The Spectrum of Spitz Nevi

A Clinicopathologic Study of 83 Cases

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Objective: To achieve a clinicopathologic classification of Spitz nevi by comparing their clinical, dermoscopic, and histopathologic features.

Design: Eighty-three cases were independently reviewed by 3 histopathologists and preliminarily classified into classic or desmoplasic Spitz nevus (CDSN, n = 11), pigmented Spitz nevus (PSN, n = 14), Reed nevus (RN, n = 16), or atypical Spitz nevus (ASN, n = 14); the remaining 28 cases were then placed into an intermediate category (pigmented Spitz-Reed nevus, PSRN) because a unanimous diagnosis of either PSN or RN was not reached.

Setting: University dermatology and pathology departments and general hospital pathology departments.

Patients: A sample of subjects with excised melanocytic lesions.

Main Outcome Measure: Frequency of dermoscopic patterns within the different histopathologic subtypes of Spitz nevi.

Results: Overlapping clinical, dermoscopic, and histopathologic findings were observed among PSN, RN, and PSRN, thereby justifying their inclusion into the single PSRN diagnostic category. Asymmetry was the most frequent indicator of histopathologic ASN (79%; n = 11); in only 4 cases did dermoscopic asymmetry show no histopathologic counterpart, and in those cases the discrepancy was probably the result of an artifact of the gross sampling technique carried out with no attention to the dermoscopic features.

Conclusions: Among Spitz nevi, histopathologic distinction between PSN and RN is difficult, not reproducible, and may be clinically useless. A simple clinicopathologic classification of these neoplasms might therefore be structured as CDSN, PSRN, and ASN. Asymmetry should be assessed using both dermoscopic and histopathologic analysis, and reliability in histopathologic diagnosis may be enhanced by the simultaneous evaluation of the corresponding dermoscopic images.

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held scope (also called dermatoscope), stereomicroscope, camera, or a digital imaging system. Dermoscopy is an in vivo microscopic observation, and, not surprisingly, several articles have already elucidated the histopathologic correlates of the structures shown by means of this technique.\textsuperscript{36-43} The present study was conceived to compare dermoscopic and histopathologic findings in a series of 83 Spitz cell nevi, as has already been attempted in smaller series.\textsuperscript{23,42,43}

**METHODS**

**STUDY DESIGN**

The cases reported in the present study were retrieved from the pathology files of the University of Graz in Austria and of the Universities of L’Aquila, Modena, Naples (Federico II University), and Siena, Italy. All of these cases had been diagnosed as either Spitz nevus or RN by the referring histopathologists. Clinical data as well as dermoscopic images were obtained from the referring physicians; none of the collected lesions had been known to recur or metastasize over a follow-up period of 18 to 75 months (mean follow-up time, 30.4 months).

The study was conceived as a comparative evaluation of specific histopathologic diagnoses and specific dermoscopic patterns with the aim of achieving a clinicopathologic classification of Spitz nevi. Therefore, both histopathologic slides and dermoscopic images were first blindly reviewed by the respective experts and then reevaluated to produce a combined set of dermoscopic and histopathologic data. Moreover, to refine dermoscopic and histopathologic criteria used to differentiate melanoma from benign lesions, special attention was paid to lesions showing atypical dermoscopic and/or histopathologic features.

**HISTOPATHOLOGIC EVALUATION**

In each case, the detailed histopathologic classification was based on a single hematoxylin-eosin–stained slide, which had been considered representative of the lesion by the referring pathologists. Paraffin blocks were not available for further studies. The microscopic slides were independently reviewed by 3 of us (G.F., H.P.S., and S.C.) with the adoption of the following 3 provisional categories.

**Classic or Desmoplastic Spitz Nevus**

A junctional, compound, or dermal melanocytic neoplasm associated with conspicuous epidermal hyperkeratosis or acanthosis and with little or no pigment deposition was classified as a classic or desmoplastic Spitz nevus (CDSN). Cytomorphologically, the CDSN was characterized by melanocytes with large nuclei, prominent nucleoli, and abundant ground-glass cytoplasm with polygonal (epithelioid) and often also cigar-shaped (spindle) outlines. Ancillary features include Kamino bodies, edema, telangiectasias, and fibrosis of the papillary dermis. Extensive dermal desmoplasia encircling single melanocytes is seen in the desmoplastic variant.

**Pigmented Spitz Nevus**

The PSN is a junctional or compound neoplasm composed of heavily pigmented, highly cohesive spindle and/or epithelioid melanocytes, parallel and perpendicular to the skin surface, with artifactual clefts at the interface between the nests of melanocytes and the hyperplastic epidermis. It is also characterized by cytologic features akin to the spindle- and epithelioid-cell component of the CDSN as well as by ancillary features of the CDSN.

