Criteria for the Diagnosis of Nevus

1.1 Introduction

The sharp distinction between benign nevi and malignant melanoma has increasingly come into question in recent years. The dichotomy between nevi, with no metastatic potential, and melanoma, with a metastatic capacity proportional to its thickness, and no different from that of other melanomas of the same thickness is undoubtedly an oversimplification. Surely, there is a "gray zone," which is composed of lesions that cannot be precisely classified into one of these groups.

However, there are also distinct clinicopathological entities that seem to correspond to low-grade forms of melanoma, in which distant metastasis is a rare but finite risk.

Nonetheless, the great majority of melanocytic lesions can still be confidently labeled as either nevi or melanoma, and the main duty of the pathologist is to provide a clear-cut diagnosis of benignancy or malignancy in such cases. Toward this task, we use a set of clinical and morphological criteria, summarized herein, which are features of benign nevi. We will list the criteria useful for the diagnosis of melanoma in Chap. 27.

None of the criteria in this chapter are entirely specific for nevi, and all can be occasionally found in a malignant melanoma. Moreover, it is well known that some challenging lesions contain conflicting criteria suggesting opposite diagnoses. Finally, some criteria are infrequent, or have low specificity, or suffer of high interobserver variation. For these reasons the criteria we illustrate herein must be used in clusters. A sort of checklist can be used: each single criterion must be evaluated and added to the others; the diagnosis of a nevus should be the outcome of the combination of clues to benignity found in the neoplasm.

Next to the "positive" criteria illustrated in this chapter, dermatopathologists must also consider the "negative" ones, i.e., the criteria that would tilt toward malignancy but are lacking.

Another important aspect is that criteria should be used for specific differential diagnosis. In other words a specific form of nevus should be differentiated from a type of melanoma morphologically mimicking it: Spitz nevus has to be differentiated from spitzoid melanoma, desmoplastic nevus from desmoplastic melanoma, etc. Using generic criteria to differentiate an abstract nevus from melanoma as a whole is less worthwhile, except as a learning tool for beginners.

1.2 Clinical Aspects of the Lesion

- Clinical diagnosis. Information about the clinical setting of the lesion is of considerable help in our histological work. As a rule, lesions diagnosed by experienced dermatologists as certain nevi rarely are shown to be melanomas; on the contrary, lesions that seem to be melanomas upon clinical inspection frequently prove to be wholly benign. In sum, clinically "sure" diagnoses of melanomas can be refuted without much hesitation, whereas the strong clinical impression of a nevus should be reversed only after careful histological consideration.
  The pathologist should be aware that some clinicians may put "rule out melanoma" on a pathology requisition only to justify insurance reimbursement for a procedure, rather than a sincere belief that there is a chance of melanoma.
- Macroscopic aspect. The direct inspection of the specimen can be an important step in the diagnostic pathway, and often the ABCD rules (asymmetry, border, color, diameter) can still be applied to skin specimens fixed in formalin. Small, roundish, well-circumscribed, evenly pigmented lesions are very probably nevi, whereas large, irregularly shaped, and unevenly pigmented lesions are potentially melanomas.
- Dermoscopy. The introduction of dermoscopy in clinical practice greatly enhanced the assessment of melanocytic lesions. The clinicopathological correspondences elucidated by dermoscopy are still continuously improving. Dermoscopy can provide vital information in cases of melanoma developing in a nevus or of a melanocytic lesion with focal area of regression.
  For some type of nevi, the diagnostic accuracy of dermoscopy is striking. A straightforward dermoscopic diagnosis of melanoma issued by an experienced dermatolo-

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gist should be challenged with great prudence, and serial sections should be cut. Dermoscopy can also be applied to fixed specimens, but this is not yet commonly done.

- Age of the patient. In average, the appearance of a new pigmented lesion (that is not clearly a solar lentigo or seborrheic keratosis) in a young person probably signifies a nevus, while in an older person one must suspect a melanoma. Unfortunately infantile melanomas do occur and new nevi can appear in old age. For such reasons a diagnosis should never be based on patient age if it does violence to microscopic features. This consideration notwithstanding, a few remarks deserve to be made:
  - A melanocytic lesion with many melanocytes above the dermoepidermal junction (so-called pagetoid spread) is almost always benign if excised in the first years of life, whereas it should be considered malignant unless proven otherwise after 40 years of age (unless the lesion is in special areas as genital and volar skin or is a persistent or traumatized lesion).
  - An atypical junctional proliferation should be considered benign in the first years of life, whatever the architectural disorder and the cytological aspect may be. Similar findings in an elderly patient are nearly always an indication of melanoma.
  - A Spitz nevus (nevus with large spindle or epithelioid cells) that is largely junctional or intraepidermal occurs commonly up to 50 years of age (or less). After that age a "Spitz nevus" with a mostly junctional distribution of its cells is suspected for being a melanoma.
  - A melanocytic lesion with a significant junctional component in the palate or the anogenital region of an older patient is almost by definition at least a melanoma in situ.

