Actas Dermosifiliogr. 2008;99:380-9

ORIGINAL ARTICLES

Correlation Between Clinical, Dermatoscopic, and Histopathologic Variables in Atypical Melanocytic Nevi

A. M. Morales-Callaghan,[a] J. Castrodeza-Sanz,[b] G. Martínez-García,[c] I. Peral-Martínez,[c] and A. Miranda-Romero[a]

[a]Servicio de Dermatología, [b]Servicio de Medicina Preventiva, and [c]Servicio de Anatomía Patológica, Hospital Clínico Universitario de Valladolid, Valladolid, Spain

Abstract. *Introduction.* Atypical melanocytic nevi are acquired melanocytic lesions that were described for the first time by Clark in studies of melanocytic nevi in patients with melanomas. Today, the use of dermatoscopy has made identification of this type of nevus much easier.

Objective. Our aim was to study the correlation between the clinical, dermatoscopic, and histopathologic findings of melanocytic nevi and compare our findings with those of previous studies. We also aimed to investigate the value of dermatoscopy for identifying atypical melanocytic nevi.

Material and methods. In this cross-sectional, observational study, 200 melanocytic lesions were analyzed in 166 patients examined between January 1, 2005 and December 31, 2005. We recorded the clinical, dermatoscopic, and histopathologic characteristics of each lesion and established the correlation between the different findings on a case-by-case basis. We then determined the agreement between diagnoses and assessed the value of dermatoscopy for identifying atypical melanocytic melanoma.

Results. The clinical characteristics associated with atypical histology were a macular component ($P<.001$), irregular borders, and presence of 3 or more colors. Asymmetry, diameter greater than 5 or 6 mm, and progression were not associated with atypical histopathologic characteristics ($P>.05$). Agreement between clinical and histologic diagnosis was weak ($\kappa=0.38$), whereas the agreement between dermatoscopic and histologic diagnosis was moderate ($\kappa=0.52$). The area under the receiver operating characteristic curve for the model that included dermatoscopy was larger than that for the model that only included clinical data, and this difference was statistically significant.

Conclusions. Atypical clinical features were not found to correspond to atypical histology. Dermatoscopy improved the accuracy of clinical diagnosis of atypical melanocytic nevus.

Key words: atypical melanocytic nevus, dermatoscopy, correlation.

ESTUDIO DE CORRELACIÓN CLÍNICA, DERMATOSCÓPICA E HISTOPATOLÓGICA DE NEVUS MELANOCÍTICOS ATÍPICOS

Resumen. *Introducción*. Los nevus melanocíticos atípicos (NMA) son lesiones melanocíticas adquiridas descritas por primera vez por Clark en estudios de nevus melanocíticos (NM) en pacientes con melanomas. Actualmente, el uso de la dermatoscopia ha facilitado en gran medida la identificación de esta variante de nevus.

Objetivo. Estudiar la correlación entre los hallazgos clínicos, dermatoscópicos e histopatológicos de los NM a estudio y comparar nuestros resultados con trabajos previos. Establecer el valor de la dermatoscopia para la identificación de NMA.

Material y métodos. Estudio observacional, transversal de 200 lesiones melanocíticas correspondientes a 166 pacientes, llevado a cabo desde el 1 de enero de 2005 hasta el 31 de diciembre de 2005. Describimos las características clínicas, dermatoscópicas e histopatológicas de cada lesión y establecimos la correlación entre los diferentes hallazgos obtenidos, caso por caso. Posteriormente determinamos la concordancia entre

Correspondence:
Ana María Morales-Callaghan
C/ Barcelona, 67, 1ª
50017 Zaragoza, Spain
acallaghan@aedv.es

Manuscript accepted for publication September 14, 2007

diagnósticos y establecimos el valor de la dermatoscopia para la identificación de NMA.

Resultados. Las características clínicas que se asociaron a atipia histológica fueron componente macular (p < 0,001), bordes irregulares y presencia de tres o más colores. La asimetría, diámetro mayor de 5 o 6 mm o la evolución no se correspondieron con atipia desde el punto de vista histopatológico (p > 0,05). La concordancia entre diagnóstico clínico e histológico fue baja (índice kappa ponderado [Kp]: 0,38), mientras que entre diagnóstico dermatoscópico e histológico fue moderada (índice Kp: 0,52). Mediante curvas ROC (*receiver operating characteristic*) comprobamos que el modelo que contenía la dermatoscopia presentaba un incremento bajo la curva estadísticamente significativo respecto al modelo que sólo incluía los datos clínicos.

Conclusiones. La atipia clínica no es equivalente a atipia histológica. La dermatoscopia mejora la precisión del diagnóstico clínico de NMA.

Palabras clave: nevus melanocítico atípico, dermatoscopia, correlación.

Introduction

Atypical moles are acquired melanocytic lesions that were described for the first time by Clark et al[1] in a study of melanocytic nevi in patients with melanoma. This variant of mole is at the center of one of the hottest debates in the field of dermatology. It seems reasonable to accept the existence of a histologic variant of nevus with particular architectural and, more importantly perhaps, cytologic features that, while not exactly the "missing link" between nevus and melanoma, is associated with melanoma more frequently than other types of moles.[2,3] Various epidemiologic studies have shown a statistically significant correlation between the presence of clinically atypical moles and the risk of developing melanoma. While a single atypical mole, for example, has been associated with a 2-fold increased risk of developing melanoma, 10 or more moles have been associated with a 12-fold increased risk. Atypical moles, therefore, seem to be a marker for risk rather than a specific risk in themselves.[4-6] Atypical moles should be diagnosed exclusively on the basis of dermatopathologic findings as clinicopathologic findings have been generally found to be poorly correlated.[7,8] The term *atypical mole* has been gaining ground over other terms used to describe the same condition, including *dysplastic nevus*, *Clark nevus*, *B-K mole syndrome*, and even *familial atypical mole melanoma*.