**Reed Nevus**

An (almost) exclusively junctional neoplasm, the RN is composed of heavily pigmented, monomorphic, small to medium-sized spindle melanocytes, mainly arranged parallel to the skin surface. Typically, the RN is structured without sharp demarcation between the nests of melanocytes and the overlying epidermis, with the latter showing little or no hyperkeratosis-akanthosis. Ancillary findings can include a bandlike dermal infiltration of melanophages.

**Atypical Spitz Nevus**

A junctional or compound lesion not fulfilling the histopathologic criteria of melanoma, the atypical Spitz nevus (ASN) has at least 1 of the following histopathologic features: asymmetry, poor lateral circumscription, predominance of single melanocytes over nests in lesions of at least 4 mm in diameter, ulceration, presence of large dermal sheets of melanocytes, lack of maturation in the dermis, evidence of deep dermal mitotic figures, and extensive involvement of the subtcutis.

**Pigmented Spitz-Reed Nevus**

A further provisional category was introduced after the histopathologic study: pigmented Spitz-Reed nevus (PSRN). This category included lesions that had been diagnosed as either PSN or RN by each histopathologist but without unanimous agreement. The lack of unanimity was probably owing to the presence of largely overlapping microscopic features. The PSRN category was adopted only a posteriori to compensate for the strict requirement from the beginning of the study that the histopathologists arrive at a definitive diagnosis in every case. Cases were discarded if any other diagnostic discrepancy was raised.

**DERMOSCOPIC EVALUATION**

Clinical data concerning the age and sex of patients and the size and location of the lesions were collected from the referring physicians, who had also recorded the color of the lesions and classified them as pink-red, brown, or black. Cases with incomplete clinical data were excluded from the study.

Dermoscopic images were available as JPEG files either obtained from 35-mm color slides acquired by a Dermaphot lens (Heine Optotechnik, Herrsching, Germany) mounted on a standard reflex camera or by using a digital imaging dermoscopy system (Videocap system; DS Medica, Milan, Italy, or Molemax system; Derma Instruments, Vienna, Austria).

Reevaluation of the dermoscopic images was made by 1 of us (G.A.) blinded to the histopathologic diagnosis. Dermoscopic evaluation was made using the standard pattern analysis criteria set forth by Pehamberger et al\textsuperscript{30} and recently refined by Argenziano et al.\textsuperscript{30}

**RESULTS**

Eighty-three cases were obtained from 25 male and 58 female patients ranging in age from 1 to 58 years...
The most common lesion sites were the limbs (81%; n=67), followed by the trunk (14%; n=12). Only 3 cases (5%) occurred on the face. Most neoplasms were described as brown (39%; n=32) or black (54.2%; n=45). Only 6 lesions (7%) were pink-red. Their sizes ranged from 3 to 9 mm (mean size, 5.4 mm).

Based on the given criteria, all 3 histopathologists unanimously agreed on the diagnoses in 11 cases (13%) as CDSN; 14 cases (17%) as PSN; 16 cases (19%) as RN; and 14 cases (17%) as ASN. The remaining 28 cases (34%) received a diagnosis of either PSN or RN by each histopathologist without unanimous agreement. These cases were thus placed into the PSRN category.

Table 1. Clinical Characteristics of 83 Cases of Spitz Nevus by Provisional Histopathologic Type

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CDSN (n = 11)</th>
<th>PSN (n = 14)</th>
<th>RN (n = 16)</th>
<th>PSRN (n = 28)</th>
<th>ASN (n = 14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient age, range (mean), y</td>
<td>5-50 (19.3)</td>
<td>2-48 (21.6)</td>
<td>1-58 (22.0)</td>
<td>4-55 (22.2)</td>
<td>8-34 (17.3)</td>
</tr>
<tr>
<td>Sex ratio, M:F</td>
<td>3:8</td>
<td>5:9</td>
<td>6:10</td>
<td>8:20</td>
<td>3:11</td>
</tr>
<tr>
<td>Lesion site, No.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head or neck</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Trunk</td>
<td>2</td>
<td>1</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Limbs</td>
<td>9</td>
<td>12</td>
<td>12</td>
<td>22</td>
<td>12</td>
</tr>
<tr>
<td>Size, range (mean), mm</td>
<td>5-9 (7.0)</td>
<td>4-8 (5.4)</td>
<td>3-6 (4.6)</td>
<td>3-7 (4.8)</td>
<td>4-9 (6.1)</td>
</tr>
<tr>
<td>Color, No.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pink-red</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Brown</td>
<td>6</td>
<td>5</td>
<td>5</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>0</td>
<td>9</td>
<td>11</td>
<td>21</td>
<td>4</td>
</tr>
</tbody>
</table>

Abbreviations: ASN, atypical Spitz nevus; CDSN, classic or desmoplastic Spitz nevus; PSN, pigmented Spitz nevus; PSRN, pigmented Spitz-Reed nevus; RN, Reed nevus.
*See the “Methods” section for a definition of these nevus types.

