, Cary, NC). All reported *P* values were for 2-sided tests.

RESULTS

Of the 1898 patients with melanoma in our review, 933 had data on the clinical color of their tumor; 342 patients with AMM and 591 patients with PMM were identified. The median follow-up time for patients was 5.91 years. Patients with AMM had their disease diagnosed at an older age than did patients with PMM (median age, 59 vs 51 years [$P < .001$]). Sex was not significantly different between those with AMM and those with PMM ($P = .141$), though 193 of 342 AMMs (57%) were found in men versus 149 of 342 (44%) in women.

Abbreviations used:

AMM: amelanotic malignant melanoma
CI: 95% confidence interval
DN: dysplastic nevus
FH: family history
NMSC: nonmelanoma skin cancer
OR: odds ratio
PMM: pigmented malignant melanoma
UV: Ultraviolet

Differences between melanoma risk factors and phenotype of patients with AMM and those in patients with PMM were examined (Tables I and II). Patients with AMM were significantly more likely to have a history of nonmelanoma skin cancer (NMSC) (35% vs 21% [$P < .001$]) but less likely to have a family history (FH) of melanoma (17% vs 23% [$P = .024$]). Patients who developed AMM were significantly less likely to have more than 50 nevi (25% vs 59% [$P < .001$]) and were also less likely to have a history of dysplastic nevi (DNs) (18% vs 40% [$P < .001$]). Patients with red hair (excluding red highlights) were more likely to have AMM than were patients with other hair colors (23% vs 14% [$P = .042$]). Although a FH of red hair was more common among patients with AMM, the difference was not statistically significant (57% vs 49% [$P = .164$]). Similarly, a higher proportion of patients with both red hair and a FH of red hair developed AMM, but the difference was not statistically significant (37% vs 20% [$P = .133$]). Fitzpatrick skin type I was identified in a greater proportion of those with AMM than in those with PMM, though this result was borderline significant (73% vs 63% [$P = .054$]). Ultraviolet (UV) exposure, tanning bed use, history of immunosuppression, other hair colors, and eye color did not vary significantly between patients with AMM and patients with PMM in our cohort.

The histologic features and locations of AMMs and PMMs were compared (Table III). The median Breslow depth was significantly greater for AMMs than for PMMs (3.0 vs 1.5 mm [$P < .001$]), and the median mitotic rates were also significantly greater for AMMs (5 vs 2 mitoses/high-power field [$P < .001$]). AMMs were more likely to be ulcerated (41% vs 29% [$P < .001$]) but less likely to have regression (10% vs 20% [$P < .001$]) or to arise from a precursor nevus (15% vs 31% [$P < .001$]). Notably, AMMs were less likely than PMMs to have radial growth (56% vs 77% [$P < .001$]). Presence of tumor-infiltrating lymphocytes was similar for AMMs and PMMs (78% vs 74% [$P = .277$]). AMMs were more likely to be nodular (34% vs 21% [$P < .001$]) and less likely to be of the superficial spreading melanoma subtype (25% vs 49% [$P < .001$]). The lentigo maligna subtype was distributed approximately equally between AMMs and PMMs (3% vs 2% [$P = .334$]). AMMs were significantly more likely to be found on the head and/or neck (26% vs 15% [$P = .002$]) and less likely on the trunk (32% vs 40% [$P = .004$]) than PMMs were.

In patients with multiple melanomas (Table IV), we found that 20% (11 of 54) presented with an AMM, with 45% of these patients (5 of 11) developing a future AMM and 55% (6 of 11) developing a future PMM. Of the 80% of patients (43 of 54) presenting with a PMM, 86% (37 of 43) developed a future PMM and 14% (6 of 43) developed a future AMM. The time between each subsequent melanoma diagnosis decreased for our cohort. We also found that the mean Breslow depth of the first melanoma was thicker than that of all subsequent melanomas; the mean Breslow depth for a first melanoma was 1.78 mm versus 0.52 mm for a second versus 0.61 for a third versus 0.93 for a fourth versus melanoma in situ for a fifth.

