Dysplastic Nevus
Why This Term Should be Abandoned in Dermatoscopy

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KEYWORDS

• Melanoma • Dysplastic • Congenital • Follow-up • Nevi • Dermatoscopy • Dermatopathology

KEY POINTS

- The hypothesis that the "dysplastic" nevus is a precursor of melanoma has not been supported by empiric data. The term "dysplastic nevus" is a misnomer because in pathology "dysplasia" describes an intermediate state between a benign and a malignant neoplasm.
- The statement that the diagnosis of a dysplastic nevus is based only on histopathologic criteria and does not correlate with clinical criteria is a clever way to immunize the concept against falsification.
- The strong correlation between melanoma risk and the phenotype of large and numerous nevi has erroneously been interpreted as a causal relationship.
- The terms "dysplastic" and "atypical" nevus are often used by clinicians and pathologists to express their diagnostic uncertainty but it has nothing to do with biologic uncertainty.
- There are parts of a melanoma that may look like a nevus clinically, dermatoscopically, and histopathologically, which led to the unjustified assumption that the inconspicuous part of the melanoma is a precursor nevus.

INTRODUCTION

From the outset the concept of the "dysplastic" nevus encompassed 2 different hypotheses: (1) that the dysplastic nevus is a precursor of melanoma,[1–3] and (2) that the dysplastic nevus is a marker of melanoma risk.[4–6] The first hypothesis makes a prognosis pertaining to individual lesions; the second is related to the prognosis of individuals. Although there is good evidence that the presence of multiple large nevi is indeed a marker of melanoma risk, the precursor hypothesis has been falsified by empiric data.[7,8] Both hypotheses were set forth by Wallace H Clark Jr more than 30 years ago. The first hypothesis was described in Clark's own words, as follows: "Six evident lesional steps of tumor progression form the neoplastic system that affects the human epidermal melanocyte: (1) the common acquired melanocytic nevus; (2) a melanocytic nevus with lentiginous melanocytic hyperplasia, ie, aberrant differentiation; (3) a melanocytic nevus with aberrant differentiation and melanocytic nuclear atypia, ie, melanocytic dysplasia; (4) the radial growth phase of primary melanoma; (5) the vertical growth phase of primary melanoma; and (6) metastatic melanoma."[2] This model of Clark's became accepted universally by dermatologists and dermatopathologists, attaining the status of paradigm.[9] Despite refutation of the hypothesis that the dysplastic nevus is a precursor of melanoma, the term "dysplasia" has not been abandoned.[10] It is a misnomer because in pathology "dysplasia" describes an intermediate state between a benign and a malignant neoplasm, which the dysplastic nevus is not. This article is aims to explore why the term "dysplastic nevus" has not been dropped and why this term is dispensable from a

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dermatoscopic point of view. The most important reasons the term "dysplastic nevus" has not vanished despite its inadequacy are as follows: (1) the successful attempts to immunize the concept of dysplasia against falsification, (2) the confusion of correlation with causal relationship with regard to the dysplastic nevus syndrome, (3) the confusion of diagnostic uncertainty with biologic uncertainty, (4) the confusion of portions of melanoma that look like nevi with portions of nevi that look like melanoma, (5) the term "dysplastic nevus," although inadequate, served clinicians, pathologists, and patients well, and (6) the partition into 2 different camps of doctors, believers and nonbelievers, that did not bring forward a productive, scientific discussion based on critical arguments but an unfruitful vendetta in which each side took up rigid positions.

SUCCESSFUL ATTEMPTS TO IMMUNIZE THE CONCEPT OF DYSPLASIA AGAINST FALSIFICATION

It has often been stated that the diagnosis of a dysplastic nevus is based on histopathologic criteria and does not correlate with clinical or dermatoscopic criteria. This argument is often used to refute clinical or dermatoscopic data that contradict the precursor hypothesis[7,8,11–14] and it is a clever way to immunize the concept against falsification. If clinical and dermatoscopic atypia would not in some way correlate with histopathologic "dysplasia," in other words, if there were no clinical or dermatoscopic criteria for the dysplastic nevus, it could not be diagnosed by clinicians and dermatoscopists. It could only be diagnosed by dermatopathologists. This is not the case for any other type of nevus. Even Spitz nevi can be diagnosed clinically and dermatoscopically with some specificity,[15,16] although cytologic features are so important for their diagnosis. If a nevus has to be excised to see dysplasia, then any attempts to verify or falsify the hypothesis that the dysplastic nevus is a precursor lesion are doomed to fail. Once the lesion is excised, its future remains unclear forever and, for this reason, the opinion that the dysplastic nevus can only be diagnosed histopathologically immunizes the concept of dysplasia against falsification, which is not comparable to the situation of precursors of epithelial skin cancer, for example, actinic keratoses. From original clinical observations, it is known that the proportion of actinic keratoses that will progress to invasive squamous cell carcinoma within a certain period of time is relevant.[17,18] In the case of actinic keratosis there is empiric evidence that some of them will progress to squamous cell carcinoma. On the other hand thousands of atypical nevi were monitored in patients with the dysplastic nevus syndrome with digital dermatoscopy but a transformation to melanoma was not observed.[19–21] Practically no melanomas were detected arising in those nevi. Most if not all of the small number of melanomas detected during follow-up were melanomas from the outset and showed no associated nevus histopathologically.[22]

If the dysplastic nevus could only be diagnosed histopathologically, it would also be difficult to explain why so many nevi that are excised for diagnostic reasons are diagnosed as dysplastic nevi histopathologically. If they are picked only by chance, then they must be very common, more common than common nevi! It cannot be both ways. Either nevi referred to as being "atypical" by clinicians are likely to be dysplastic on pathology and then it must be accepted that most atypical/dysplastic nevi never progress to melanoma or clinicians and dermatoscopists pick dysplastic nevi only by chance. The question then remains as to why dysplastic nevi are so common among excised lesions.