Table 2. Dermoscopic Patterns of 83 Cases of Spitz Nevus by Provisional Histopathologic Type

<table>
<thead>
<tr>
<th>Dermoscopic Pattern</th>
<th>CDSN</th>
<th>PSN</th>
<th>RN</th>
<th>PSRN</th>
<th>ASN</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starburst</td>
<td>0</td>
<td>8</td>
<td>9</td>
<td>16</td>
<td>2</td>
<td>35</td>
</tr>
<tr>
<td>Globular</td>
<td>6</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>2</td>
<td>16</td>
</tr>
<tr>
<td>Atypical and/or multicomponent</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>8</td>
<td>15</td>
</tr>
<tr>
<td>Homogeneous</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Reticular, classic</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Reticular, superficial</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Hypopigmented</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>11</td>
<td>14</td>
<td>16</td>
<td>28</td>
<td>14</td>
<td>83</td>
</tr>
</tbody>
</table>

Abbreviations: ASN, atypical Spitz nevus; CDSN, classic or desmoplastic Spitz nevus; PSN, pigmented Spitz nevus; PSRN, pigmented Spitz-Reed nevus; RN, Reed nevus.
*See the “Methods” section for a definition of these nevus types.

Table 2 details the distribution of the 83 lesions according to the dermoscopic pattern and the histopathologic diagnosis. A great variability was observed in the dermoscopic appearance of Spitz nevi. Remarkably, however, the starburst, globular, and atypical patterns accounted for 66 (80%) of the 83 cases, thus representing the major dermoscopic patterns of Spitz nevi.

Cases of PSN, RN, and PSRN basically showed a similar distribution of dermoscopic patterns. In particular, the starburst pattern, previously reported as highly characteristic of RN,23,30 was present in 9 (56%) of 16 cases of RN but also in 8 (57%) of 14 cases of PSN and in 16 (57%) of 28 cases of PSRN. Figures 1, 2, 3, and 4 illustrate the dermoscopic-pathologic correlations in cases of RN and PSN, with both lesions showing a starburst pattern on dermoscopy. Because of the largely overlapping clinical, dermoscopic, and histopathologic features among PSN, RN, and PSRN, we propose the denomination PSRN as a unifying diagnostic category for all of these cases.

The association between dermoscopic and histopathologic atypia was remarkable but not absolute. Asymme-
try was by far the most common histopathologic feature of ASN (11/14; 79%) followed by the presence of deep dermal mitotic figures (n = 3).

More than half (8/15; 53%) of the lesions showing an atypical and/or multicomponent dermoscopic pattern were found to be histopathologically atypical as well. Figure 5 and Figure 6 illustrate a case of a Spitz nevus showing dermoscopic and histopathologic features, respectively, of atypia. Among the lesions showing dermoscopic atypia with no histopathologic counterpart (7/15), 3 lesions showed a dermoscopic image characterized by a diffuse bluish pigmentaition suggestive of a regression structure or a blue-whitish veil. In these cases histopathologic analysis revealed that the bluish pigmentation was simply due to a bandlike infiltrate of melanophages.

More interestingly, in 4 cases, dermoscopic atypia was due to a striking asymmetry that was not represented on histopathologic sections. This finding might point toward an underestimated limitation of histopathologic examination, namely, gross sampling carried out with no special attention to the clinical (dermoscopic) features of a given pigmented lesion. It has been already demonstrated that dermoscopy can turn
histopathologists’ attention to the suggestive area in melanocytic lesions; therefore, the histopathologic diagnosis can be radically different when dermoscopic information is not taken into account. Figure 7 and Figure 8 display dermoscopic and histopathologic images, respectively, of a Spitz nevus in which a poor gross sampling technique presumably led to discrepancies between dermoscopic and histopathologic features.

COMMENT

In recent years, dermoscopy has become the conceptual and practical link between the macrocosm of clinical dermatology and the microcosm of histopathology, allowing the clinician to visualize structures that are not discernible by the naked eye. The present study provides an example of how dermoscopy can integrate the clinical and histopathologic data about melanocytic skin neoplasms.