In the multivariate model, a history of NMSC, history of DNs, histologic regression, Breslow depth, and presence of a precursor lesion remained significant. In addition, a history of NMSC (odds ratio [OR], 2.48; 95% confidence interval [CI], 1.65-3.73 [$P < .001$]) and deeper Breslow depth (OR, 1.13; 95% CI, 1.07-1.20 [$P < .001$]) were associated with an increased odds of having AMM. A history of DNs (OR, 0.34; 95% CI, 0.22-0.53 [$P < .001$]), histologic regression (OR, 0.58; 95% CI, 0.34-0.99 [$P = .047$]), and presence of a precursor lesion (OR, 0.60; 95% CI, 0.38-0.93 [$P = .024$]) were negatively associated with AMM.

AMM was significantly more likely than PMM to both be clinically misdiagnosed (25% vs 12% [$P < .001$]) and pathologically misdiagnosed (12% vs 7% [$P = .008$]). Patients with AMM also had poorer survival than patients with PMM ($P = .001$) (Fig 1). The 5-year survival rates were 0.84 (95% CI, 0.80-0.87) for patients with PMM and 0.77 (95% CI, 0.72-0.82) for patients with AMM. Our study found that overall, 74 of 302 patients with AMM (25%) died of melanoma compared with 93 of 540 patients with PMM (17%), with a median follow-up time of 5.10 years for those with AMM and 6.03 for PMM.

DISCUSSION

Our study represents the largest cohort of patients with clinical AMM to date with a comprehensive examination of patient phenotype, clinicopathologic correlates, and differences in rates of misdiagnoses and survival between AMM and PMM. Our results

Table I. Patient characteristics and risk factors for amelanotic versus pigmented melanoma

Characteristic	Amelanotic melanoma (n = 342)	Pigmented melanoma (n = 591)	Odds ratio (95% confidence interval)	*P* value
Sex, n (%)				.141
Female	44% (149/342)	49% (287/591)	0.81 (0.67-1.07)	
Male	57% (193/342)	52% (304/591)		
Median age at melanoma diagnosis, y (min-max)	59 (17-95)	51 (16-95)	1.03 (1.02-1.04)	<.001
Fitzpatrick skin type I	73% (85/116)	63% (175/277)	1.60 (0.99-2.58)	.054
Family history of melanoma	17% (57/335)	23% (135/579)	0.67 (0.48-0.95)	.024
History of immunosuppression*	16% (55/339)	15% (83/569)	1.13 (0.78-1.64)	.506
Mole density greater than 50 nevi	25% (28/112)	59% (129/277)	0.38 (0.24-0.62)	<.001
History of dysplastic nevi	18% (59/334)	40% (236/585)	0.32 (0.23-0.44)	<.001
History of extensive UV exposure†	83% (110/133)	84% (268/319)	0.91 (0.53-1.56)	.847
History of NMSC	35% (117/338)	21% (120/581)	2.03 (1.51-2.75)	<.001
Any tanning salon use	26% (21/81)	35% (84/243)	0.66 (0.38-1.16)	.150

Max, Maximum; *min*, minimum; *NMSC*, nonmelanoma skin cancer; *UV*, ultraviolet.
*Immunosuppression refers to (1) immunosuppression in patients with underlying immunosuppressive disease (eg, chronic lymphocytic leukemia, HIV), treated with long-term systemic immunosuppressive medications or (2) immunosuppression in patients who have been immunosuppressed secondary to organ transplant or chemotherapy for a prior malignancy.
†Extensive exposure defined by a history of multiple blistering sunburns and long periods of time outdoors according to patient self-report.

Table II. Phenotypic characteristics of patients with melanoma

Characteristic	Amelanotic melanomas	Pigmented melanomas	Odds ratio (95% confidence interval)	*P* value
Hair color				
Red hair vs other colors	23% (23/101)	14% (39/278)	1.81 (1.02-3.21)	.042
Red	23% (23/101)	14% (39/278)	—	
Red highlights only	13% (13/101)	13% (36/278)	—	
Blond	23% (23/101)	27% (74/278)	—	
Brown	41% (41/101)	44% (122/278)	—	
Black	1% (1/101)	3% (7/278)	—	
Family history of red hair*	57% (50/87)	49% (124/254)	1.42 (0.87-2.31)	.164
Both red hair and family history of red hair	37% (23/63)	20% (29/146)	1.63 (0.86-3.11)	.133
Eye color				
Blue vs other colors	59% (55/94)	53% (136/255)	1.23 (0.77-1.99)	.389
Blue	59% (55/94)	53% (136/255)	—	
Green	5% (5/94)	5% (14/255)	—	
Hazel	17% (16/94)	16% (42/255)	—	
Brown	19% (18/94)	25% (63/255)	—	

