Dermatology Practical & Conceptual

Two-step-7-Pink Rule: A Practical Tool for the Dermoscopic Evaluation of Fully Amelanotic Skin Lesions

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ABSTRACT

Introduction: The diagnosis of fully amelanotic skin tumors is difficult on clinical and dermoscopic examination.

Objectives: We sought to identify an accurate and user-friendly dermoscopic algorithm to differentiate between benign and malignant pink lesions.

Methods: The database of 1 referral center was retrospectively reviewed for images of non-inflammatory fully amelanotic skin lesions. Two dermatologists jointly assessed a validation set of images for dermoscopic criteria and constructed a diagnostic algorithm, the 2-step-7-pink rule (2S-7PR). Two external clinicians, with different skills in dermoscopy and blinded to the final diagnosis, separately evaluated images from the validation test sets using the prevalent criterion method and the new 2S-7PR algorithm.

Results: A total of 763 lesions from 652 patients were included in the validation set database, of which 68.3% were malignant and 31.7% were benign. Three suspicious dermoscopic criteria were included in the first step of the 2S-7PR: polymorphous or sharply focused vessels, scales or crusts, and erosions or ulcerations; and 4 non-suspicious criteria were included in the second: white collarette, white scar-like area, vascular lacunae, and necklace pinpoint vessels. High levels of specificity and sensitivity were calculated in the validation and test phases for both the expert and non-expert evaluators, the former achieving higher levels of both sensitivity and specificity by employing the 2S-7PR compared to the prevalent method, and the latter only improved specificity.

Conclusions: The present study showed that an algorithm focused on a few reproducible and easily recognizable criteria could improve diagnostic accuracy in the management of amelanotic lesions.

Introduction

The diagnosis of amelanotic solitary cutaneous lesions is among the most arduous challenges facing dermatologists, as the differential diagnosis of such lesions includes benign tumors, potentially fatal skin malignancies as well as inflammatory and infectious conditions [1-9]. Amelanotic (pink) lesions are defined by the complete absence of melanin pigmentation at clinical and dermoscopic examination, with a prevalence of white, pink, and red colors. Previous studies exploring the role of dermoscopy in diagnosing pink lesions also included hypomelanotic lesions, where some pigmented structures were still identifiable [7,10,11]. Pigmented criteria proved to be more specific than non-pigmented ones, playing a leading role in the diagnostic choice [12].

When melanin pigmentation is totally absent, the lack of contrast between contiguous structures impairs our ability to identify specific elements and the differential diagnosis is mainly guided by the evaluation of vascular morphology and distribution [13-15]. Whereas many different sets of criteria have been formulated for pigmented lesions so far, yet to date, a limited number of diagnostic algorithms exist for pink lesions [1,16,17]. The appropriate application of such criteria, however, requires clinical confidence and relatively advanced skill in dermoscopy, making their usefulness less accessible to novices.

Objectives

The aim of the present study is to identify an easy and practical set of dermoscopic criteria that would distinguish benign from malignant truly amelanotic skin lesions.

Methods

Study Population

We (SM and ML) retrospectively and consecutively reviewed the databases of 1 third- level referral center for skin cancer diagnosis (Reggio Emilia) for truly amelanotic skin lesions, from January 1, 2008, to December 31, 2019.

All images were captured using glass plate/gel photographic devices (DermLite Photo). Only lesions with high-quality clinical and dermoscopic pictures were selected; both polarized and non-polarized dermoscopic images were included, the latter only if gentle pressure had been applied during the acquisition phase.

Truly amelanotic lesions were defined as those completely lacking melanin pigmentation (brown, blue, or black) at both clinical and dermoscopic examinations. Lesions with blue, purple, or black colors were included only when these colors were produced by blood (e.g., vascular lacunae, hematic crusts). The database was revised by a physician with high experience in dermoscopy (RP).

Histopathology was considered the gold standard for the final diagnosis; and cases lacking histological confirmation were only included if a follow-up of a minimum of 12 months was available and the clinical/dermoscopic diagnosis was assumed as final diagnosis after re-evaluation by an expert (RP). Lesions of inflammatory or infectious etiology were not included.