The identification of atypical moles is much easier now thanks to the use of dermoscopy and the publication of findings related to characteristic dermoscopic patterns of these moles. The first of these studies was performed by Hoffman-Wellenhof et al[9] at the dermatology departments of the University of Graz, Austria, the University of Tübingen, Germany, and the University of Aquila, Italy. The researchers classified digital dermoscopic images of 829 atypical moles from 15 men and 8 women according to the predominant dermoscopic features identified. They first analyzed the structural features of the moles and classified them according to whether they had a reticular pattern, a globular pattern, a homogeneous pattern, or a combination of these patterns. Next, they classified them according to their pigmentation: central hypopigmentation or hyperpigmentation, eccentric peripheral hypopigmentation or hyperpigmentation, or multifocal hypopigmentation or hyperpigmentation. The outcome of this study was a dermoscopic classification system that is currently used worldwide.

It is known that the dermoscopic and histopathologic features of atypical moles are correlated and that each dermoscopic structure has a histopathologic equivalent.[10] The combined use of dermoscopy and conventional histopathology means that skin tumors can now be analyzed using separate yet complementary methods. Histologic sections, for example, provide a vertical view of lesions, while dermoscopic images provide a horizontal view of the entire lesion. This is why it is somewhat difficult to correlate dermoscopic and histopathologic findings with precision. Nonetheless, the complementary horizontal perspective offered by dermoscopy is a valuable addition to the findings offered by conventional histology.

Soyer et al[11] were the first to report a correlation between dermoscopic features and different histologic findings. Some years later, Yadav et al[12] published a study on the correlation between histopathologic findings and dermoscopic structures but they did not correlate their results on a case-by-case basis. Rather, they correlated the best clinical and dermoscopic examples for a particular finding with the best histology photomicrographs, but the data were not necessarily from the same patient.

In a later study, Soyer et al[13] published findings on the correlation between clinical and pathologic findings for pigmented skin lesions. They described the use of a standardized pathology protocol and digital dermoscopic images to assess the correlation on a case-by-case basis.

Although the method was highly sophisticated and precise, it did not allow for the direct correlation of histopathologic and dermoscopic findings by visual examination.

In a more recent study, Blum et al[14] used the atypical mole dermoscopic classification system to determine whether these pigmented lesions were benign or malignant. They retrospectively classified 254 suspicious melanocytic lesions from 205 patients on the basis of the dermoscopic classification system (which groups lesions according to their structural features: reticular, globular, or homogeneous patterns, or a combination of 2 of these) and the pigmentation of the lesions (uniform, central, and central or peripheral hypopigmentation or hyperpigmentation). They also added a new category, which was a combination of all 3 dermoscopic patterns in the same lesion. They found that reticular, globular, and homogeneous patterns were more common in moles that in melanomas but that the 3-structure pattern was more common in melanomas. They also found that uniform pigmentation and central hyperpigmentation were more common in moles, and that peripheral and multifocal hypopigmentation and hyperpigmentation were more common in melanomas. They concluded that dermoscopy was a useful tool for discriminating between benign and malignant lesions, and that lesions with 3 dermoscopic patterns or peripheral hyperpigmentation were more likely to be malignant.

In the most recent study of the correlation between dermoscopic and histopathologic findings, Bauer et al[15] retrospectively evaluated 301 equivocal pigmented lesions in 2 skin lesion clinics (Graz and Tübingen). In one of the centers, an initial diagnosis was made on the basis of clinical, histopathology, and, where necessary, immunohistochemical findings. In the other center, hematoxylin-eosin-stained sections, patient age and sex, tumor location, and dermoscopic images were analyzed. Two diagnoses were made: the first on the basis of clinical and histopathology findings alone and the second on the basis of clinical, histopathology, and dermoscopic findings. Agreement—measured using the κ statistic—was high between the initial diagnosis and the diagnosis based on clinical and histopathology findings only, but it was even higher when dermoscopic images were added. It therefore seems that dermoscopy is a useful tool for improving the diagnosis of equivocal melanocytic lesions.

We performed a cross-sectional, observational study of 200 melanocytic lesions, with a particular emphasis on atypical moles, in order to establish a correlation between clinical, dermoscopic, and histopathologic findings using descriptive statistical analysis. Because such a correlation has not been clearly established by any of the studies conducted to date, and because most of these studies have been retrospective, we set out to correlate findings for melanocytic nevi on a case-by-case basis.

Materials and Methods

We evaluated 200 melanocytic lesions from 166 patients. An initial diagnosis was proposed by 2 dermatologists at the dermatology department of our hospital following an analysis of clinical data and dermoscopic images. Both dermatologists had experience in dermoscopy. The study was performed between January 1, 2005 and December 31, 2005. Diagnosis in all cases was confirmed through a histopathologic study performed by a single pathologist from the pathology department.

We included randomly selected lesions that fulfilled both clinical and dermoscopic criteria for melanocytic lesions. We excluded lesions that were located on the palms or soles, on mucous membranes or the face, or under nails as these sites have characteristic anatomical features that produce dermoscopic images that are not comparable with images from other sites.