*Among immediate family members.

suggest that patients with AMM tend to have their melanoma diagnosed at an older age than do patients with PMM, and they may be *less* likely to possess certain classic melanoma risk factors, including FH of melanoma, high mole count (>50 nevi), and history of DNs. Importantly, without these specific melanoma risk factors, patients may be not be readily identified as being at risk of melanoma. Our results corroborate the finding of Vernali et al that absence of back nevi was associated with AMM.[8] Our methodology notably collected phenotypic data from the clinician report, which may be a more accurate assessment than patient questionnaires.

This is the first cohort study to document the association between red hair and AMM. The red hair phenotype is attributed to specific loss of function variants in melanocortin 1 receptor gene (*MC1R*), a polymorphic gene and regulator of pigment phenotype.[12-14] We hypothesize that patients with red hair generate more pheomelanin, thus having a higher likelihood of melanomas lacking dark pigment. Although we also examined FH of red hair, we did

Table III. Pathologic features and locations of amelanotic versus pigmented melanoma

Feature/location	Amelanotic melanomas	Pigmented melanomas	Odds ratio (95% confidence interval)	*P* value
Median Breslow depth, mm (min-max)	3.0 (0.2-55) (n = 308)	1.5 (0-32) (n = 532)	1.16 (1.11-1.22)	<.001
Median mitotic rate, count/mm^2 (min-max)	5 (0-60) (n = 269)	2 (0-85) (n = 466)	1.05 (1.03-1.07)	<.001
Superficial spreading subtype	25% (71/289)	49% (244/496)	0.34 (0.24-0.46)	<.001
Nodular subtype	34% (98/289)	21% (103/496)	1.96 (1.41-2.71)	<.001
Lentigo maligna subtype	3% (9/289)	2% (10/496)	1.56 (0.63-3.89)	.334
Radial growth	56% (135/240)	77% (324/422)	0.39 (0.28-0.55)	<.001
Vertical growth	98% (250/254)	95% (407/429)	3.38 (1.15-9.92)	.019
Ulceration*	41% (120/294)	29% (143/493)	1.69 (1.25-2.29)	<.001
Presence of tumor-infiltrating lymphocytes	78% (203/260)	74% (323/434)	1.22 (0.85-1.76)	.277
Tumor regression	10% (25/259)	20% (90/441)	0.42 (0.26-0.67)	<.001
Melanoma arising from precursor nevus	15% (44/284)	31% (147/471)	0.40 (0.28-0.59)	<.001
Location				
Head and neck† vs other locations	26% (88/342)	15% (90/591)	1.87 (1.34-2.60)	.002
Trunk vs other locations	32% (108/342)	40% (236/591)	0.66 (0.50-0.88)	.004
Extremities vs other locations	37% (127/342)	37% (221/591)	0.66 (0.50-0.88)	.700

*Ulceration was defined according to the American Joint Committee on Cancer criteria as the histopathologic absence of intact epidermis over a portion of the primary tumor.
†With regard to the melanomas occurring on the head and neck, 28% (25 of 88) of the amelanotic tumors were located on the scalp, whereas 12% (11 of 90) of the pigmented tumors occurred on the scalp.

Table IV. Clinical pigmentation and locations of melanomas in patients with multiple primary melanomas

Tumor color		
	Amelanotic	Pigmented
First melanoma	20% (11/54)	80% (43/54)
All subsequent melanomas	45% (5/11)	86% (37/43)

Time course				
	Melanoma 1 to melanoma 2	Melanoma 2 to melanoma 3	Melanoma 3 to melanoma 4	Melanoma 4 to melanoma 5
Mean time to subsequent melanoma, y (range)	3.91 (0-37)	3.04 (0-12)	0.35 (0-6)	Unknown

Tumor characteristics					
	Melanoma 1	Melanoma 2	Melanoma 3	Melanoma 4	Melanoma 5
Breslow depth, mm	1.78 (0-28) (n = 88)	0.52 (0-4.5) (n = 88)	0.61 (0-5.25) (n = 25)	0.93 (0-2.5) (n = 8)	Melanoma in situ (n = 1)
Location					
Head and neck	15% (13/87)	10% (9/88)	8% (2/25)	25% (2/8)	
Trunk	32% (28/87)	40% (35/88)	44% (11/25)	25% (2/8)	100% (1/1)
Extremities	49% (43/87)	49% (43/88)	48% (12/25)	50% (4/8)	

not find a significant association with AMM. This may be due to the study size, patient recall bias, and variable degrees of penetrance of *MC1R* and variation among different family members.