Information regarding patient age, gender, lesion location and diagnosis was also extracted from the database. A validation set was consecutively constructed by retrieving lesions from January 1, 2008, to December 31, 2017, and 100 lesions were also selected as test set, from January 1, 2018, to December 31, 2019, and matched with validation set images for age, gender, body site and diagnosis.

Study Workflow

Two dermatologists (RP and ML) jointly evaluated the validation set database to detect the presence of specific dermoscopic criteria. In case of disagreement, a third experienced physician (CL) was asked to solve the issue. An algorithm was thus constructed, called 2-step-7-pink rule (2S-7PR), that would distinguish between benign and malignant amelanotic lesions. Both the validation and the test set databases were then shown to 2 external physicians, 1 with high

Table 1. Demographic and Clinical Characteristics.

Variables		Diagnosis Benign	Diagnosis Malignant	Total	P Value
Mean age ± SD		51.5 ± 23.3	73.7 ± 14.3	66.7 ± 20.5	<0.001
Gender	M	115 (55.3%)	296 (66.7%)	411 (63.0%)	0.005
	F	93 (44.7%)	148 (33.3%)	241 (37.0%)	
Total		208	444	652	
Body site	Head/neck	55 (22.7%)	358 (68.7%)	413 (54.1%)	<0.001
	Trunk	77 (31.8%)	70 (13.4%)	147 (19.3%)	
	Upper limbs	21 (8.7%)	29 (5.6%)	50 (6.6%)	
	Lower limbs	47 (19.4%)	44 (8.4%)	91 (11.9%)	
	Others	17 (7.0%)	14 (2.7%)	31 (4.1%)	
	Unknown	25 (10.3%)	6 (1.2%)	31 (4.1%)	
Total		242	521	763	

SD = standard deviation.

(GP) and 1 with intermediate (NL) experience in dermoscopy, blinded for the final diagnosis. They were instructed on the prevalent method [17] and the new 2S-7PR algorithm and were asked to independently apply both of these algorithms on the validation set database. The same process was then repeated on a test set database by the same evaluators, to assess their learning curve and to reduce the bias given by the lack of familiarity with the new algorithms.

Statistical Analysis

Proportions were calculated for qualitative variables and were compared via the chi-square test. Means ± standard deviations (SD) or medians with interquartile ranges (IQR) were calculated for quantitative variables, after assessment for normal distribution, then compared using the Student T or the Mann-Whitney U test accordingly. In order to define which dermoscopic criteria were independently associated with the final diagnosis (benign vs. malignant) a step-wise backward multivariate logistic regression model was constructed, including those variables significantly associated to the outcome in univariate analysis.

An algorithm was finally constructed by testing different combinations of the selected criteria. A panel of experts (EM, CL and GA) evaluated the best option taking into consideration both the diagnostic accuracy and the reproducibility (ease of use by both experts and novices). To evaluate the diagnostic accuracy, sensitivity and specificity were calculated. Statistical significance was set at $P < 0.05$.

Results

Study Population

A total of 763 lesions from 652 patients (411 [63.0%] males and 241 [37.0%] females; median age: 66.7 years) were retrieved from the database and selected for the validation set. More than half of the included lesions were located on the head and neck regions (413; 54.1%), one-fifth were located on the trunk (147; 19.3%); on the lower limbs (91; 11.9%). Demographic and body site data for the validation set are reported in Table 1.

As for the diagnosis, 521 (68.3%) lesions were malignant and 242 (31.7%) were benign. Malignant lesions included 244 (32.0%) invasive squamous cell carcinomas, 239 (31.3%) basal cell carcinomas, 19 (2.5%) melanomas, 9 (1.2%) in situ squamous cell carcinomas, 8 (1.0%) adnexal malignancies, and 2 (0.3%) vascular malignancies. Benign lesions included 75 (9.8%) vascular benign lesions, 37 (4.8%) pyogenic granulomas, 35 (4.6%) benign nevi, 22 (2.9%) adnexal benign lesions, 21 (2.8%) clear cell acanthomas, 20 (2.6%) Spitz/Reed nevi, 20 (2.6%) dermatofibromas, and 12 (1.6%) miscellaneous benign lesions. Lesion-specific diagnoses are reported in Table S1.

