Differentiation of combined nevi and melanomas: Case-control study with comparative analysis of dermoscopic features

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Summary

Background and objectives: Combined nevi (CN) show two or more components of major nevus subtypes and simulate melanomas. We investigated a panel of dermoscopic features and three dermoscopic algorithms for differentiating CN from melanomas.

Patients and methods: Retrospective, blinded case-control study using dermoscopic images of 36 CN and 36 melanoma controls. Twenty-one dermoscopic features validated for the diagnosis of melanocytic lesions, the number of colors, and three dermoscopic algorithms were investigated (ABCD rule of dermoscopy, Menzies scoring method, 7-point checklist).

Results: Five of seven features indicative of nevi were observed significantly more frequently in CN than in melanomas (all \( p < 0.05 \)) and two were exclusively found in CN. Eleven out of 14 features indicative of melanomas were observed significantly more frequently in melanomas than in CN (all \( p < 0.03 \)) and five were exclusively found in melanomas. The mean (± SD) number of colors in CN was lower than in melanomas (2.1 ± 0.6 versus 3.4 ± 0.7; \( p < 0.001 \)). Among tested algorithms the ABCD rule of dermoscopy performed best (sensitivity 91.7 %, specificity 77.8 %).

Conclusions: The ABCD rule of dermoscopy differentiated CN from melanomas most efficiently. Additional knowledge of dermoscopic features to be expected exclusively in either CN or melanomas should help dermatologists to make a correct clinical diagnosis.

Introduction

Dermoscopy is a helpful tool for the differentiation of benign nevi and cutaneous melanomas [1–4]. As shown in previous meta-analyses, dermoscopy markedly improves the sensitivity and specificity of melanoma diagnosis in comparison to examination with the unaided eye [5–7]. While the sensitivity of melanoma detection may be decreased with melanomas that do not (yet) show the typical dermoscopic traits, the specificity (true-negative rate) may be hampered by benign melanocytic nevi mimicking cutaneous melanomas. Among these benign “melanoma simulators” (pigmented) Spitz nevi and combined nevi (CN) are frequently encountered upon histopathological examination [8].

The current definition of CN was largely adapted from the first two large case series reported in 1977 [9, 10]. According to the present histopathological definition, CN show two or more different types of nevus components in one lesion. The various nevus components may be derived from the three major groups of nevi, i.e. common nevi, blue nevi, and Spitz nevi. In a recent histopathological analysis of 180 CN, the most frequent combination was that of a common nevus and a blue nevus (79.4 %), followed by a common nevus and a Spitz nevus (18.3 %), while only 2.2 % of cases showed the combination of a blue nevus and a Spitz nevus [11].
A correct preoperative diagnosis of CN is rarely given in the clinic. In the study of Scolyer et al. this was the case in only 2.4% of lesions [11]. Most clinicians suspected either “melanoma” or “dysplastic nevus” due to the presence of multiple colors, asymmetry, raised nodules within flat lesions, and/or a history of recent change [11]. Case series of CN describing the results of dermoscopic examinations are rare. De Giorgi et al. investigated the dermoscopic features of CN in a small series of only 15 cases [8]. However, verification bias may limit the reported results as the two dermoscopy experts in this study were not blinded to the histopathological diagnosis. Until today, there are no direct head-to-head comparative studies investigating the differences in dermoscopic patterns between CN and cutaneous melanomas.

The aim of our case-control study was to compare the dermoscopic features of CN to those of cutaneous melanomas as controls in a blinded fashion, and to statistically assess the discriminative power of these features.

Materials and Methods

Retrieval of cases

In this multicenter case-control study, data from 36 histopathologically confirmed CN (exemplified in Figure 1) that were diagnosed over a period of six years (December 2011–January 2018) were retrospectively collected from the dermatology departments of the university medical centers of Heidelberg (UKH) and Göttingen (UKG), and from the Department of Dermatology II, Medical Center Thalkirchner Strasse in Munich (MCM). The study was approved by the local ethics committee and performed in accordance with the principles of the Declaration of Helsinki. The data were obtained by searching histopathological and dermoscopic image databases for the diagnosis “combined nevus”. Cases retrieved from histopathological databases were included when corresponding dermoscopic images of sufficient quality were available. Cases retrieved from dermoscopic image databases were included whenever a histopathological report confirming the diagnosis of a CN was available. In non-excised lesions (2 of 36 cases), lesions were required to be unanimously diagnosed as CN (clinically and dermoscopically) by two experts (CF, FT) with unremarkable follow-up examinations.