Our starting point was the adoption of a provisional histopathologic classification, which clearly demonstrated the great difficulties in distinguishing PSN from RN because of frequent overlapping histopathologic findings between these 2 entities. Moreover, PSN and RN, as well as their intermediate provisional counterpart, PSRN, showed basically the same dermoscopic features; in fact, the 3 major dermoscopic patterns—starburst, globular, and atypical—accounted for most cases included in this study (66/83; 80%), with no preferential distribution among cases of PSN, RN, and PSRN. Indeed, even the starburst pattern, previously considered to be typical of RN, was observed in 56% of cases (n=8) classified by histopathologists as clear-cut PSN.

As a corollary, the growth sequence reported by Pizzichetta et al in a case of PSN—the progressive transformation of a globular pattern into a starburst and, in turn, into a homogeneous one—underscores the observation that there is no close correlation between dermoscopic patterns and the histopathologic categories of PSN and RN. In our opinion, these data suggest that, in most cases, a clinicopathologic distinction between PSN and RN cannot be adequately supported. We therefore propose the following clinicopathologic classification of Spitz nevi.

1. CDSN: A subdivision of this category into 2 separate entities is justified on the basis of the previous histopathologic data. However, further studies on larger series are needed to elucidate the dermoscopic correlates of these types of melanocytic neoplasms.

2. PSRN: This category includes the provisional entities PSN, RN, and PSRN of the present study. A further subclassification of this category is difficult to apply, necessarily subjective, and clinically useless.
3. ASN, Either Epithelioid or Spindle-Cell Type: We retain this category because our review of data from the literature on cases of metastasizing spitzoid neoplasms demonstrates that the presence of even 1 atypical feature can be associated with an aggressive clinical course (data not shown).

The occurrence of an atypical (multicomponent) dermoscopic pattern in Spitz nevi is well recognized, as is the occurrence of melanomas with dermoscopic features of Spitz nevi. There are some theoretical and practical reasons why the dermoscopic-pathologic correlation of this group of lesions is often problematic. First, some concepts introduced in the literature have been confusing, and among these is the relationship between the so-called Spitz nevus with atypia and metastasis and the classic spitzoid melanoma. Moreover, the histopathologic features of lesions with spitzoid features are often not definitive, creating substantial diagnostic interobserver disagreement. Finally, when dermoscopy clearly reveals features of a Spitz nevus, sometimes the histopathologic analysis of the same lesion supports a diagnosis of a melanoma. Remarkably, the “spitzoid melanoma” does not have a distinctive dermoscopic counterpart. These diagnostic problems have led to the common practice in recent years of surgically removing all lesions in adults that show dermoscopic features akin to Spitz nevi.

The occurrence of dermoscopically unexpected histopathologic atypia can be easily explained: histopathologic analysis examines lesions at higher magnification and, most importantly, in their deeper portions. Certain histopathologic criteria of atypia (dermal sheets of melanocytes, absence of maturation, pleomorphic nuclei, mitotic figures, and asymmetrical features in the deeper portions of a given lesion) will never be seen under dermoscopy. On the other hand, it is more difficult to explain the absence of histopathologic atypia in dermoscopically atypical lesions.

In the present study, we found 7 lesions determined to be atypical (multicomponent) by dermoscopy that were devoid of histopathologic features of atypia. Among these lesions, we found that a potential source of dermoscopic overestimation was a bandlike dermal infiltrate of melanophages, a common ancillary feature of pigmented spindle-cell nevi. In fact, in 3 cases, this feature was responsible for a diffuse bluish pigmentation of the lesion, a worrisome dermoscopic feature that suggests the presence of either regression or a blue-whitish veil. In addition, and even more interestingly, 4 cases showed a striking dermoscopic asymmetry, which was not adequately represented on histologic sections. This was presumably due to the gross sampling technique, which had been carried out without consideration of the clinical (dermoscopic) features of the lesion. The various methods of gross sampling of cutaneous neoplasms, among them the “rule of halves,” do not all take into account the clinical features of the lesions. It is probably impractical for a histopathologist to review the dermoscopic features every time a melanocytic lesion is submitted to histologic examination; however, at least in selected cases, it would be important to minimize sampling errors by customizing the gross sampling technique to the dermoscopic picture of the same lesion. In these cases, the first cut made according to the rule of halves might be guided by the most representative dermoscopic features.

In cases in which melanoma is difficult to diagnose, the attention of the histopathologist should be directed to the areas of highest diagnostic relevance by means of dermoscopy. Data from the present study suggest that asymmetry is an important indicator of histopathologic atypia in Spitz nevi and that this feature deserves special attention in a setting of dermoscopic-pathologic correlation.

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