2S-7PR Algorithm Construction

A multistep analysis was conducted to identify the dermoscopic criteria independently associated with malignant and benign amelanotic lesions. Univariate analysis was first conducted, and the following criteria were detected: white collarette, central white scar, necklace pinpoint vessels, comma vessels, vascular lacunae, linear vessels, in focus vessels (arborizing or short-fine), white follicles, erosions, ulceration, scales/crusts, polymorphic vessels, dotted vessels, negative network, papillomatous structures. These criteria were then included in a stepwise backward multivariate regression model together with the most important demographic and clinical variables (age on visit, gender, body site) (Table S2).

Table 2. Multivariate Logistic Regression Analysis*.

Variables	OR	95% CI for OR		P Value
		Lower bound	Upper bound	
In focus vessels (arborizing or short-fine)	8.30	4.29	16.04	<0.001
Erosions	4.76	1.23	18.40	0.024
Ulceration	3.40	1.80	6.42	<0.001
Scales/crusts	2.95	1.26	6.89	0.012
Polymorphic vessels	2.69	1.25	5.80	0.012
White collarette	0.02	0.00	0.30	0.005
Central white scar	0.00	0.00	n.c.	0.999
Necklace pinpoint vessels	0.00	0.00	n.c.	0.998
Vascular lacunae	0.02	0.00	0.123	<0.001

*Variables entered on step 1: age on visit, gender, body site, white collarette, Central white scar, necklace pinpoint vessels, comma vessels, vascular lacunae, linear vessels, in focus vessels (arborizing or short-fine), white follicles, erosions, ulceration, scales/crusts, polymorphic vessels, dotted vessels, negative network, papillomatous structures. CI = confidence interval; n.c. = not calculable; OR = odds ratio.

