Validation of Dermoscopy as a Real-time Noninvasive Diagnostic Imaging Technique for Actinic Keratosis

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Objective: To validate dermoscopy as a real-time noninvasive diagnostic imaging technique for actinic keratosis (AK).

Design: Prospective study to validate a diagnostic test.

Setting: Dermatology department of a tertiary university hospital in Fuenlabrada, Madrid, Spain.

Patients: A total of 178 patients with a clinical diagnosis of AK participated in the study.

Main Outcome Measures: An independent blinded comparison was performed between dermoscopy results and histopathological findings, the gold standard for the diagnosis of AK. All the patients underwent both diagnostic tests.

Results: One hundred seventy-eight lesions were evaluated. The concordance between dermoscopy results and histopathological findings was 0.917. The sensitivity of dermoscopy for the diagnosis of AK was 98.7%, with a specificity of 95.0%, a positive likelihood ratio of 19.74, and a negative likelihood ratio of 0.01. A diagnostic algorithm that combined follicular openings and erythematous pseudonetwork demonstrated a sensitivity of 95.6% and a specificity of 95.0% for the diagnosis of AK.

Conclusions: The sensitivity and specificity of dermoscopy for the diagnosis of AK were high, as was the concordance between dermoscopy results and histopathological findings. As a real-time noninvasive diagnostic imaging technique for AK, dermoscopy may be incorporated in the management of patients with these lesions.


Actinic keratosis (AK) is defined as an in situ intraepidermal carcinoma or precancerous disease that occurs in areas of skin exposed to sunlight, characterized by the presence of an abnormal proliferation and differentiation of epidermal keratinocytes, with a risk for progression to infiltrating squamous cell carcinoma (SCC). In the United States, AK represents the third most frequent condition for which dermatologic consultation is sought, accounting for 11.2% of visits. The risk for transformation to SCC is 0.075% to 0.096% per AK lesion per year. This risk is cumulative in patients with multiple AK lesions and can reach 10% within 10 years or up to 20% among immunocompromised patients or those who remain untreated. Squamous cell carcinoma is a clinical, biological, and histopathological continuum of AK and is the principal cause of death from nonmelanoma skin cancer*. Therefore, patients with AK are candidates for periodic follow-up dermatologic evaluation as outpatients.

Dermoscopy is a real-time noninvasive diagnostic imaging technique. For the user, its optical system renders the corneal layer translucent to improve vision, with original magnification ×10 to ×400. The technique increases the diagnostic accuracy of clinical evaluation by the dermatologist. The aim of dermoscopy is to overcome the imprecision and limits of clinical diagnosis that are associated with histopathological investigation, considered the gold standard technique by the scientific community. The dermoscopic signs of AK are erythematous pseudonetwork, surface scale, linear-wavy vessels, and follicular openings. The overall dermoscopic pattern of AK is a “strawberry” appearance. The primary objectives of the present study were to validate dermoscopy as a real-time noninvasive diagnostic imaging technique for AK (based on the presence of the strawberry pattern) and to measure the sensitivity, specificity, posi-
This prospective study was conducted in the Department of Dermatology, Fuenlabrada University Hospital, Madrid, Spain, during a 12-month period from June 1, 2006, through May 31, 2007. The study inclusion criterion was clinical suspicion of AK (ie, erythematous plaque with surface scale in an area of skin exposed to sunlight). Inclusion was not limited by the size of the lesions or by their clinical forms (ie, atrophic vs hypertrophic or pigmented vs nonpigmented). The study exclusion criteria were the following: pregnancy or breastfeeding, associated conditions that were contraindications to the use of local anesthesia to perform biopsy, and clinical suspicion of skin cancer melanoma or nonmelanoma (signs of infiltration, marked hyperkeratosis, or the presence of a hemorrhagic crust or bleeding). The ethics committee of Severo Ochoa Hospital, Madrid, Spain, evaluated and approved the research project. Informed consent was obtained from all study patients in accord with the principles of the Declaration of Helsinki. For a CI of 95% and the proportion of false-negative results was 1.3%.

### METHODS

In total, 178 lesions on 178 patients were clinically considered AK. All the patients agreed to participate in the study and signed the consent form. One hundred fifteen lesions (64.6%) were observed in men, and 63 lesions (35.4%) were observed in women. Patient age ranged from 37 to 97 years (mean age, 67 years). The most frequent sites of the lesions were the face (139 lesions [78.1%]) and the scalp (36 lesions [20.2%]); the remainder were on the back or the upper extremities.