Moreover, data and dermoscopic images of 36 histopathologically confirmed cutaneous melanomas were collected as controls from image repositories of the departments of dermatology at UKH and MCM.

Morphological matching of melanomas

All CN in this study showed unstructured homogeneous blue or blue-gray areas (Figure 1). We aimed to exclude this frequent morphological feature of CN from becoming a key distinctive feature in comparison to melanomas. To this end, all melanoma cases were positively selected for the dermoscopic presence of gray-blue areas (feature #8) so as to visually match the appearance of CN in this study. With this approach we “deactivated” the discriminatory power of homogeneous blue areas, and thus ruled out an erroneous simple differentiation of CN from superficial spreading or lentigo maligna melanomas (which are mostly negative for this dermoscopic feature).

Assessment of dermoscopic features

The attribution of dermoscopic features to each of 36 combined nevi and 36 melanomas was performed in a blinded fashion by two dermatologists experienced in dermoscopy (AS, HAH) within a randomly composed dermoscopic image set (n = 72 images). In the first round of analysis each dermoscopic image was assessed for the presence or absence of 21 dermoscopic features. Seven features [1, 12] have been...
described previously as indicative of nevi: (1) unstructured homogeneous pigmentation, (2) delicate regular network, (3) homogeneous intensity of pigmentation, (4) regularly arranged brown globules, (5) thinning-out borders (overall), (6) symmetry of shape in one axis, and (7) symmetry of shape in > 1 axis. Fourteen features [1, 12] have been described previously as indicative of melanomas: (8) gray-blue areas, (9) negative network, (10) broadened-irregular network, (11) irregular intensity of pigmentation, (12) irregularly arranged brown globules, (13) irregularly arranged black dots, (14) radial streaming/pseudopods, (15) border ends abruptly (partly), (16) border ends abruptly (overall), (17) borders thin out (partly), (18) asymmetry of shape, (19) atypical vascular patterns, (20) regression patterns and (21) ulceration. While all aforementioned features were qualitatively assessed for their presence or absence in each lesion, we added one quantitative feature, namely (22) number of colors.

In the second round of analysis, the dermoscopic features attributed to each case were used to apply three further diagnostic dermoscopic algorithms validated for the differentiation of benign nevi and melanoma, i.e. Menzies scoring method [13], ABCD rule of dermoscopy [14], and the 7-point checklist [15]. For the ABCD rule of dermoscopy, a total dermoscopic score (TDS) of > 4.75 was used as a cut-off to raise the suspicion of melanoma.

Statistical evaluation

Statistical analysis was performed with IBM® SPSS® Statistics version 25 (IBM North America, NY, USA) and R version 3.4.2 (R Foundation for Statistical Computing, Vienna, Austria). The data were prospectively entered and stored in a Microsoft Excel database (Microsoft, Redmond, WA, USA). Plausibility, accuracy, and completeness were verified.

We determined the overall frequency of each dermoscopic criterion in the study set and then calculated the proportion of melanomas in which a given criterion was present (sensitivity) and the proportion of CN in which a given criterion was absent (specificity). The accuracy was calculated as the sum of true-positive and true-negative diagnoses divided by the number of all cases. Moreover, the diagnostic performance of the dermoscopic algorithms was also assessed by calculating the aforementioned statistical parameters. The diagnostic performance of algorithms resulting in a quantitative score (continuous variable) with a defined cut-off for the diagnoses of melanoma (ABCD rule of dermoscopy, 7-point checklist) was further assessed by plotting receiver operating characteristic (ROC) curves and calculating the area under the curve (AUC). P-values were calculated with Fisher’s exact test or a two-sided Student’s t-test to evaluate the statistical significance of the association between each categorical or numerical variable and the histopathological diagnosis, respectively. P-values < 0.05 were considered to indicate statistical significance. In addition, the most relevant dermoscopic features were analyzed with multivariate logistic regression analysis after stepwise variable selection by p-value. Three thresholds (< 0.05, < 0.1, and < 0.2) were used as stopping criteria for the variable selection.