Diagnosis of melanocytic lesions was therefore based on clinical, dermoscopic, and histopathologic findings. The first step in the process was to construct a clinical history for each patient in accordance with a standardized protocol. The following data were collected: patient sex and age, skin phototype, location and clinical features of lesion (symmetry, borders, colors, length of long axis and short axis, the presence or not of a macular or papular component, lesion progression, and the presence or not of bleeding).

A presumptive clinical diagnosis was established on the basis of the data collected. Each lesion was then photographed using a digital camera (Olympus Camedia 5050, Olympus Imaging America Inc, Pennsylvania, USA) and immediately afterwards examined using a manual dermatoscope (Dermlite DL100; DIAGNISCAN Derma Instruments, Vienna, Austria). Images of the lesions were then captured using a DermLite FOTO system (DIAGNISCAN Derma Instruments) fitted to a digital Nikon Coolpix 4500 camera (Nikon Corporation, Tokyo, Japan) and stored using PhotoMAX 2.1 software (Derma Medical Systems, Vienna, Austria).

The following dermoscopic data were recorded for each lesion: structural pattern (globular, reticular, homogeneous, a combination of 2 of these, a combination of all 3 patterns, or no pattern) and type of pigmentation (uniform, central hyperpigmentation, peripheral hyperpigmentation, central hypopigmentation, peripheral hypopigmentation, or multifocal pigmentation). Diagnosis was based on the predominant dermoscopic pattern(s) and type of pigmentation. We also established the existence of asymmetrical structures and blue or whitish structures as these are closely associated with a diagnosis of melanoma.

Following examination of the dermoscopic data collected and evaluation of each image by 2 dermatologists with experience in dermoscopy, a presumptive diagnosis was established on the basis of the predominant dermoscopic pattern(s) using the pattern analysis diagnostic algorithm.

The lesions were excised once the clinical and dermoscopic diagnoses had been made. Samples for histologic analysis were taken immediately after clinical and dermoscopic examination. The entire lesion was excised in each case. The pathologist described the lesions using terminology proposed by the United States National Institutes of Health and established a pathologic diagnosis. All the lesions were examined by the same pathologist.

Statistical Analysis

All of the study data collected were entered into Microsoft Excel spreadsheet software and statistical analysis was performed using version 11.5 of the SPSS statistical package for Windows. Absolute frequencies and relative frequencies (expressed as percentages) were calculated for qualitative variables and means and SDs for quantitative variables.

Associations between different study categories were assessed using Pearson χ^2 contingency table analysis and analysis of variance was used for multiple comparisons. The level of statistical significance was set at a value of $P < .05$ and 95% confidence intervals (CI) were also calculated.

Contingency tables including the weighted κ statistic were used to analyze the level of agreement between clinical, dermoscopic, and histopathologic diagnoses. Level of agreement was determined on the basis of the value of the weighted κ statistic according to the following scale: 0-0.2, insignificant; 0.2-0.4, low; 0.4-0.6, moderate; 0.6-0.8, good; 0.8-1, very good.[16]

Finally, logistic regression models were applied to compare the value of dermoscopic diagnosis with respect to clinical diagnosis using histopathologic diagnosis as the criterion standard. We first developed univariate logistic regression models to determine which variables were significantly associated with the presence of atypical moles, and then applied different multivariate logistic regression models in which we sequentially included and excluded variables in accordance with their statistical significance and clinical importance until we obtained the best-fit model for predicting the presence of atypical moles.[17] We compared the validity of the different models using receiver operating characteristic (ROC) curves. Finally, because one of our aims was to assess the diagnostic value of dermoscopy, we compared the predictive power of the model that included clinical variables only with that of the model that included clinical and dermoscopic variables.

Results

Descriptive Analysis (Frequencies)

We studied 200 lesions from 166 patients: 64 (32%) male and 136 (68%) female. The age of the patients ranged from 8 to 84 years, with a mean (SD) age of 33.7 (14.5) years. The most common skin phototypes were types II (44% of patients) and III (41.5%). None of the patients had phototype VI. The most common lesion site was the trunk, with 155 lesions (77.5% of total), and particularly the back, with 106 lesions (53%).

Of the 200 lesions, 144 (72%) were asymmetrical and 56 (28%) were symmetrical. Forty-six lesions (23%) had regular borders and 154 (77%) irregular borders. The predominant colors were black, dark brown, and light brown; 96 lesions (48%) had 3 colors, 57 (28.5%) 2 colors, and 40 (20%) 4 colors. Only 1 lesion (0.5%) had just 1 color (black). Long-axis diameters of the lesions measured between 2 mm and 120 mm, with a mean (SD) size of 7.9 (8.6) mm, and short-axis diameters ranged from 1 mm to 70 mm, with a mean size of 5.1 (5) mm.

In total, 181 lesions (90.5%) had a macular component, compared to 125 lesions (62.5%) with a papular component. Correspondingly, 19 lesions (9.5%) had no macular component and 75 (37.5%) had no papular component. Both components were present in 106 lesions (53%) and either one or the other in 94 lesions (47%).

In terms of lesion progression, 154 lesions (77%) were considered to be clinically unstable (with changes reported by patients) while 34 lesions (17%) were considered to be stable. Lesion progression was unknown in 12 lesions (6%).

Seven (3.5%) of the lesions had presented bleeding at some stage, compared to 193 lesions (96.5%) which had not.