Most patients (144 patients) had skin phototype II. The remaining patients had skin phototype III (28 patients) or skin phototype I (6 patients).

The dermoscopic diagnoses and histopathological diagnoses for 178 lesions are summarized in Table 1 and Figure 1. The histopathological types of AK were not recorded because such determination was excluded from the pathologist’s usual practice for biopsy specimens of these lesions. Furthermore, the pathologist was blinded to the dermoscopic diagnosis.

Using histopathological findings as the gold standard test result, the sensitivity of dermoscopy for the diagnosis of AK was 98.7%, and the specificity was 95.0%. The proportion of false-positive results was 5.0%, and the proportion of false-negative results was 1.3%.

### RESULTS

<table>
<thead>
<tr>
<th>Table 1. Comparison of Dermoscopic and Histopathological Diagnoses of Actinic Keratosis (AK) Among 178 Lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermoscopic Diagnosis</td>
</tr>
<tr>
<td>-----------------------</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

*Using histopathological findings as the gold standard test result, the sensitivity of dermoscopy for the diagnosis of AK was 98.7%, and the specificity was 95.0%. The proportion of false-positive results was 5.0%, and the proportion of false-negative results was 1.3%.*

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tive predictive value was 99.4%, and the negative predictive value was 90.5%. The concordance between dermoscopic results and histopathological findings, calculated using the statistic, was 0.917. Dermoscopic diagnosis of AK had a positive likelihood ratio of 19.74 and a negative likelihood ratio of 0.01. The 4 dermoscopic signs of AK are listed in Table 2, along with their individual sensitivities, specificities, indexes, and positive and negative likelihood ratios. Classification trees were used for the descriptive analysis, seeking the combination of dermoscopic signs that best predicted the histopathological results. A diagnostic algorithm that combined follicular openings and erythematous pseudonetwork demonstrated a sensitivity of 95.6% and a specificity of 95.0% for the diagnosis of AK.

Table 2. Sensitivity, Specificity, χ² Index, and Positive and Negative Likelihood Ratios Among 4 Dermoscopic Signs of Actinic Keratosis

<table>
<thead>
<tr>
<th>Dermoscopic Sign</th>
<th>No./Total No. (%) [95% CI]</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>χ² Index</th>
<th>Positive Likelihood Ratio</th>
<th>Negative Likelihood Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythematous pseudonetwork</td>
<td>116/158 (73.4) [66.2-80.6]</td>
<td>20/20 (100.0) [97.5-100.0]</td>
<td>0.383</td>
<td>Infinity</td>
<td>0.27</td>
<td></td>
</tr>
<tr>
<td>Surface scale</td>
<td>148/158 (93.7) [89.6-97.8]</td>
<td>7/20 (35.0) [11.6-58.4]</td>
<td>0.307</td>
<td>1.44</td>
<td>0.18</td>
<td></td>
</tr>
<tr>
<td>Linear-wavy vessels</td>
<td>104/158 (65.8) [58.1-73.5]</td>
<td>19/20 (95.0) [83.0-100.0]</td>
<td>0.282</td>
<td>13.16</td>
<td>0.36</td>
<td></td>
</tr>
<tr>
<td>Follicular openings</td>
<td>136/158 (86.1) [80.4-91.9]</td>
<td>19/20 (95.0) [83.0-100.0]</td>
<td>0.556</td>
<td>17.22</td>
<td>0.15</td>
<td></td>
</tr>
</tbody>
</table>

Figure 1. Flowchart of patients in the study. AK indicates actinic keratosis; SK, seborrheic keratosis; and SL, solar lentigo.

COMMENT

The present study validated dermoscopy used on lesions selected by visual inspection as a real-time noninvasive diagnostic imaging technique for AK by comparing dermoscopy results with histopathological findings, achieving a sensitivity of 98.7% and a specificity of 95.0%. The concordance (χ² index) between dermoscopy results and histopathological findings was 0.917. Based on considerations by the Evidence-Based Medicine Working Group, the positive and negative likelihood ratios (19.74 and 0.01, respectively, in this series) are clinically relevant to the interpretation of results because they respectively reflect increased and decreased likelihood that a diagnosis may or may not be accurate in a significant manner with respect to not performing a diagnostic test.