1.3 Site of the Lesion

Melanocytic lesions situated on the milk line, on genitalia, and on other special sites are frequently benign despite the alarming histology. Melanomas are exceedingly rare in acral skin and on the mucous membranes of youngsters. Despite their atypical features these lesions have almost invariably a benign outcome.

An atypical lesion of the back with fibrosis and regression can be a traumatized nevus or a Clark or dysplastic nevus with exaggerated collagen deposition and not a melanoma. We are reluctant to sign out a melanoma on the buttocks at almost any age, as most of the "melanomas" in this site are probably atypical Spitz or congenital nevi.

1.4 Small Dimension of the Lesion

The lateral dimension of a lesion can be easily estimated at the microscope. As a rule of thumb, a lesion less than 3 mm in diameter, in which nests predominate at the junction, is probably a nevus (Figs. 12.2 and 20.8). There are exceptions and small melanomas (melanomas smaller than 6 mm) do exist. Moreover, benign lesions such as Clark nevus and congenital nevi can be much broader than 6 mm.

The small dimensions are, however, a handy criterion if combined with other details: for example, a small lesion on volar skin with more nests than single cells at the junction is undoubtedly a nevus (a melanoma must reach a large size before forming nests). A caveat with these criteria is that one does not know from just looking at a slide if one is viewing the long or short dimension of a lesion. Hence, the standard for clinicians should be to include clinical measurements of a pigmented lesion, whether the biopsy is in whole or in part.

1.5 Symmetry of Silhouette of the Lesion

One of the most important distinctive characteristics of a benign melanocytic neoplasm is the symmetry of its silhouette (Figs. 5.16, 12.5, and 18.1). This symmetry can be immediately appreciated if we draw an imaginary vertical line at the center of the lesion: if the two resulting halves are similar to one another, the lesion is most probably benign. The symmetry of the silhouette is, in fact, supposed to be an indication of the neoplasm's even growth and, consequentially, of its benign nature.

However, the assessment of symmetry can be arduous and subject to personal judgment, and the perimeter of the lesion can change in different cross-sectional planes. Symmetry as a criterion of malignancy does not apply to metastatic melanoma, which can be perfectly symmetrical (as it is the outgrowth of a single clone of cells with an even growth rate) and to spitzoid melanomas in children.

1.6 Symmetry of the Lateral Margins

A benign nevus grows radially in a regular and "symmetrical" way; consequently, if the two lateral edges of a melanocytic lesion are similar, the lesion is most probably benign (Figs. 4.1 and 4.9). In other words, if the junctional nests at both lateral borders are of the same size, shape, and disposition and have the same cytological details, the lesion is most likely a nevus. On the contrary, different morphological details at the two borders may indicate a melanoma. This is even more likely if cells are in nests at one border and aligned singly on the other.

1.7 Symmetry in the Horizontal Levels of the Lesion

A benign nevus should show homogeneous histological details at each single level of its thickness. A handy way to study this aspect is to divide the lesion in parallel strips and check if cells have the same size, nuclear and nucleolar details, and cytoplasm characteristics inside each single strip (Figs. 18.1 and 18.6). In each level, cells must also aggregate in nests, cords, or files, which are uniform in size and shape, and must be surrounded by similar amounts of collagen or lymphocytes. In sum, each of these imaginary "strips" must have its own homogeneous ("symmetrical") appearance.

1.8 Symmetry of Distribution of the Pigment

Pigment is usually distributed evenly in nevi (Figs. 10.6, 14.1, and 14.4), whereas it is often asymmetrically dispersed in melanoma. Symmetrical distribution does not mean that the entire lesion should be uniformly pigmented, but that the pigment, if present, should have a similar arrangement in the two halves of the neoplasm. For example, some superficial congenital nevi have an "umbrella" of pigmented melanocytes in their uppermost dermal nests and around a central follicle, while the deep part of the lesion is nearly amelanotic.

1.9 Symmetry in the Distribution, Size, and Shape of Junctional Nests

A reliable clue for a nevus is the presence of numerous, discrete roundish nests at the junction (Fig. 4.6). This especially applies if the nests are small and evenly distributed without skip areas or interposed lentiginous zones. Among nevi, only Clark nevi routinely have variably sized or confluent junctional nests.

1.10 Symmetry of the Epidermal Pattern

A uniform epidermal hyperplasia (Figs. 12.3, 14.2 and 14.3) is typical of a nevus. This hyperplasia can be strikingly symmetrical and is more evident at the center of the lesion and tapers toward the lateral borders. Generally speaking, uniformly elongated or thickened rete ridges are even present in nevi with unusual cytological details. A melanoma grows in the epidermis in an uneven fashion, and the rete ridges are effaced or asymmetrically altered. In melanomas foci of epidermal hyperplasia irregularly alternate with uneven thinning or even ulceration of the epidermis, and the rete ridges are chaotically enlarged, thinned, or utterly destroyed. One can even look only at the epidermis of a lesion using a keratin stain and predict with reasonable accuracy if the lesion is benign or malignant.