Clinical Features

1. Diameter. We did not find a statistically significant association between lesion diameter and either the presence or absence of histologic atypia (P>.05).
2. Borders. Clinically irregular lesion borders were observed in 85% of histopathologically confirmed atypical moles and in 67.1% of moles without atypia (common moles); this difference was statistically significant (P=.018).
3. Asymmetry. The correlation between asymmetry and histopathologic diagnosis was not statistically significant (P=.09) as the percentages of histopathologically confirmed atypical moles (79.2%) and common moles (62.8%) were very similar.
4. Colors. Sixty-eight percent of atypical moles had 3 or more colors, mostly black, dark brown, and light brown; 32% had 2 colors; 42%, 3 colors; 22%, 4 colors; and 4%, 5 colors.
5. Lesion progression. Lesion progression was evaluated subjectively by patients, with changes being reported in 71% of atypical moles and 81% of common moles.
6. Macular and papular components. All the atypical moles had a macular component, either in association with or

Table 1. Macular Components and Histopathologic Diagnosis[a,b]

Macular Component	Histologic Diagnosis								
	Atypical Moles	Common Moles	Congenital Nevus	Blue Nevus	Spitz/Reed Nevus	Nevus Spilus	Melanoma	Others	Total, No.
Yes	104	51	6	3	1	1	6	9	181
No	0	19	0	0	0	0	0	0	19
Total	104	70	6	3	1	1	6	9	200

[a]Data are expressed as absolute figures (No. of lesions).
[b]χ^2, 38.99; $P < .0001$.

Table 2. Dermoscopic Structures and Histopathologic Diagnosis[a]

Dermoscopic Patterns	Histologic Diagnosis								
	Atypical Moles	Common Moles	Congenital Nevus	Blue Nevus	Spitz/Reed Nevus	Spilus Nevus	Melanoma	Others	Total
Reticular	20	3	0	0	0	1	0	0	24
Globular-reticular	23	7	2	0	0	0	0	0	32
Reticular-homogeneous	17	10	0	0	0	0	1	2	30
Globular	6	6	1	0	0	0	0	1	14
Globular-homogeneous	10	29	2	0	1	0	1	1	44
Homogeneous	0	1	0	3	0	0	0	0	4
3-structure	28	13	1	0	0	0	3	1	46
Other	0	1	0	0	0	0	1	4	6
Total	104	70	6	3	1	1	6	9	200

[a]Data are expressed as absolute figures (No. of lesions).

independently of a papular component (Table 1). In contrast, 88.6% of common moles had a papular component, either in association with or independently of a macular component.

Dermoscopic Features

The predominant dermoscopic pattern in the atypical moles identified in our study was the 3-structure pattern (27.3%), followed closely by the reticular-globular pattern (22.1%), the reticular pattern (19.2%), and the combined reticular-homogeneous pattern (16.3%). The predominant pattern in moles without atypia was clearly the globular-homogeneous pattern (observed in 41.4% of all common moles). This was followed by the 3-structure pattern (18.6%) and the combined reticular-homogeneous pattern (14.3%) (Table 2).

The most common type of pigmentation in atypical moles was multifocal pigmentation (39.4%) (Figure 1), followed by central hyperpigmentation (17.3%), uniform pigmentation (15.3%), and peripheral hyperpigmentation (12.5%), all with similar percentages. The least common type of pigmentation was peripheral hyperpigmentation, seen in just 5.6% of the lesions (Figure 2).

Seventy-six percent of the moles with atypia had asymmetrical dermoscopic features, compared to 80% of those without atypia.

Finally, 43 (23%) of the 200 lesions studied had blue-whitish structures (not counting blue nevi). Of these, 51% were atypical moles (Figure 3); 18.6% were common moles; 14%, other types of lesions; 11.6%, melanomas; and 2.3%, congenital nevi.

Diagnostic Agreement

The level of agreement between clinical and histopathologic diagnosis was low, with a weighted κ statistic value of 0.38 (Table 3). There was clear diagnostic agreement between the 2 diagnostic methods for 68.7% of atypical moles; 25% of lesions that had been clinically diagnosed as atypical

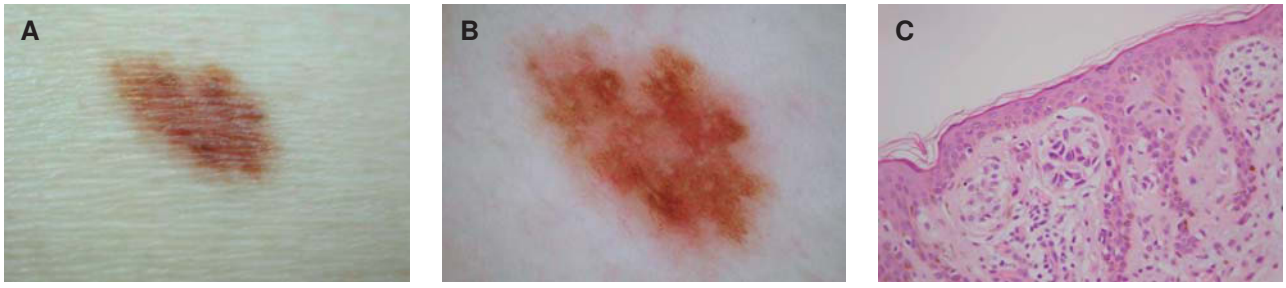

Figure 1. A, Clinical diagnosis: atypical mole. B, Dermoscopic diagnosis: atypical mole. C, Histopathologic diagnosis: melanocytic nevus with moderate atypia in the junctional component (hematoxylin–eosin, original magnification ×40).