The aim of this study was to validate dermoscopic criteria for AK. The features most consistently found on dermoscopy were follicular openings and erythematous pseudonetworks. The lesions clinically suspicious of AK and included in the study were analyzed.
Follicular openings (Figure 2A) showed the highest concordance with the histopathological diagnosis (κ index, 0.556). This dermoscopic sign had more balanced values of sensitivity and specificity. Erythematous pseudonetwork (Figure 2B) was the most specific of 4 dermoscopic signs evaluated. On dermoscopy, the normal superficial vascular plexus is seen as a regular blurred network of wide vessels. When AK forms, edema and elastosis develop, producing a dermoscopic pattern of erythematous pseudonetwork. One of the characteristics of aging skin is a loss of the vascular bed, and most AK lesions are observed in older individuals. The vessels in AK may be present in the most atrophic areas of the epidermis and dermis, around the orifices of the adnexa and follicles. The combination of dermoscopic signs was sought that provided the highest diagnostic accuracy using classification trees. According to this descriptive method, the results herein demonstrate that the diagnosis of AK could be based on the combination of follicular openings and erythematous pseudonetwork, with a sensitivity of 95.6%, a specificity of 95.0%, and a κ index of 0.801. The diagnostic accuracy of this com-

<table>
<thead>
<tr>
<th>Variable</th>
<th>Erythematous Pseudonetwork</th>
<th>Surface Scale</th>
<th>Linear-Wavy Vessels</th>
<th>Follicular Openings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>χ^2 statistic</strong></td>
<td>. . .</td>
<td>2.7</td>
<td>3.2</td>
<td>19.2</td>
</tr>
<tr>
<td><strong>P value</strong></td>
<td>. . .</td>
<td>.01</td>
<td>.08</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Surface scale</td>
<td>2.7</td>
<td>. . .</td>
<td>6.8</td>
<td>3.5</td>
</tr>
<tr>
<td><strong>χ^2 statistic</strong></td>
<td>.10</td>
<td>. . .</td>
<td>.009</td>
<td>.06</td>
</tr>
<tr>
<td><strong>P value</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linear-wavy vessels</td>
<td>3.2</td>
<td>6.8</td>
<td>. . .</td>
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<td>.001</td>
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Abbreviation: Ellipsis, not applicable.
The presence of dotted or glomerular openings was the most specific feature associated with AK. Those authors found that the presence of dotted or glomerular openings (Figure 2D) represented a highly specific (95.0%) but not particularly sensitive (65.8%) dermoscopic sign. The dermoscopic vascular pattern is considered more relevant in nonpigmented skin lesions such as AK. Proof of this in the present study is the high positive predictive value (99.0%) for the presence of these characteristic vessels. Assessment of the possible relationships across dermoscopic criteria showed that the vascular pattern was associated with surface scale and with follicular openings. The presence of erythematosus pseudonetwork showed a statistically significant correlation with the presence of follicular openings. This association is logical given the origin of the pseudonetwork, described in the previous paragraph. An evaluation was also performed of the relationship between the dermoscopic signs of AK and epidemiological data. Statistically significant associations were found with 2 dermoscopic signs: linear-wavy vessels were more common in men, and follicular openings were less common in patients younger than 50 years. The dermis underlying an AK lesion manifests actinic elastosis and vascular ectasia, correlating with the vascular structures visualized on dermoscopy. In this series, actinic elastosis was significantly more common in men than in women, a finding that may be explained by greater occupational exposure to sunlight among men. The fact that follicular openings were more common in older patients may be explained by the aging of the skin, which leads to approximately a 23% reduction in sebum production per decade, with greater cutaneous xerosis and more compaction of the stratum corneum.

Dermoscopy may be a promising technique for noninvasive detection of AK, perhaps overcoming the imprecision and limits of clinical diagnosis that are associated with histopathological investigation. Among various studies, the positive predictive value for clinical diagnosis has ranged between 74% and 81%. In this study, clinical diagnosis and dermoscopic diagnosis achieved positive predictive values of 88.7% and 99.4%, respectively. Notably, these values are higher than those reported for reflectance confocal microscopy, which is a noninvasive diagnostic tool with results closely linked to histopathological findings. Actinic keratosis may be considered a precursor of SCC. The authors of a retrospective study proposed a progressive dermoscopic model in which AK develops into intraepidermal carcinoma and invasive SCC. The present study extends their results by providing the sensitivity and specificity for 2 of their evaluated criteria, namely, erythematosus pseudonetwork and follicular openings. According to their findings, a red erythematosus pseudonetwork was seldom seen in intraepidermal carcinoma or invasive SCC, and it was the most specific feature associated with AK. Those authors found that the presence of dotted or glomerular vessels and discrete yellow-white opaque scales was significantly associated with intraepidermal carcinoma, while the present study found surface scales to be the least specific among 4 dermoscopic signs of AK.