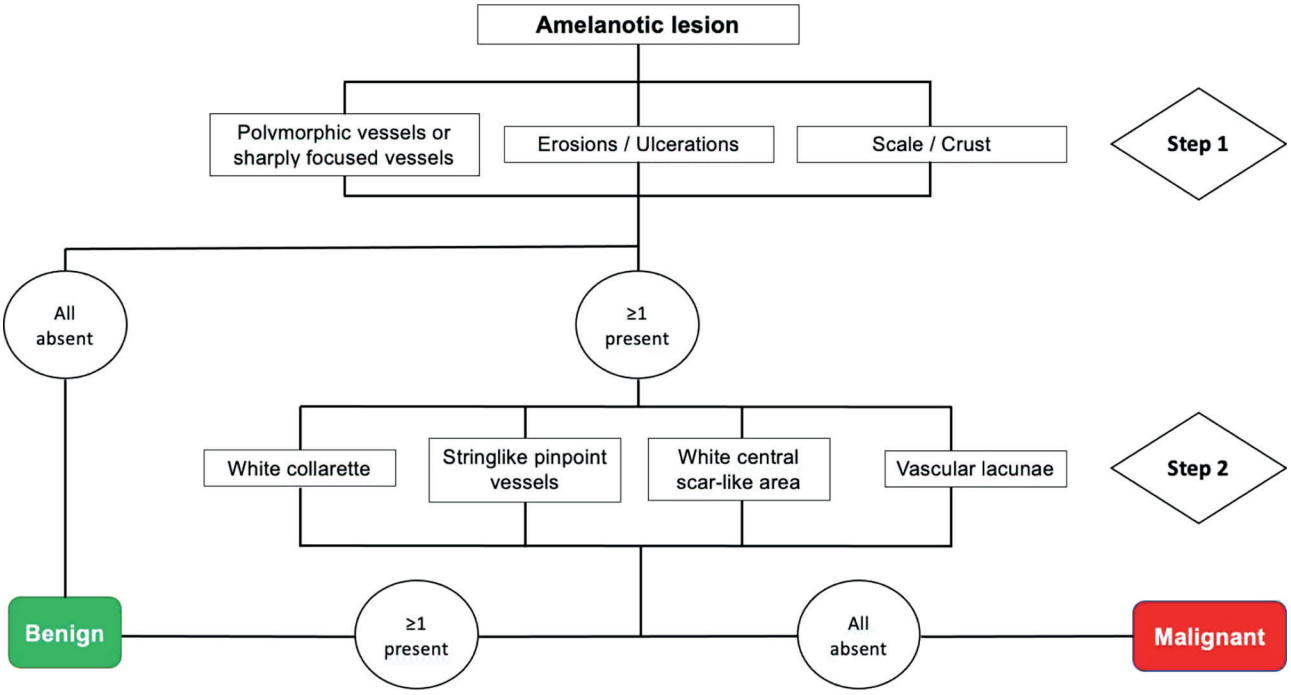

Figure 1. The 2-step-7-pink rule.

Dermoscopic criteria, independently and significantly associated with the final diagnosis (benign versus malignant) according to the multivariate logistic regression model, are reported in Table 2. Different algorithms were thus constructed combining these criteria, which were then evaluated by a panel of experts. A 2-step algorithm consisting of 7 criteria (2-step-7-pink rule) was chosen by consensus as the best in terms of ease of use and diagnostic accuracy (99.2% sensitivity and 75.2% specificity).

The first step of the 2S-7PR included 3 suspicious criteria: polymorphous or sharply focused vessels, scales or crusts and erosions or ulcerations. In of the event that all these criteria were absent, the lesion was considered benign, otherwise a second step was conducted evaluating 4 non-suspicious criteria (white collarette, white scar-like area, vascular lacunae, and necklace pinpoint vessels). If at least 1 of these criteria was present, the lesion was considered benign, otherwise it was classified as malignant. The stepwise approach of the 2S-7PR is shown in Figure 1 and exemplified in Figures 2-4.

2S-7PR Validation

The 2S-7PR algorithm was then validated by 2 external evaluators and its performance was compared with the prevalent

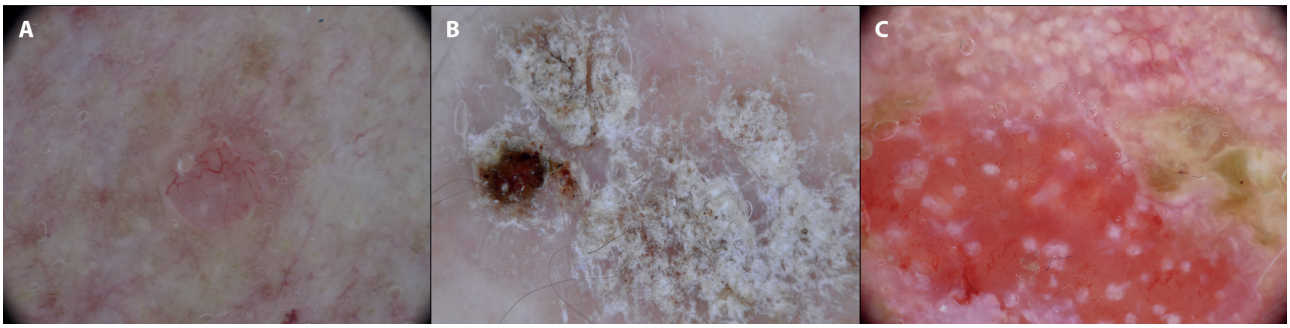

Figure 2. Malignant neoplasms of epithelial origin. (A) Basal cell carcinoma (BCC), (B) in situ squamous cell carcinoma (SCC), and (C) invasive squamous cell carcinoma. All lesions show malignant features, respectively sharply focused vessels for BCC, scale and crust for in situ SCC and scale and ulceration for invasive SCC. The absence of all four benign features identifies them as malignant lesions.