Results

Characteristics of patients and lesions

Combined nevi (n = 36) were found in 36 patients (63.9 % male) with a mean age (± SD) of 42.7 (± 22.5) years (Table 1). Out of 34 cases that were validated by histopathology, the most frequent combination was that of a common (compound) nevus with a blue nevus (32 of 34, 94.1 %). Two cases showed other forms of combination. One was combination of a common (compound) nevus with a pigmented Spitz nevus and another was a common (compound) nevus with a deep penetrating nevus. In two cases the diagnosis of CN was based on the clinical and dermoscopic examinations and further supported by an uneventful dermoscopic follow-up. Non-excised CN was observed in a 5-month-old and a six-year-old male patient. The majority of CN was either located on the trunk (44.4 %) or on the face (30.6 %).

Melanomas (n = 36, all invasive) were originally observed in 36 patients (58.3 % male) with a mean age (± SD) of 61.4 (± 13.1) years (Table 1). Melanoma histotypes included superficial spreading melanomas (SSMs, 86.1 %) and nodular melanomas (NMs, 13.9 %), and the mean (± SD) Breslow thickness was 1.3 mm (± 0.7 mm). Most melanomas were localized on the trunk (55.6 %) and upper extremities (25 %).

Dermoscopic features of CN versus melanomas

All 72 dermoscopic images of CN and melanomas were randomly combined into one image set and then assessed for 22 dermoscopic criteria (Table S1a–b, online supplement only). While 21 features were qualitatively assessed for their presence or absence in each lesion, we also included one quantitative feature that addressed the number of colors (Table S1a–b, online supplement only). As mentioned in the Methods section, all combined nevi showed areas of unstructured homogeneous (blue) pigmentation (feature #1) which causes a morphological overlap with gray-blue areas (feature #8) as found in melanomas (Figure 1). As we had selected melanoma controls for the presence of gray-blue areas, features #1 and #8 were also found positive in all melanomas (Table S1a–b, online supplement only), thus abolishing the discriminative power of this feature.
Five out of seven features indicative of nevi were significantly more frequent in CN than in melanomas (all \( p < 0.05 \)) and two of these features (homogeneous intensity of pigmentation, regularly arranged brown globules) were never observed in melanomas (Figure 2a). At the same time, 11 out of 14 features indicative of melanomas were significantly more frequent in melanomas than in CN (all \( p < 0.03 \)) and five of these features were found exclusively in melanomas (irregularly arranged black dots, regression patterns, broadened-irregular network, negative network, ulceration) (Figure 2b).

The mean (± SD) number of colors in CN (2.1 ± 0.6) was significantly lower than in melanomas (3.4 ± 0.7; \( p < 0.001 \)).

**Application of validated dermoscopic algorithms**

In addition to analyzing the individual dermoscopic features, we also applied three established and validated dermoscopic algorithms designed for the detection of melanoma, namely the ABCD rule of dermoscopy [14], the 7-point checklist [15], and the Menzies scoring method [13]. For the ABCD rule of dermoscopy a total dermoscopy score (TDS) of > 4.75 was used as a cut-off to raise the suspicion of melanoma. The best result with regard to accuracy (sum of true-positive and true-negative diagnoses divided by the number of all cases) was attained by the ABCD score of dermoscopy (84.7 %; 95 % CI [74.7 %–91.3 %]), followed by the 7-point checklist (75 %; 95 % CI [63.9 %–83.6 %]), and the Menzies scoring method (73.6 %; 95 % CI [62.4 %–82.4 %]).

The ABCD score of dermoscopy, 7-point checklist, and Menzies scoring method yielded a sensitivity and specificity of 91.7 % (95 % CI [78.2 %–97.1 %]) and 77.8 % (95 % CI [61.9 %–88.3 %]), 100 % (95 % CI [90.4 %–100 %]) and 50 % (95 % CI [34.5 %–65.5 %]), and 100 % (95 % CI [90.4 %–100 %]) and 47.2 % (95 % CI [32.0 %–63.0 %]).