Limitations of the present study include that no anatomicoclinical classification of AK (eg, atrophic vs hypertrophic or pigmented vs nonpigmented) was performed. Correlations between the dermoscopic criteria and the histopathological and clinical types of AK could be a subject for future studies. As with most diagnostic techniques in the health sciences, correct dermoscopic technique requires training. The dermoscopy herein was performed by a dermatologist with considerable experience in dermoscopy. Future studies will be designed to determine interobserver variability in the technique.

The findings of the present study have major practical applications in the field of skin cancer. The use of dermoscopy is described for the diagnosis of AK; this noninvasive technique can be performed in the office as part of daily clinical practice and provides immediate results, with consequent prognostic and therapeutic implications. Because dermoscopy is not a costly technique, its use is important not only for the individual patient and physician but also for the health system in general. Dermoscopy may be incorporated as a noninvasive strategy for the diagnosis of AK and in the management of patients with these lesions.

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Author Contributions: Drs Huerta-Brogeras, Olmos, Borburo, Hernández-Núñez, Castaño, Romero-Maté, Martínez-Sánchez, and Martínez-Morán had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.


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Additional Contributions: Jesús Juan Ruiz, PhD, provided advice on the statistical analysis.

REFERENCES


Notable Notes

Beauty Tips From Ancient Queens

The quest for beauty stretches back into antiquity. Here are some favorite beauty recipes from queens of yesteryear.

Poppaea Sabina (30-65 CE) was the second wife of the Roman Emperor Nero. She spared no effort to maintain her beauty, bathing regularly in donkey’s milk. She spared no effort to maintain her beauty, bathing regularly in donkey’s milk. Poppaea Sabina (30-65 CE) was the second wife of the Roman Emperor Nero. She spared no effort to maintain her beauty, bathing regularly in donkey’s milk. She spared no effort to maintain her beauty, bathing regularly in donkey’s milk. According to the Roman author Pliny the Elder, donkey’s milk was thought to eliminate facial wrinkles and keep the skin smooth and delicate, while preserving its whiteness. Unrefrigerated milk, such as used by Poppaea, naturally sours to aid in the production of lactase, an α-hydroxy acid, which has exfoliant properties. Perhaps Poppaea’s skin benefited from such lactic acid production, assuming that it formed in her milk bath.

Jezebel was a wicked queen of Israel who reigned during the ninth century BCE, until a rebellion against the monarchy developed. Leading the insurrection was Jehu, a newly anointed king, who was ordered to exact retribution against Jezebel. Knowing what danger she was in, Jezebel adorned herself with an eye paint, biblically termed Puch (II Kings 9:30), hoping to seduce Jehu and thereby save her life. Puch was an eye cosmetic that when applied to the lids and lashes gave the illusion of enlarging the eyes. The exact identity of Puch is not known, although it has been suggested that it might have contained antimony sulfide, which was used as an eye cosmetic in ancient Egypt, along with lead-based compounds. Jehu was unimpressed by Jezebel’s appearance and had her thrown from the palace window and killed.

In ancient Persia, some 2500 years ago, all eligible women were forced to participate in a beauty contest, with the winner becoming the queen for a king named Achausverosh. According to the Bible (Esther 2:12), the women underwent 6 months of anointing with “oil of myrrh.” Oil of myrrh probably was unripe olive oil prepared with myrrh (Commiphora myrrha). This cosmetic caused the skin to glow and had a deplatory function. Today, myrrh is used as a fragrance in cosmetics, and oil is used as a skin moisturizer with possible medical benefits. The beauty contest winner was Esther, who was Jewish. She was beautiful but also had great charm owing to her modesty and virtue. As queen, Esther helped to save the Persian Jews from annihilation as commemorated by the holiday of Purim.

Human nature being what it is, the ancient quest for beauty goes on. There is nothing wrong with trying to be attractive, as long as we remember that good looks often fade with time and thus do not determine an individual’s worth. Rather, true lasting beauty is found in the nobility of a person’s character and in the degree to which someone is guided by human and spiritual values.

Contact Dr Hoenig at 601 N Flamingo Rd, Ste 201, Pembroke Pines, FL 33028 (gooddocjh@yahoo.com).