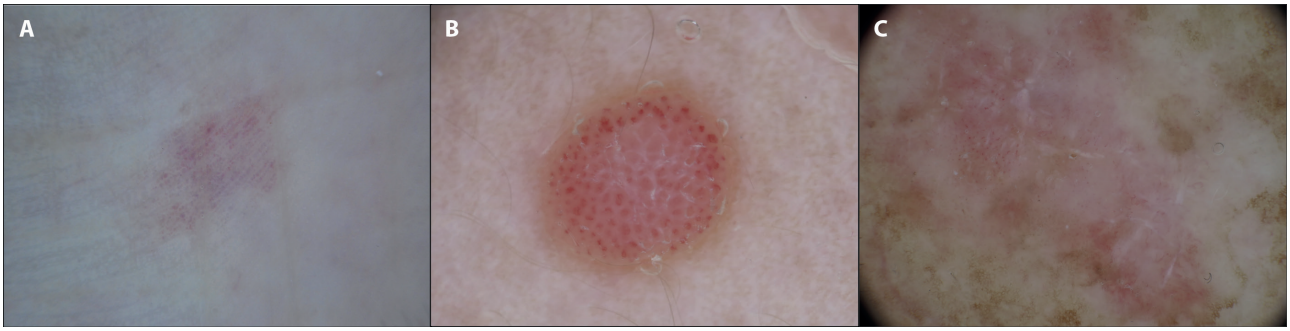

Figure 3. Melanocytic neoplasms. (A) Acral nevus, (B) Spitz nevus, and (C) invasive melanoma. The absence of all 3 malignant features identifies lesions A and B as benign. The presence of polymorphous (dotted, hairpin, linear irregular) vessels and the absence of benign features defines lesion in (C) as malignant.

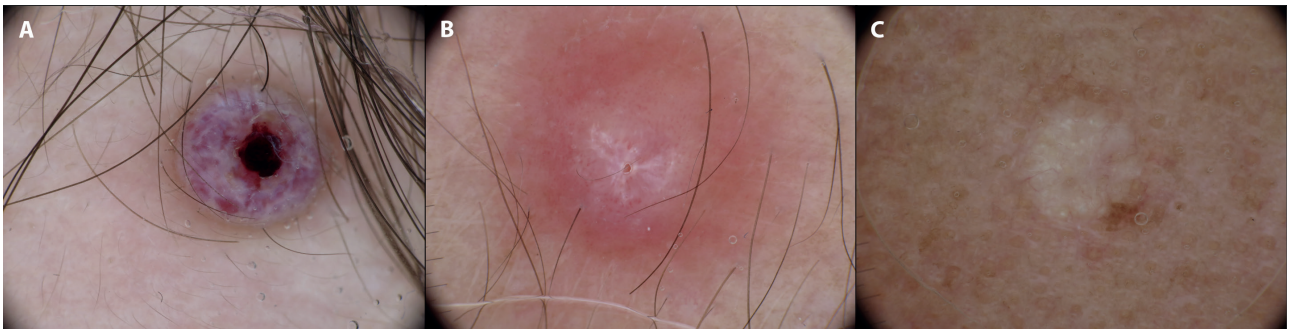

Figure 4. Miscellaneous benign lesions. (A) Angioma, (B) dermatofibroma, and (C) syringoma. The presence of (A) hematic crust and a (B) small central erosion require further evaluation, but (A) vascular lacunae and a (B) central scar-like area allow the observer to label both lesions as benign. The lesion in (C) shows no malignant features.

method. Interestingly, specificity levels of the 2S-7PR were higher than the prevalent method for both evaluators (expert: 81.8% vs 77.7% non-expert: 77.7% versus 71.5%), but only the experienced evaluator reached higher levels of sensitivity using the 2S-7PR approach compared to the prevalent method (expert: 96.0% versus 88.1% non-expert: 91.9% versus 92.7%)

In the test set similar results were obtained with higher levels of specificity for both evaluators when using the 2S-7PR as compared to the prevalent method (expert: 83.4% versus 76.9% non-expert: 75.0% versus 67.9%), and higher levels of sensitivity only for the expert evaluator (expert: 95.8% versus 91.1% non-expert: 90.3% versus 90.3%).

