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Dermoscopic diagnosis of amelanotic/hypomelanotic melanoma

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DEAR EDITOR,

Amelanotic/hypomelanotic melanoma (AHM) is a subtype including melanomas with little or no melanin pigmentation, amelanotic melanoma (AM); it represents 2-8 % of all melanomas.[1-2] AM may be difficult to diagnose because of lack of pigmentation and symmetry: recently, germline mutations have been reported in the MC1R gene and to a certain extent also in the MITF gene.[3]

Few studies have described the dermoscopic features of thin (≤ 1 mm) and thick (> 1 mm) AHM; this latter compared with thin AHM showed a greater frequency of hairpin, peripheral vessels, large blue-gray ovoid nests, central vessels, ulceration, large vessels and pink color.[2]

In our previous study, thick *vs* thin AHM showed a greater frequency of irregular pigmentation and milky-red areas.[4]

In this retrospective study, 184 consecutive histopathologically diagnosed amelanotic/hypomelanotic nodular melanomas (AHNM, 41), amelanotic/hypomelanotic superficial spreading melanomas (AHSSM, 37), and amelanotic/hypomelanotic non-melanocytic lesions (AHNML) plus amelanotic/hypomelanotic benign melanocytic lesions (AHBML), 106 (i.e., 51 basal cell carcinoma, 28 seborrheic keratosis and 27 compound/dermal nevi) from 15 participating Italian centers, during 2007-2011, were dermoscopically evaluated to assess validity of dermoscopy in AHNM detection. The dermoscopic evaluation and statistical analysis have already been described.[4-5] To quantify the dermoscopic features of AHNM *vs.* AHSSM and AHNM *vs.* AHNML and AHBML, unconditional logistic regression models were applied to compute odds ratios (ORs) and corresponding 95% confidence intervals (CIs). The multivariate analysis of dermoscopic features of AHNM *vs*. AHSSM showed that blue-whitish veil (OR, 5.16) and structureless pattern (OR, 4.45) were significantly, independently associated with AHNM (Table 1). The blue-white veil has already been significantly associated with nodular melanoma (NM) because of its histopathological correlation with melanin in the mid-dermis.[6]

The structureless pattern (devoid or with too few structures to constitute a pattern, except for the presence of blood vessels)[7] may be correlated with reduced structures reported in thick *vs* thin AHM.[2,4]

When evaluating at multivariate analyses the dermoscopic features of AHNM *vs*. AHNML and AHBML, we found that structureless pattern (OR, 481.44), hypopigmented pseudo-lacunas (OR, 132.22), polymorphous vessels associated with milky red globules/areas (OR,

296.53), little blue-black color (OR, 132.24), polymorphous vessels combined with red homogeneneous areas (OR, 95.99), and homogeneous disorganized pattern (OR, 117.07) were significantly associated with an increased risk of AHNM (Table 1).

Pseudo-lacunas or "clods" may also be found in haemangioma, seborrheic keratosis, dermal nevus, melanoma and AHNM;[8,9] in this latter hypopigmented pseudo-lacunas appeared irregular in size, shape, color and distribution. (Figure 1).

We found a greater frequency of polymorphous vessels combined with milky red globules/areas and/or red homogeneous areas (structureless areas of red homogeneous colour) in AHNMs; these combinations of vascular structures have already been associated with > 2 mm thick AHM;[10] in our study, 75.6% of AHNM had a thickness >2 mm and only 19.5% a thickness (1 -2 mm), in which more frequently dotted and linear irregular vessels should be found. Therefore, we did not find a significant presence of dotted and linear irregular vessels in this study, differently from our previous.[4]

Little blue-black color, a combination of two colors involving <10% of lesion surface, may be seen on the pink-reddish background along with polimorphou vessels, addressing AHNM diagnosis; blue-black color, extending more than 10% was significantly associated with pigmented NM.[5]

The homogeneous disorganized pattern, found in AHNM, may be differentiated from homogeneous pink pigmentation seen in common nevi in very fair skinned persons, because of more shades of pink, asymmetrically distributed intermixed with polymorphous vessels and milky red areas/globules (Fig. 1).

Dermoscopy may be useful for the diagnosis of AHNM, thanks to visualization of features associated with deep tumor extension (blue-whitish veil, polymorphous vessels, little blue-black color, pseudo-lacunas) not visible to the naked eye.

However, thin AM or pink melanoma were dermoscopically more difficult to diagnose than pink thick melanomas because we found high sensitivity (87.8%) and high specificity (87.7%) to correctly classify AHNM as melanoma, but a lower sensitivity (51.4%) to correctly classify AHSSM as melanoma. This may depend on higher percentage of AM, 28 out 37 (75.7%) among AHSSM, differently from our previous study in which only 10 out of 44 (23%) were AM, while (77%) were hypomelanotic, easier to diagnose (sensitivity and specificity for all AHMs irrespective of nodular or SSM were 89% and 96% respectively).[4]

The accurancy of AM dermoscopic diagnosis could increase with the help of reflectance confocal microscopy (RCM);[11] a combined approach should result in accurate AM diagnoses.[3,]

Our study limitations regarding the retrospective design, the limited selection of control group diagnoses, and different dermoscopy used (i.e., 63.1% and 36.9% of images were taken with a camera using non-polarized and polarized dermoscopy respectively, and the rest had missing information, influencing the visualization of vessels, red areas, and shiny white lines, better visualized with polarized dermoscopy),[12] do not allow drawing firm conclusions on the leading role of dermoscopy in AHM detection.