### Table 1 Patients ‘and lesions’ characteristics.

|                      | Melanomas (n = 36) | Combined nevi (n = 36) |
|----------------------|--------------------|------------------------|
| **Gender**           |                    |                        |
| Male                 | 21 (58.3 %)        | 23 (63.9 %)            |
| Female               | 15 (41.7 %)        | 13 (36.1 %)            |
| **Age**              |                    |                        |
| Mean                 | 61.4               | 42.7                   |
| SD                   | 13.1               | 22.5                   |
| **Subtype**          |                    |                        |
| SSM                  | 31 (86.1 %)        | –                      |
| NM                   | 5 (13.9 %)         | –                      |
| **Combined Nevi**    |                    |                        |
| Compound + blue nevus| –                   | 32 (94.1 %)            |
| Compound + Spitz nevus| –                   | 1 (2.9 %)              |
| Compound + deep penetrating nevus | – | 1 (2.9 %) |
| **Breslow thickness (mm)** |               |                        |
| Mean                 | 1.3                | –                      |
| SD                   | 0.7                | –                      |
| **Localization**     |                    |                        |
| Scalp                | 2 (5.6 %)          | –                      |
| Face                 | –                   | 11 (30.6 %)            |
| Trunk                | 20 (55.6 %)        | 16 (44.4 %)            |
| Upper Extremity      | 9 (25.0 %)         | 3 (8.3 %)              |
| Lower Extremity      | 5 (13.9 %)         | 6 (16.7 %)             |

**Abbr.:** SD, standard deviation; SSM, superficial spreading melanoma; NM, nodular melanoma.
respectively. In a pairwise statistical comparison with McNemar’s test, the specificity of the ABCD score of dermoscopy was significantly higher than the Menzies score ($p = 0.003$) and the score of the 7-point checklist ($p = 0.006$). At the same time we found no significant differences between the sensitivities of the three diagnostic algorithms (all $p > 0.250$).

We also compared the diagnostic performance of algorithms that provide a quantitative score (continuous variable) with a defined cut-off for the diagnoses of melanoma (ABCD rule of dermoscopy, 7-point checklist) by plotting receiver operating characteristic (ROC) curves and calculating the area under the curve (AUC) (Figure 3). A pairwise statistical comparison with the method of Hanley et al. [16] did not reveal a significant difference ($p = 0.448$) between the ROC AUC of the ABCD rule of dermoscopy (AUC 0.935; 95 % CI [0.878–0.992]) and the 7-point checklist (AUC 0.964; 95 % CI [0.927–1]).

**Multivariate logistic regression analysis**

In order to determine the most relevant dermoscopic features for the differentiation of combined nevi and melanomas, we conducted a multivariate logistic regression analysis after stepwise variable selection by $p$-value. To this end, different thresholds ($< 0.05$, $< 0.1$, $< 0.2$) were used as stopping criteria. At the more stringent thresholds of $< 0.05$ and $< 0.1$, three features remained in the final model (Table 2). A higher number of colors ($p = 0.001$) and the feature “irregularly arranged brown globules” ($p = 0.002$) were independently and significantly associated with the diagnosis of melanoma, while the feature “symmetry of shape in $> 1$ axis” was associated with the diagnosis of combined nevi ($p = 0.011$). At a lower threshold of $< 0.2$ two more features were included into the final model, i.e. “irregular intensity of pigmentation” and “regular delicate network”. Of note, no valid $p$-values could be calculated for a number of features that were found exclusively either in melanomas (irregularly arranged black dots, regression patterns, broadened-irregular network, negative network, ulceration) or in CN (homogenous intensity of pigmentation, regularly arranged brown globules), thus preventing their inclusion in the regression model. Nevertheless, these features represent important indicators for the differentiation of CN and melanomas.

**Discussion**

The combination of two or more different types of melanocytic nevi in a single lesion was defined as a combined nevus (CN) and is frequently misdiagnosed as melanoma on the basis of clinical and dermoscopic examination [11]. With our study we aimed at systematically investigating the validity of 22 dermoscopic criteria and three established diagnostic algorithms for their performance in differentiating CN from melanoma.

Several aspects of our approach are unique in comparison to earlier studies. First, we chose a case-control study design and matched melanoma controls morphologically to CN cases by requiring melanomas to show blue-gray areas that were
also present in all CN. With this strategy, prominent blue-gray areas in CN lost their discriminative effect and we attained a set of dermoscopic images well-suited to comparative analysis of dermoscopic features and algorithms. In contrast, the only previous dermoscopic case series investigated 15 CN and focused solely on a descriptive analysis of dermoscopic features [8]. While these results may be helpful to uncover frequent dermoscopic features of CN, clinicians did not learn which features could be used to safely differentiate CN and melanomas. Secondly, we applied a predefined panel of 22 dermoscopic features and three established algorithms in our study, all validated for the differentiation of nevi and melanomas. This approach allowed us to make a systematic statistical evaluation, while others had used rather ill-defined narrative descriptions of dermoscopic findings for each case [8, 17–21].