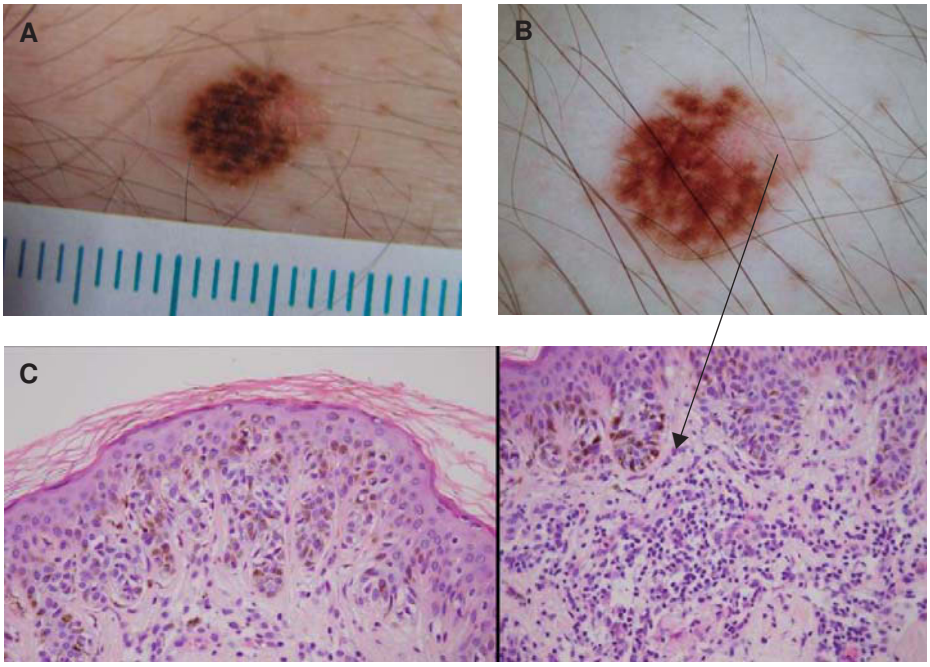

Figure 2. A, Clinical diagnosis: melanoma in situ. B, Dermoscopic diagnosis: melanoma in situ. C, Histopathologic diagnosis: melanocytic nevus with low-grade atypia. On the right (arrow), close-up of inflammatory infiltrate corresponding to area indicated in B (hematoxylin–eosin, original magnification ×40).

moles were actually common moles. The other false positive results corresponded to congenital nevus (n=2), Spitz/Reed nevus (n=1), melanoma (n=3), and other (n=1). The level of agreement between dermoscopic and histopathologic diagnosis, however, was greater, with a weighted κ statistic value of 0.52 (moderate agreement) (Table 4). Dermoscopy produced a true positive rate of 74.5% for atypical moles; 20.3% of the lesions were common moles while the others were congenital nevi (n=2), a Spitz/Reed nevus (n=1), and other (n=1).

Logistic Regression Models

On evaluating statistically significant associations between the study variables and the presence of atypical moles using univariate and multivariate logistic regression models, we found that age (odds ratio [OR] 0.98; 95% CI, 0.96-0.99; *P*=.045), atypical clinical features (OR, 5.2; 95% CI, 2.8-9.6; *P*<.0001), and atypical dermoscopic features (OR, 12; 95% CI, 6-24; *P*<.0001) were all significant predictors. Male sex (OR, 1.5; 95% CI, 0.8-2.7, *P*=.19) and fair skin (OR, 1.6; 95% CI, 0.9-2.7; *P*=0.12) were very close to statistical significance.

The final model was applied using dermoscopic variables alone, and following adjustment for other variables, this model was the only one that produced a statistically significant fit. The corresponding sensitivity and specificity were 69% and 85%, respectively.

Finally, we compared the ROC curves for clinical diagnosis alone and for clinical and dermoscopic diagnosis combined, following adjustment for age, sex, and skin

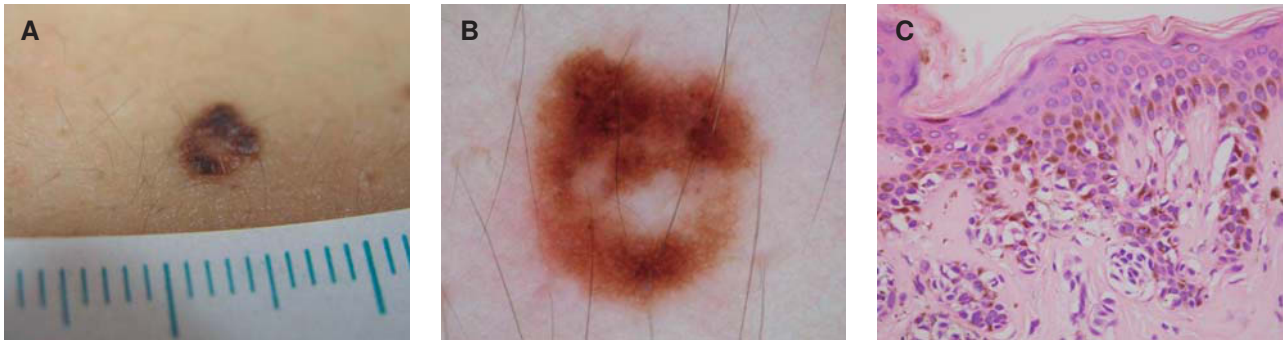

Figure 3. A, Clinical diagnosis: atypical mole. B, Dermoscopic diagnosis: atypical mole. Central area of regression. C, Histopathologic diagnosis: melanocytic nevus with moderate atypia in the junctional component (hematoxylin–eosin, original magnification, ×40).