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Figure Legend

Fig 1. Amelanotic/hypomelanotic nodular melanoma. (a) In the clinical image of this 2.5 mm thick AHM located on the right leg of a 21-year-old man, a shiny pink reddish symmetrical nodule can be observed (inserts). Dermoscopically, the melanoma reveals a diffuse homogeneous disorganized pigmentation with different shades of pink asymmetrically distributed, intermixed with polymorphous vascular pattern including dotted (small arrow), linear irregular, (large arrow), irregular hairpin (small top arrows), milky red areas (asterisk) and hypopigmented pseudo-lacunas (arrowheads) irregular in size, shape and distribution.

In addition, irregular brown globules/dots and white shiny lines can also be observed, as clue features to add to the above cited criteria in differentiating AHNM from other lesions.

Table 1. Most frequent dermoscopic features of AHNM *versus* AHSSM and of AHNM *versus* AHBML+AHNNM: Univariate and multivariate analyses of 184 amelanotic/hypomelanotic skin lesions

Dermoscopic features	AHNM (N. 41) N. (%)	AHSSM (N. 37) N. (%)	OR (95% CI)[1] Univariate	OR (95% CI)[1] Multivariate[2]
Blue-whitish veil	14 (34.2)	5 (13.5)	3.32 (1.06-10.40) p=0.04	5.16 (1.32-20.25) p=0.02
Structureless pattern	27 (65.9)	16 (43.2)	2.53 (1.01-6.33) p=0.05	4.45 (1.46-13.58) p=0.009
Polymorphous vessels + milky red globules/ areas	9 (22.9)	2 (5.4)	4.92 (0.99-24.51) p=0.05	3.93 (0.68-22.63) p=ns
	AHNM (N. 41) N. (%)	AHBML + AHNML (N. 106) N. (%)		

Structureless pattern	27 (65.9)	10 (9.4)	18.51 (7.40-46.30)	481.44 (14.26-995.55)
			p<0.0001	p=0.0006
Hypopigmented pseudo lacunas	19 (46.3)	6 (5.7)	14.39 (5.15-40.20)	138.22 (6.73-995.55)
			p<0.0001	p=0.001
More one shade of pink	16 (39.0)	5 (4.7)	12.93 (4.32-38.65)	
			p<0.0001	p=ns
Blue-whitish veil	14 (34.2)	7 (6.6)	7.33 (2.69-19.98)	
			p<0.0001	p=ns
Shiny white lines	20 (48.8)	15 (14.2)	5.78 (2.54-13.13)	
			p<0.0001	p=ns
Asymmetric pigmentation pattern	32 (78.1)	44 (41.5)	5.00 (2.18-11.54)	
			p=0.0002	p=ns
Irregular blotches	11 (26.8)	4 (3.8)	9.35 (2.78-31.49)	
			p=0.0003	p=ns
Irregular dots/globules	21 (51.2)	21 (19.8)	4.25 (1.96-9.24)	
			p=0.0003	p=ns
Regression structures	16 (39.0)	13 (12.3)	4.58 (1.95-10.76)	

			p=0.0005	p=ns
Black color	9 (22.0)	2 (1.9)	14.62 (3.00-71.18)	
			p=0.0009	p=ns
Polymorphous vessels + milky red globules/ areas	9 (22.0)	1 (0.9)	29.53 (3.60-242.01)	296.53 (11.05-995.55)
			p=0.002	p=0.0007
Little blue-black color	7 (17.1)	1 (0.9)	21.62 (2.09-154.72)	132.24 (0.92-995.55)
			p=0.009	p=0.05
Polymorphous vessels + red homogeneous areas	6 (14.6)	1 (0.9)	18.00 (2.09-154.72)	95.99 (1.49-995.55)
			p=0.009	p=0.03
Homogeneous disorganized pattern	6 (14.6)	3 (2.8)	5.89 (1.40-24.79)	117.07 (4.15-995.55)
			p=0.02	p=0.005

AHNM=amelanotic/hypomelanotic nodular melanoma; AHSSM=amelanotic/hypomelanotic superficial spreading melanoma; AHBML=amelanotic/hypomelanotic benign melanocytic lesions; AHNML=amelanotic/hypomelanotic nonmelanocytic lesions. [1]Odds ratio (OR) and 95% confidence interval (CI). [2]Unconditional logistic regression including all significant features in the univariate analysis. ns=no significant. *p value* ≤0.05 was considered statistically significant.