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Opinion

The melanocytic nevus described by Clark et al. What is its nature? What should it be named? An answer from history and from logic

Mark A. Hurt

Cutaneous Pathology,
WCP Laboratories, Inc., Maryland Heights, MO, USA

Mark A. Hurt, MD,
Cutaneous Pathology,
WCP Laboratories Inc., 2326 Millpark Dr., Maryland Heights, MO 63043-3530, USA
Tel: +1 314 991 4470
Fax: +1 314 991 4309
e-mail: markhurt@aol.com

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The article by Shapiro et al.,[1] which summarizes a survey of respondents on the words or phrases they use to identify the melanocytic nevus described by Clark et al.[2] in 1978, shows that over 70% of The American Society of Dermatopathology (ASDP) members and nearly 85% of The American Academy of Dermatology (AAD) members preferred one of the following phrases: "dysplastic nevus", "nevus with architectural disorder", "atypical nevus", or "atypical melanocytic hyperplasia". Only about 11% of the ASDP members and less than 5% of the AAD members identified the nevus as either a "Clark's nevus" or a "compound nevus", thereby avoiding the designations "dysplastic", "architectural disorder", and "atypical".

This article revealed one important fact about the nature of the melanocytic nevus that has for over 26 years eluded and confounded dermatopathologists, pathologists, and dermatologists alike. The fact is that the disparate, inconsistent *nomenclature* applied to this particular type of melanocytic nevus reflects a *conceptual* conundrum that exists in the minds of susceptible histopathologists. This nomenclature results in producing confusion and uncertainty and implies that melanoma cannot be excluded in these lesions *vis-à-vis* the pairing of the terms "atypical", "dysplastic", or "disordered" (implying that one cannot exclude malignancy) with "melanocytic nevus" (a phrase of certainty that refers to a hamartoma or benign neoplasm). The *actual* melanocytic nevus in question is, however, either a hamartoma or a benign neoplasm that never killed anyone and never will. Its diagnosis should, therefore, be clean, clear, and unequivocal.

What is the origin of this uncertainty? Why have 26 years, two consensus conferences (resulting in no consensus), and tens of millions of dollars of National Institutes of Health's grant money failed to produce a rational, uniform approach to the diagnosis of this type of melanocytic nevus?

In my opinion, there are several reasons for this failure, chief among which are:

1. The problem of nomenclature
2. The problem of circular reasoning
3. The problem of dysplasia
4. The problem of pathogenesis vs. diagnosis

1. The problem of nomenclature

When, in 1978, Clark et al.[2] described the melanocytic nevi of patients with the "B-K mole syndrome", they noted (in their Table 2) that the lesions were composed of "nests of melanocytes and individual melanocytes orderly in structure, plus quite atypical melanocytes". Yet, in the 1992 consensus conference, the name agreed on to represent this same class of lesions was "nevus with architectural disorder",[3] and the consensus did not require that its melanocytes be "atypical". Thus, a lesion described originally as having an "orderly structure" with "quite atypical melanocytes" was, 14 years later, described as a "nevus with architectural disorder" that may or may not have "atypical" melanocytes. It is no wonder that diametrically opposed descriptions of the same type of lesion resulted in the lack of consensus.

2. The problem of circular reasoning

In 1980, Elder et al.[4] described melanocytic nevi with histopathological features similar to those seen in "B-K mole syndrome" that occurred in patients who had no family history of melanoma. Elder et al. stated that:

> "Though the syndrome was first recognized in patients with 200 or more dysplastic nevi, presentation with ten or fewer or even a single lesion is not uncommon."

Here, the authors attempted to prove that patients had the "dysplastic nevus syndrome" if their melanocytic nevi showed "melanocytic dysplasia" histopathologically. The following quotation illustrates this viewpoint fully:

> "all patients who clinically exhibit a dysplastic nevus syndrome have at least two selected nevi removed for histologic study. If the lesions histologically show melanocytic dysplasia, the patients are assigned to the dysplastic nevus syndrome."

In other words, the patients were selected, because they already had a "dysplastic nevus syndrome" clinically, but in order to establish that they had the "dysplastic nevus syndrome", the histopathological features of at least two of these *special* melanocytic nevi were required to *establish* the diagnosis of the "dysplastic nevus syndrome". Would this mean also that if the nevi did not have "dysplasia", the patients would *not* have the "syndrome" when they were known already to have it clinically? No answer was ever given. Elder et al. conveyed, perhaps unwittingly, that patients with the "dysplastic nevus syndrome" have "dysplastic" nevi, and when a patient has a "dysplastic" nevus, he has the "syndrome". Circular reasoning such as this must be rejected as illogical and non-scientific, but those authors did not reject it.