Table 3. Diagnostic Agreement Between Clinical and Histopathologic Diagnosis[a,b]

Clinical Diagnosis	*Histologic Diagnosis*								
	Atypical Moles	*Common Moles*	*Congenital Nevus*	*Blue Nevus*	*Spitz/Reed Nevus*	*Spilus Nevus*	*Melanoma*	*Others*	*Total*
Atypical mole	77	28	2	0	1	0	3	1	112
Common mole	23	39	3	0	0	0	0	2	67
Congenital nevus	1	0	1	0	0	0	0	0	2
Blue nevus	1	1	0	3	0	0	0	0	5
Spitz/Reed nevus	1	0	0	0	0	0	0	0	1
Nevus spilus	0	0	0	0	0	1	0	0	1
Melanoma	1	1	0	0	0	0	3	3	8
Others	0	1	0	0	0	0	0	3	4
Total	104	70	6	3	1	1	6	9	200

[a]Data are expressed as absolute figures (No. of lesions).
[b]Weighted κ statistic, 0.38.

Table 4. Diagnostic Agreement Between Dermoscopic and Histopathologic Diagnosis[a,b]

Dermoscopic Diagnosis	*Histologic Diagnosis*								
	Atypical Moles	*Common Moles*	*Congenital Nevus*	*Blue Nevus*	*Spitz/Reed Nevus*	*Spilus Nevus*	*Melanoma*	*Others*	*Total*
Atypical mole	88	24	2	0	1	0	0	1	118
Common mole	12	43	3	0	0	0	2	1	59
Congenital nevus	1	0	1	0	0	0	0	0	2
Blue nevus	1	0	0	3	0	0	0	0	4
Spitz/Reed nevus	1	0	0	0	0	0	0	0	1
Nevus spilus	0	0	0	0	0	1	0	0	1
Melanoma	1	2	0	0	0	0	4	3	10
Others	0	1	0	0	0	0	0	4	5
Total	104	70	6	3	1	1	6	9	200

[a]Data are expressed as absolute figures (No. of lesions).
[b]Weighted κ statistic, 0.52.

phototype. Clinical and dermoscopic diagnosis had a greater area under the curve (AUC) than clinical diagnosis alone. The AUC was 0.720 for the clinical model and 0.785 for the dermoscopic model, and the difference (0.065) was statistically significant (Figure 4).

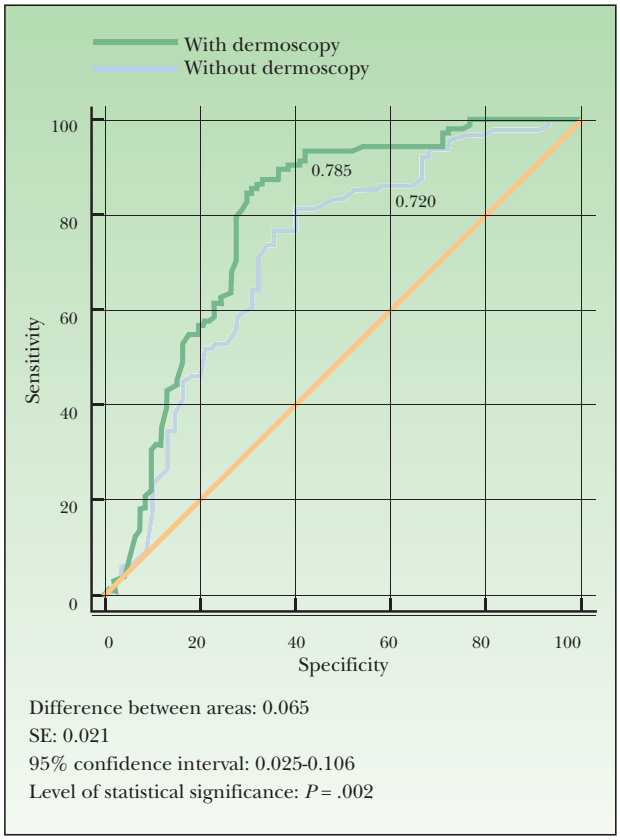

Figure 4. Comparison of receiver operating characteristic curves from models with and without dermoscopic variables.

Discussion

Various studies have shown that, in the case of melanocytic nevi, there is little correlation between histopathologic atypia and atypical clinical features (a diameter of more than 5 or 6 mm, ill-defined or irregular borders, the presence of several colors, and a combination of macular and papular components).[8,18,19] Indeed, the definition of an atypical mole should be exclusively pathologic, as the level of agreement between clinical and pathologic findings is generally low.[7,8]

In the present study, we analyzed each of the clinical features associated with atypical moles and studied their correlation with the presence or absence of histologic atypia.

To the best of our knowledge, nobody has analyzed the correlation between lesion diameter and atypia in melanocytic nevi since Clark et al.[1]

Nonetheless, on analyzing our findings and extrapolating results from other melanoma studies,[20] lesion diameter does not seem to be a reliable marker for melanocytic atypia. We believe, however, that lesion contour might be a reliable marker because irregular borders are more common in atypical moles and melanomas than in other types of melanocytic lesions.