1.11 Uniform Cellular Density

A similar density of the cellular content (within the same level of the dermis) is always a good clue to the benign nature of a lesion (Figs. 5.14 and 6.5). Particularly, a uniform distribution of the melanocytes at the junction, or even above it, is indicative of a nevus. For example, a Spitz nevus or a nevus of acral-volar skin can have impressive pagetoid spread, but cells are uniformly distributed in the epidermis, and one can appreciate the fact that the cellular density per unit area is similar throughout the lesional epidermis (in acral nevi, evenly beneath the sulci superficiales). Also, cellular density in the dermis is homogeneous at each single level of the ideal nevus. The number of cells per unit area is basically similar in the same level, and the modes of aggregation of the cells such as nests, cords, strands, and syncytia are uniform.

1.12 Early, Preponderant Aggregation in Discrete Nests

Most acquired nevi probably start with a lentiginous stage, after which melanocytes aggregate to form nests. Therefore the finding of prominent nests of melanocytes at the dermoepidermal junction in a narrow (e.g., <4 mm) lesion is strong evidence of benignity. Melanomas take years to form nests which consequently appear only in broader lesions. Additional findings that point to a nevus are nests that are round, similar to each other, and distributed uniformly along the junction without skip areas.

Areas of epidermis with melanocytes aligned in single units (in a so-called lentiginous pattern) should be absent or inconspicuous. Inside the nests, cells are quite tightly packed and similar to each other in morphological details and in pigmentation. Mitoses should be rare and not seen in clusters. Finally, two discrete nests usually bookend each lateral borders of an ideal nevus which, as a rule, "starts with a nest and ends with a nest."

1.13 "Maturation"

Maturation is a misnomer indicating two different phenomena. The first consists in a seeming shrinkage of melanocytes whose size diminishes in the deeper part of the lesion (16.7, 20.3).

The second form of "maturation" consists in the schwannian metaplasia of the melanocytes, which become achromic and elongated and start to synthesize basement membrane material and fibrillary collagen.

These two events do not really represent maturation (a mature melanocyte synthesizes melanin and transmits it through elongated dendrites), but both are nice clues to the benign character of the neoplasm.

Attention should be paid to the fact that neural "maturation" occurs in desmoplastic, neurotropic, and neural differentiated melanomas. Moreover, maturation (i.e., diminished size of the melanocytes) has been noted in the so-called nevoid melanoma and in metastatic melanomas. To make things more confused, many nevi can be entirely devoid of "maturation." For example, the absence of a downward gradient of cellular differentiation is the rule in all types of blue nevi.

Along with diminished cellular size, smaller nuclei, smaller nucleoli, less cytoplasm, and less pigmentation are all correlates of maturation. Maturation probably reflects the dependency of melanocytes on growth factors made by keratinocytes. Even in melanoma, staining for HMB45 is often less in deep dermal, than in junctional cells. While "maturation with descent" is a well-established cliché, in many nevi "activation with ascent" is a more accurate assessment.

1.14 Cellular Monomorphism, Lack of Atypia and Necrosis, and Low Mitotic Rate

The absence of nuclear pleomorphism and hyperchromasia and the lack of large eosinophilic nucleoli are all comforting indications of the innocent nature of melanocytes (Figs. 8.3 and 8.7).

Although many exceptions exist, stereotypical benign melanocytes have a uniformly thin nuclear membrane with evenly distributed speckled chromatin. The nuclear contour is smooth and regular. A pinpoint single nucleolus is sited in the center of the cell. The cytoplasm in most nevi contains evenly distributed melanin or may lack melanin. Necrosis is absent in nevi, with rare exceptions. These include traumatized nevi, in which cells with pyknotic nuclei can be present in the upper part of a lesion.

Mitoses can occur in any type of melanocytic nevus. However, the presence of mitoses in significant number ("easily found") or mitoses gathered in clusters and – most importantly – mitoses in the deep portion of the lesion are findings favoring a melanoma.

Mitoses are an important additional clue of malignancy when coupled with other criteria; in other words whereas a single mitosis is an acceptable finding in an innocent-looking lesion, the presence even of a single mitosis in a neoplasm with conspicuous nuclear pleomorphism or atypia makes melanoma more likely. We would like to say that in a benign melanocytic neoplasm, one can accept mitoses or pleomorphism, but not both together.

Often, nevi with a seemingly high mitotic rate will have a comfortably low proliferative fraction in a Ki-67 immunostain; the reason for this discrepancy is not clear.

1.15 Negative Immunohistochemical and Genomic Characterization

Immunostaining and molecular studies provide useful and occasionally decisive findings for diagnosis. These results should always be evaluated according the peculiar characteristics of the different entities and in concordance with the morphological findings. We illustrate some results of these ancillary techniques in the different chapters. As a rule we never trust the final diagnosis to these procedures alone. To be sure, deep sequencing of melanocytic neoplasms has the potential to provide a comprehensive assessment of its malignant potential, but this technique is not yet in routine use. For most immunohistochemical methods, decisive results are only seen in cases that present little challenge by conventional microscopy.