What Elder et al. did not consider also was a negative control study to investigate melanocytic nevi in patients who had no family history of melanoma and who harbored few melanocytic nevi. They failed also to address the histological features of melanocytic nevi less than 5 mm in diameter. Such studies conducted years later revealed that melanocytic nevi with the pattern described by Clark et al. in 1978,[2] and Elder et al. in 1980,[4] were identified commonly in the negative control groups, proving beyond doubt that there was nothing special about the histopathology of any of these melanocytic nevi in predicting whether an individual had multiple melanocytic nevi or melanoma.[5,6]

3. The problem of dysplasia

In order to make the case for the use of the term "dysplasia" in melanocytic proliferations, its advocates had to define what they meant by that word. In their article on "tumor progression" in melanocytic proliferations in 1984, Clark et al.[7] defined "dysplasia" in the following way:

> "It has been stated that the peripheral extent of growth of intraepidermal melanocytes defines the lateral margins of the dermal component of nevi and that the nesting of melanocytes within the epidermis, in preparation for migration into the dermis, is apparently the first manifestation of the pathway of differentiation (R. J. Reed, unpublished data). From the present study of normal nevi in the sequential decades of life, this view seems reasonable. (page 1150)
>
> The phenomenon of continued intraepidermal growth of melanocytes at the shoulder of a normal nevus may thus be termed aberrant differentiation: the normal nevic pathway of differentiation is flawed. (page 1154)
>
> Cytologically, atypical melanocytes may appear in the area of persistent melanocytic growth at the shoulder of a nevus (aberrant differentiation). Such atypical cells vary from one nevus to another, but two forms are apparent. The first is seen within a prominent area of lentiginous melanocytic hyperplasia. Characteristically, it appears as a large, hyperchromatic nucleus surrounded by a rather sparse amount of cytoplasm, frequently showing artifactual shrinkage. We have described this type

> of atypia as lentiginous melanocytic dysplasia.
>
> The second form of atypical melanocyte is larger, owing to an abundance of cytoplasm, and usually contains finely divided pigment. This cytoplasm rarely shows artifactual shrinkage and surrounds a large nucleus that tends to be spherical and somewhat less chromatic than those of lentiginous melanocytic atypia. We have termed this second type of atypia epithelioid melanocytic dysplasia. These atypical cells may be mixed with areas of lentiginous melanocytic atypia, or they may be present as isolated cells at the shoulder of a nevus or in the epidermis over the central region of a nevus. (pages 1154–1155)
>
> In this paper we use the term melanocytic dysplasia to include both persistent lentiginous melanocytic hyperplasia and melanocytic nuclear atypia. However, the sine qua non of melanocytic dysplasia remains melanocytic nuclear atypia. (page 1159)"

This message about dysplasia was mixed and ill defined, the authors' prodigious efforts notwithstanding. There was never any evidence that the extension of melanocytes peripherally in the epidermis, beyond the dermal component of a melanocytic nevus, signified anything more than a specific pattern identified in some melanocytic nevi. Moreover, the statement about Reed's unpublished data that was quoted by Clark et al.[7] had no basis in scientific fact; it was merely an arbitrary assertion that should have been challenged at the time of its publication but was not. Additionally, no one at the time challenged the concept of "normal nevus" as a contradiction in terms (all melanocytic nevi are pathological, including the one Clark et al.[2] described, even though all are benign), but it should have been challenged and rejected. Furthermore, "persistent lentiginous melanocytic hyperplasia" is nothing more than a synonym for melanocytic neoplasia, and a poor synonym at that. Hyperplasia *per se* implies a temporary state biologically that reverts to normal after the cause is removed. In contrast, neoplasia (whether benign or malignant) is a permanent condition as a rule, regardless of cause. Finally, because Clark et al.[7] stated that "nuclear atypia" was the "sine qua non of melanocytic dysplasia", there was no need to include structural patterns within the definition.

To complicate matters further, the phrase "nuclear atypia" (whatever that means) has been applied to both benign and malignant melanocytic proliferations. Spitz's nevus is an example of a melanocytic neoplasm with the most consistently pleomorphic cytology, yet Spitz's nevus is a *benign* neoplasm. Conversely, many examples of melanoma contain relatively small, monomorphous melanocytes; the diagnosis is established primarily by its structure, rather than by its cytology.