On the basis of our findings, asymmetry cannot be considered a reliable indicator for distinguishing between atypical and common moles (*P*=.09). Nonetheless, like other authors,[21] we found that atypical moles had 3 or more colors (mostly black, dark brown, and light brown). Annessi et al[8] found that the atypical moles with a macular component had a greater level of dysplasia on histologic examination. We also found that a large proportion of the moles we studied had histologic dysplasia. It seems, therefore, in light of our findings and those of Annessi et al, that most atypical lesions have atypia in the junctional component, and this explains why moles with a macular component are more likely to be atypical than those with just a papular component. No reliable conclusions can be drawn on lesion progression from our study because it was evaluated subjectively by each patient. We do, however, believe that melanocytic lesions tend to progress naturally and change over time.

The identification of atypical moles is much easier now thanks to the use of dermoscopy and findings from studies designed to identify characteristic dermoscopic patterns.[9,14,22] We found that the predominant dermoscopic pattern in atypical moles was the 3-structure pattern; in moles without atypia, in contrast, it was clearly the combined globular-homogeneous pattern. The most common type of pigmentation in the atypical moles we analyzed was multifocal pigmentation. Authors such as Hoffmann-Wellenhof et al,[9] Blum et al,[14] and Fikrle and Pizinger[22] found differences in terms of predominant patterns and different types of pigmentation.

Asymmetrical dermoscopic structures and regression areas (blue-whitish structures) are both important features in the diagnosis of melanoma.[23-27] In our study, however, we did not find a good level of agreement between dermoscopic asymmetry and histopathologic atypia but we did find a statistically significant association between the presence of blue-whitish structures and histopathologic atypia (*P*<.001). We would like to stress how important it is for authors to clarify their definition of blue-whitish structures. In some cases, for example, the definition covers the blue-whitish veil (Zalaudek et al[25]), whereas in others it does not (Massi et al[23]).

While some studies have found clinical and histologic atypia to be significantly correlated,[7,28,29] other, more recent, studies have shown that this correlation is questionable in

many cases.[8,18,19,22,30] Annessi et al,[8] for example, on assessing the correlation between clinical atypia and histologic dysplasia using the weighted κ statistic, found that this correlation was not significant according to their criteria (κ=0.17). We also calculated the level of agreement between clinical, dermoscopic, and histopathologic diagnosis using the weighted κ statistic, and, like Annessi et al, found a low level of agreement (κ=0.38) between clinical and histopathologic diagnosis. The level of agreement improved considerably, however, when we compared dermoscopic and histologic diagnoses (κ=0.52, moderate level of agreement). It would therefore appear that dermoscopy improves diagnostic accuracy for atypical moles.

Finally, we wished to investigate whether the diagnosis of atypical moles could be improved in terms of sensitivity and specificity by adding dermoscopy to the diagnostic process, something which has proven to be the case for melanoma.[20,31-34] To do this, we developed multivariate logistic regression models, and on applying ROC curves, found that dermoscopy was a useful technique for discriminating between atypical and common moles, as the model that included dermoscopy had a significantly larger AUC than the model that did not.

We therefore conclude that, despite its limitations, dermoscopy is a useful tool for improving diagnostic accuracy in the area of melanocytic lesions. Our findings also suggest that it is a valuable tool for helping dermatologists working in routine clinical practice to diagnose atypical moles.

Acknowledgments

We thank all the members of the Dermatology Department at the Hospital Clínico Universitario de Valladolid for their invaluable help.

Conflicts of Interest

The authors declare no conflicts of interest.