Thirdly, we combined CN cases and melanoma controls in one randomly composed image set which was rated for the presence or absence of dermoscopic features by two experienced readers (consensus board) in a blinded fashion. Unlike one earlier study that reported results of an unblinded assessment of dermoscopic features in CN [8], our strategy helped to exclude a possible verification bias that might have influenced results by a tendency to detect nevus-associated features in CN and melanoma-associated features in melanomas.

Our analyses revealed a number of single dermoscopic features that were found exclusively in either CN or melanomas. These features may provide important clues for clinical differentiation of both entities. A homogeneous intensity of pigmentation or regularly arranged brown globules was observed exclusively in CN and never in melanomas, while

Figure 3 Receiver operating characteristic (ROC) curve of dermoscopic algorithms that provide a quantitative score (7-point checklist, ABCD rule of dermoscopy). The circles indicate the point of operation of each dermoscopic algorithm (blue circle: 7-point checklist [sensitivity 100 %, specificity 50 %]; green circle: ABCD rule of dermoscopy [sensitivity 91.7 %, specificity 77.8 %]). The area under both ROC curves showed no significant difference (7-point checklist ROC AUC 0.964 versus ABCD rule of dermoscopy ROC AUC 0.935, p = 0.448).

Table 2 Results of multivariate logistic regression analysis.

| Dermoscopic feature                       | OR    | 95 % CI        | p      |
|------------------------------------------|-------|----------------|--------|
| Number of colors                         | 25.82 | [5.37–479.31]  | 0.002  |
| Irregularly arranged brown globules      | 62.30 | [7.42–1690.06] | 0.002  |
| Symmetry of shape in > 1 axis            | 0.01  | [0.0002–0.22]  | 0.011  |

Only dermoscopic features with p-values below the threshold of p < 0.05 were entered into the multivariate regression model. Using a less stringent threshold of p < 0.1 did not change the depicted results.
irregularly arranged black dots, regression patterns, broadened-irregular network, negative network, or ulcerations were only observed in melanomas and never in CN. Some other features were observed in both entities, but were significantly more frequent in either CN or melanomas. For these features our multivariate regression analysis suggested a significant association of “symmetry of shape in > 1 axis” with a diagnosis of CN. In contrast, a higher number of colors or irregularly arranged brown globules was observed significantly more often in melanomas. Combined knowledge of the exclusive criteria and criteria that were significantly more frequent in either entity should help the dermatologist to make a correct clinical diagnosis.

We also compared three dermoscopic algorithms for their performance in differentiating CN and melanomas, namely the ABCD rule of dermoscopy [14], the 7-point checklist [15], and the Menzies scoring method [13]. Our data revealed a superior performance of the ABCD rule of dermoscopy (significantly higher specificity at a comparable sensitivity). With this algorithm, 28 of 36 CN (77.8 %) and 33 of 36 melanomas (91.7 %) were correctly identified. The specificity of both of the other algorithms was only around 50 %, thus leading to many false-positive results with (potential) unnecessary excision in half of the CN cases.

Our study had some limitations. First, this case-control study included only one CN with a Spitz nevus component. In agreement with the study by de Giorgi [5] this case was classified as being malignant when applying the ABCD rule of dermoscopy and other algorithms. Therefore, our results may be useful for differentiating CN with a blue nevus component from melanomas, but may not be generalized to other nevus combinations, especially not to combinations including a Spitz nevus component. Moreover, as histopathological differentiation of a Spitz nevus component from a melanoma component within a nevus may also be difficult, we always recommend complete excision for such lesions. Secondly, despite the fact that this study reports on the largest dermoscopic collection of CN cases, it would be desirable to confirm our results with larger clinical studies in future. Thirdly, the histopathological diagnosis of CN was made at the three participating centers without further confirmation by a central review board. While all dermatopathologists involved agreed with the common definition of CN (as given in this manuscript), this approach may have introduced some level of heterogeneity.

In conclusion, this first head-to-head comparative study of dermoscopic features in CN and melanomas showed that the majority of CN cases may be correctly differentiated from melanomas by using the ABCD rule of dermoscopy or by knowledge regarding dermoscopic features that are expected to be exclusively or significantly more frequent in either diagnosis.

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