Despite repeated attempts, Clark et al. never offered a clear and consistent definition of melanocytic dysplasia, much less clarified how such a phrase might resolve the understanding of the natural history of certain patterns of melanocytic nevi that were termed, originally, "dysplastic".

4. The problem of pathogenesis vs. diagnosis

Clark et al.[7] linked the term "precursor" to melanoma by way of the so-called "dysplastic" melanocytic nevus. In their abstract, they remarked that

> "The common acquired melanocytic nevus is viewed as a focal proliferation of melanocytes, destined in most instances to follow a programmed pathway of differentiation that leads to disappearance of the nevus. If the pathway of differentiation is not followed, characteristic lesions result, and such lesions are regarded as the formal histogenetic precursors of melanoma. Such a developmental flaw is termed aberrant differentiation, and the resultant precursor lesion is designated melanocytic dysplasia. The vast majority of melanocytic nevi showing melanocytic dysplasia are terminal lesions that do not progress to melanoma. If melanoma is to develop via a precursor lesion, however, the nevus with melanocytic dysplasia is that precursor. When melanomas do develop, they develop focally within the precursor".

In one respect, Clark et al.[7] were correct to make this association between melanocytic nevi and melanomas; in another respect, they were wrong to do so. They were correct to note that melanomas are associated sometimes with melanocytic nevi, but this fact was already well known at the time of their article. They were wrong, however, to infer that the "precursor" was *only* that of a melanocytic nevus. Because of this speculation by Clark et al.,[7] there has been a widespread misconception that melanocytic nevi somehow convert themselves *wholesale* into melanomas, despite the fact that Clark et al.[7] stated that "when melanomas do develop, they develop focally within the precursor". What *is* true is that melanomas can occur in association with melanocytic nevi, but they occur most commonly as *de novo* lesions.

No one knows the mechanism(s) by which a melanocyte within control skin or within a melanocytic

nevus becomes the nidus of a melanoma. This is why the designations "precursor" and (even worse) "premalignant melanocytic dysplasia"[8] are so problematic. By the time one recognizes a given lesion for what he thinks it is, its nature is *already* determined and, in most instances, diagnosable.

To clarify this further, the term "precursor" might refer to the *field* in which the melanoma is found, or one might mean that the "precursor" is the evolutionary step immediately preceding the development of a melanoma. As the *field* must include control skin as well as any type of melanocytic nevus, this designation is unhelpful. In contrast, if one uses the term "precursor" to refer to the developmental step prior to the melanoma, he cannot prove his point, because it is impossible to observe or otherwise confirm such a "transformation" and correlate its clinical and histopathological findings *in vivo*. In sum, the concept of "precursor" is misleading and should be avoided.

As for the phrase "premalignant melanocytic dysplasia",[8] such a designation signifies that the lesion is *already* malignant, at least in a rudimentary form, else how could one know it was to become the malignancy? Thus, this phrase must be avoided also because it is unhelpful and misleading.

The *real* challenge diagnostically is whether one can differentiate particular patterns of melanocytic nevi from the melanomas that mimic them. One can, with experience, do this in most cases. The pathologist is thus able to identify a given melanocytic lesion as a melanocytic nevus, a melanoma, or a melanocytic nevus occurring in association with a melanoma. The fourth possibility is that one cannot assign the lesion to any of these categories; that is, the status diagnostically is uncertain (melanoma cannot be excluded) and should be stated as such in the pathology report. In nature, of course, there are only three possible diagnoses: melanocytic nevus, melanoma, or melanocytic nevus in association with melanoma.

Words used properly are lenses that serve to focus one's mind. Words employed with disparate, incorrect, ill-defined, or ambiguous meanings, however, achieve the opposite, a blur. "Dysplastic nevus", "nevus with architectural disorder", "atypical nevus", and "atypical melanocytic hyperplasia" are smeared or broken lenses that prevent the observer from seeing the problem clearly.

What, then, is my answer about the nature of the melanocytic nevus described originally by Clark et al.?[2] It is just *that*: it is a melanocytic *nevus*, whether one uses descriptive terminology, as I do (lentiginous melanocytic nevus[9]), or an eponym (Clark's nevus[10,11]) to convey that message.

To consider this issue any other way is to introduce a contradiction in terms: a melanocytic nevus that is *not* a melanocytic nevus. I believe, therefore, that most of the respondents to the survey of Shapiro et al.[1] should reconsider whether they should continue to use such contradictions in the diagnosis of these melanocytic nevi.

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