Patients with AMM in our study were also more likely to have a history of NMSC than were patients with PMM, suggesting sensitivity to long-term UV damage in patients with AMM. Interestingly, although the risk of melanoma among individuals with *MC1R* variants has been shown to be UV independent,[9,15] pheomelanin may produce reactive oxygen species with exposure to UV light, which may contribute to development of NMSC.[16,17] Although our study did not find statistically significant differences in self-reported extensive sun damage or tanning salon exposure between patients with

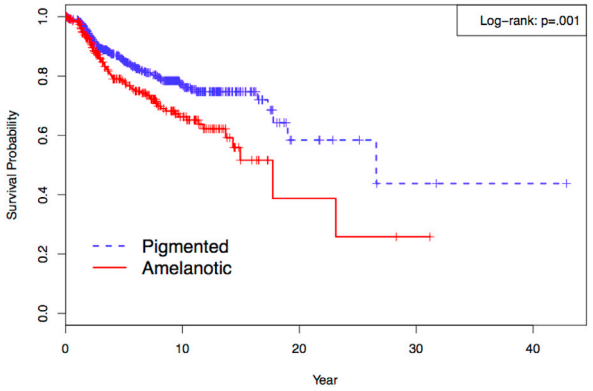

Fig 1. Differences in melanoma-specific survival probability between amelanotic and pigmented melanomas.

AMM and those with PMM, more patients with AMM in our cohort had Fitzpatrick skin type I than did patients with PMM with borderline significance, supporting the underlying sun sensitivity of these patients.

In our cohort of patients, AMMs were more frequently located on the head and/or neck, which supports a prior Surveillance, Epidemiology, and End Results database study.[2] Similar to in other studies, in our cohort, AMMs were diagnosed as more aggressive tumors with significantly greater Breslow depth, higher mitotic rate, and likelihood of ulceration than were PMMs.[2] AMMs in our cohort were more likely to be nodular and lack a precursor nevus, also corroborating findings from Thomas et al.[3] Nodular melanomas may be considered an aggressive subtype, as they have been shown to grow more rapidly and be diagnosed later than superficial spreading melanoma.[17,18] Finally, our study found that AMM tended to lack histologic regression, which may allude to less immunoreactivity in patients with AMM.[19,20] Of note, the proportion of AMMs versus that of all melanomas in our cohort was greater than in the study of Vernali et al (37.5% vs 7.5%).[8] We hypothesize that this finding may in part be influenced by the high-risk population in our clinics and the New England demographics, although further investigations would be needed to verify this hypothesis.

The AMMs in our cohort were significantly more likely to be missed clinically by physicians and misdiagnosed pathologically. Without pigmentation, melanomas may be more easily misinterpreted by clinicians as benign nevi or other diagnoses.[21] In addition, incisional and superficial biopsies may be performed more readily, with a lower clinical suspicion for malignancy than when biopsies of AMMs (which have been shown to lead to more histopathologic misdiagnosis) are performed.[22] Potentially related to misdiagnoses, AMM had poorer melanoma-specific survival than did PMM in our cohort, corroborating recent studies and underlining the need to identify patients at risk of AMM for earlier detection.[2,3]

In conclusion, the findings in this study suggest that a unique subset of associated factors, including older age, history of NMSC, and red hair may identify patients at risk of AMM. Greater awareness of any suspicious amelanotic lesions in patients with these clinical factors and a lower threshold for biopsy could lead to earlier detection. Given our finding that individuals with AMM were less likely to have a history of DNs, more than 50 nevi, or FH of melanoma, both clinicians and patients should remain alert for the risk of AMM even in patients without a "moley" phenotype or FH of melanoma. The importance of earlier diagnosis of AMM is underscored by the higher rates of misdiagnosis and poorer survival outcomes of AMM than those of PMM. The study limitations include the single-site study design, retrospective data collection from existing patient charts with some missing data, and potential patient recall bias. Genotyping of patients and re-review of histology would have expanded our findings further.

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