Conclusions

The present study further corroborates the significant contribution of dermoscopy in improving diagnostic accuracy,

when dealing with amelanotic skin lesions [18,19]. The development of the 2S-7PR rule, specifically, introduced a practical and easily operated algorithm capable of achieving very high levels of diagnostic accuracy (99.2% sensitivity and 75.2% specificity) in discriminating between benign and malignant pink neoplasms. Compared to the prevalent method, results showed increases in both sensitivity and specificity for the expert and only in specificity for the non-expert evaluator when using the 2S-7PR.

The complete absence of pigmented structures in amelanotic neoplasms deprives clinicians of a valuable source of information. As a result, the diagnosis of these lesions can be very challenging from both a clinical and dermoscopic standpoint. The formulation of a new algorithm specifically tailored to pink lesions was driven by the need for a diagnostic approach that would be at once accurate and accessible to experts as well as novices.

Nowadays, the dermoscopic assessment of these problematic lesions can rely on a very limited number of algorithms and scoring systems.

A clinically practical model for distinguishing malignant from non-malignant lesions lacking significant pigment was proposed in 2008 by Menzies et al [1] The authors utilized a total of 11 dermoscopic features, 4 benign (score -1) and 7 malignant (score +1), to describe each lesion with a numerical score. Sensitivity and specificity were tested using 2 different thresholds. The high sensitivity model required a non-negative total score (≥0) to diagnose a neoplasm as malignant with 97% sensitivity and 41% specificity, resulting in an increased chance of excision for malignancies at the expense of an overtreatment of benign lesions. On the other hand, the high specificity model required a positive total score (≥1) for the diagnosis of a malignant tumor with a sensitivity of 77% and a specificity of 79%. This significant reduction in sensitivity has an alarming implication in the potential underdiagnosis of a relatively high number of malignant neoplasms, especially when the user is a physician less experienced in dermoscopy.

In 2013, Giacomel et al [16] introduced a 3-step algorithm for pink tumors. Patient history and clinical features were preliminarily used to determine whether the lesion was part of an infectious/inflammatory disease or neoplastic. In the latter case, the tumor would be described with regard to vessel morphology (step 1), vessel arrangement and architectural pattern (step 2) and additional dermoscopic features such as ulceration or residual pigment (step 3). This helpful approach prioritized the identification of different types of vessel shape and distribution within the lesion, a result which requires a certain degree of experience in dermoscopy and is sometimes not feasible, since vascular features are not always clear.

In a recent study by Russo et al [17], the authors devised a diagnostic algorithm for amelanotic and hypopigmented lesions based on the recognition of the prevalent feature, defined as the most representative dermoscopic characteristic and/or the feature covering more than 40% of the lesion surface. The prevalent criterion was selected from among 17 dermoscopic features comprising 7 non-suspicious and 10 suspicious criteria. The main purpose of this method was pragmatic, namely, the identification of "suspicious" lesions having surgical excision as the suggested management (including Spitz/Reed nevi and pyogenic granuloma), and results showed high diagnostic accuracy (93.2% sensitivity and 83.1% specificity).

The 2S-7PR has the advantages of being an accurate algorithm, specifically developed on a population of completely amelanotic lesions, and of being a user-friendly tool, since it includes morphological criteria, such as ulceration, sharply focused vessels, and vascular lacunae, which are easily recognizable and reproducible among observers. The population was also representative of real-life epidemiology, given the high percentage of squamous and basal cell carcinomas.

Despite the interesting findings and the practical implications, this study is not without limitations. Its retrospective nature may entail some selection biases. Lesions without photographic documentation were obviously not included, leading to missing data. Lesions used to develop the algorithm had either been excised or selected for longitudinal examination, leading to a possible over-representation of clinically and dermoscopically "difficult" lesions. Furthermore, dermoscopic images were acquired using contact glass plate photographic devices: despite the application of ultrasonography gel to reduce compression, some vascular structures were undoubtedly hidden by the pressure applied on the skin.

The present study showed that the introduction of an algorithm focused on a few easily recognizable criteria could improve diagnostic accuracy in the management of pink lesions, at the same time making it more accessible to physicians less experienced in the field of dermoscopy.

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