References

1. Clark WHJ, Reimer RR, Greene M, Ainsworth AM, Mastrangelo MJ. Origin of familial malignant melanomas from heritable melanocytic lesions: the B-K mole syndrome. Arch Dermatol. 1978;114:732-8.
2. Koh HK. Cutaneous melanoma. N Engl J Med. 1991;325:171-82.
3. Tucker M, Fraser M, Goldstein A, Struewing J, King M, Crawford J. A natural history of melanomas and dysplastic nevi: an atlas of lesions in melanoma-prone families. Cancer. 2002;94:3192-209.
4. Holly EA, Kelly JW, Shpall SN, Chiu SH. Number of melanocytic nevi as a major risk for malignant melanoma. J Am Acad Dermatol. 1987;17:459-68.
5. Tucker MA, Halpern A, Holly AE, Hartge P, Elder DE, Sagebiel RW, et al. Clinically recognized dysplastic nevi: a central risk factor for cutaneous melanoma. JAMA. 1997;227:1439-44.
6. Shors AR, Kim S, White E, Argenyi Z, Barnhill RL, Duray P, et al. Dysplastic naevi with moderate to severe histological dysplasia: a risk factor for melanoma. Br J Dermatol. 2006;155:988-93.
7. Barnhill R, Roush G. Correlation of clinical and histopathologic features in clinically atypical melanocytic nevi. Cancer. 1991;67:3157-64.
8. Annessi G, Cattaruzza MS, Abeni D, Baliva G, Laurenza M, Macchini V, et al. Correlation between clinical atypia and histologic dysplasia in acquired melanocytic nevi. J Am Acad Dermatol. 2001;45:77-85.
9. Hoffman-Wellenhof R, Blum A, Wolf H, Piccolo D, KerlH, Garbe C, et al. Dermoscopic classification of atypical nevi (Clark nevi). Arch Dermatol. 2001;137:1575-80.
10. Braun RP, Kaya G, Masouyé I, Krischer J, Saurat JH. Histopathologic correlation in dermoscopy. A micropunch technique. Arch Dermatol. 2003;139:349-51.
11. Soyer HP, Smolle J, Hödl S, Pachernegg H, Kerl H. Surface microscopy: a new approach to the diagnosis of cutaneous pigmented tumors. Am J Dermatopathol. 1989;11:1-10.
12. Yadav S, Vossaert KA, Kopf AW, Silverman M, Grin-Jorgensen C. Histologic correlates of structures seen on dermoscopy (epiluminescence microscopy). Am J Dermatopathol. 1993;15:297-305.
13. Soyer HP, Kenet RO, Wolf IH, Kenet BJ, Cerroni L. Clinicopathological correlation of pigmented skin lesions using dermoscopy. Eur J Dermatol. 2000;10:22-8.
14. Blum A, Soyer HP, Garbe C, Kerl H, Rassner G, Hoffman-Wellenhof R. The dermoscopic classification of atypical melanocytic naevi (Clark naevi) is useful to discriminate benign from malignant melanocytic lesions. Br J Dermatol. 2003;149:1159-64.
15. Bauer J, Leinweber B, Metzler G, Blum A, Hofmann-Wellenhof R, Leitz N, et al. Correlation with digital dermoscopic images can help dermatopathologists to diagnose equivocal skin tumours. Br J Dermatol. 2006;155:546-51.
16. Fleiss JL. Statistical methods for rates and proportions. 2nd ed. New York: Wiley; 1981.
17. Hosmer DW, Lemeshow S. Applied Logistic Regression. New York: John Wiley & sons; 2000.
18. Andreassi L, Perotti R, Rubegni P, Burroni M, Cevenini G, Biagioli M, et al. Digital dermoscopy analysis for the differentiation of atypical nevi and early melanoma. A new quantitative semiology. Arch Dermatol. 1999;135:1459-65.
19. Seidenari S, Longo C, Giusti F, Pellacani G. Clinical selection of melanocytic lesions for dermoscopy decreases the identification of suspicious lesions in comparison with dermoscopy without clinical preselection. Br J Dermatol. 2006;154:873-9.
20. Bono A, Tolomio E, Trincone S, Bartoli C, Tomatis S, Carbone A, et al. Micro-melanoma detection: a clinical study on 206 consecutive cases of pigmented skin lesions with a diameter #< 3 mm. Br J Dermatol. 2006;155:570-3.
21. MacKie RM, Fleming C, McMahon AD, Jarret P. The use of the dermatoscope to identify early melanoma using the three-colour test. Br J Dermatol. 2002;146:481-4.
22. Fikrle T, Pizinger K. Dermatoscopic differences between atypical melanocytic naevi and thin malignant melanomas. Melanoma Res. 2006;16:45-50.

23. Massi D, de Giorgi V, Carli P, Santucci M. Diagnostic significance of the blue hue in dermoscopy of melanocytic lesions: a dermoscopic-pathologic study. Am J Dermatopathol. 2001;23:463-9.
24. De Giorgi V, Massi D, Salvini C, Sestini S, Carli P. Features of regression in dermoscopic diagnosis: a confounding factor? Two clinical, dermoscopic-pathologic case studies. Dermatol Surg. 2006;32:282-6.
25. Zaludek I, Argenziano G, Ferrara G, Soyer HP, Corona R, Sera F, et al. Clinically equivocal melanocytic skin lesions with features of regression: a dermoscopic-pathological study. Br J Dermatol. 2004;150:64-71.
26. Corona R, Mele A, Amini M, de Rosa G, Coppola G, Piccardi P, et al. Interobserver variability on the histopathologic diagnosis of cutaneous melanoma and other pigmented skin lesions. J Clin Oncol. 1996;14:1218-23.
27. Ferrara G, Argenziano G, Soyer HP, Corona R, Sera F, Brubetti B, et al. Dermoscopic and histopathologic diagnosis of equivocal melanocytic skin lesions. An interdisciplinary study on 107 cases. Cancer. 2002;95:1094-100.
28. Kelly JW, Crutcher WA, Sagebiel RW. Clinical diagnosis of dysplastic melanocytic nevi: a clinicopathologic correlation. J Am Acad Dermatol. 1986;14:1044-52.
29. Black WC, Hunt WC. Histologic correlations with the clinical diagnosis of dysplastic nevus. Am J Surg Pathol. 1990;14:44-52.
30. Burroni M, Sbano P, Cevenini G, Risulo M, Dell'Eva G, Barbini P, et al. Dysplastic naevus vs. in situ melanoma: digital dermoscopy analysis. Br J Dermatol. 2005;152:679-84.
31. Benelli C, Roscetti E, Pozzo VD, Gasparini G, Cavicchini S. The dermoscopic versus the clinical diagnosis of melanoma. Eur J Dermatol. 1999;9:470-6.
32. Steiner A, Pehamberger H, Wolf K. In vivo epiluminiscence microscopy of pigmented skin lesions II. Diagnosis of small pigmented skin lesions and early detection of melanoma. J Am Acad Dermatol. 1987;17:584-91.
33. Soyer HP, Smolle J, Leitinger G, Rieger E, Keri H. Diagnostic reliability of dermoscopic criteria for detecting malignant melanoma. Dermatology. 1995;190:25-30.
34. Mayer J. Systematic review of the diagnostic accuracy of dermatoscopy in detecting malignant melanoma. Med J Aust. 1997;167:206-10.