Other reasons the concept of dysplasia is difficult to falsify are that the histopathologic criteria used to diagnose a dysplastic nevus are vague and subjective and that the criteria are not used in a consistent way. The interobserver agreement for grading dysplasia is low because terms like nuclear atypia are highly subjective.[23] Another issue is that what currently is depicted in leading textbooks of dermatology and dermatopathology as dysplastic nevus in some instances represents a variant of a congenital nevus, in other instances, a Clark nevus.[24] These 2 nevi are fundamentally different and can be distinguished by dermatoscopy.[16] In other words, what has been termed "dysplastic nevus" is not one type of nevus (**Figs. 1** and **2**). From a dermatoscopic point of view, nevi with different patterns can be differentiated.[16] The most important patterns in this regard are the reticular pattern, the pattern of clods (globular pattern), the radial pattern (starburst pattern), and the structureless pattern. It is known that each of these patterns has different biologic significance. Nevi with a pattern of clods predominate in children; nevi with a reticular pattern predominate in adults.[25] Nevi with a radial pattern grow rapidly; nevi with a reticular pattern grow slowly.[26] Nevi with a hyperpigmented structureless pattern in the center and reticular lines at the periphery are different from nevi with a raised hypopigmented center or nevi with a pattern of clods. These nevi are different from a clinical, dermatoscopic, and biologic point of view and should not be summarized under the inadequate generic

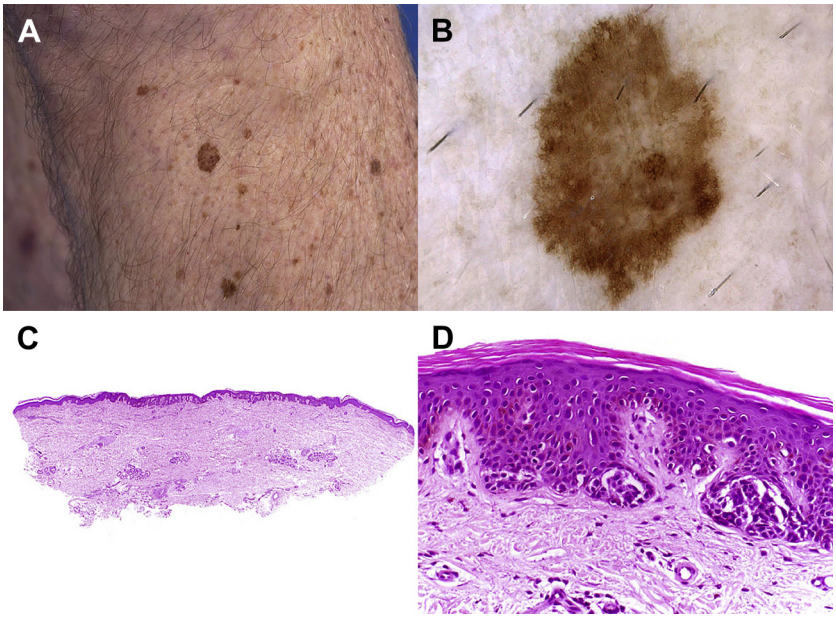

Fig. 1. Clinical (*A*) and dermatoscopic (*B*) image of a clinically "atypical" lesion, histopathologically reported as "dysplastic nevus." (*C*) and (*D*) Dermatopathologic images, revealing nests of melanocytes within tips of the rete ridges, corresponding to reticular lines seen in dermatoscopy (hematoxylin eosin, original magnification ×20). Clinical, dermatoscopic, and histopathologic appearance of this nevus is different from the lesions shown in Fig. 2. Integrating all information, the specific diagnosis should be Clark nevus and not dysplastic nevus.

term "dysplastic nevus" that does not capture these differences.

THE DYSPLASTIC NEVUS SYNDROME AND THE CONFUSION OF CORRELATION WITH CAUSE

The strong correlation between melanoma risk and the phenotype of large and numerous nevi[1] has erroneously been interpreted as a causal relationship. It was thought that the large nevi of these individuals are the precursors of their melanomas.[2] Although some melanomas may start in preexisting nevi, it is the exception and not the rule.[7] Most melanomas start de novo and not in a preexisting nevus of any type, and if they start in a preexisting nevus, it is often a completely inconspicuous nevus and not a large dysplastic one.[27] The risk of melanoma and the phenotype of large and numerous nevi are correlated because there is a common genetic background that is associated with both conditions. Some of the genes involved have been identified. It is known that some melanoma families with the dysplastic nevus syndrome bear mutations in the CDKN2A or in the CDK4 locus.[28–32] The cause for the increased risk to develop melanoma is genetically determined and one cannot decrease that risk by removing the nevi. That the dysplastic nevus syndrome is genetically determined is supported by the fact that many so-called dysplastic nevi are actually congenital.[24] Many patients with the dysplastic nevus syndrome have multiple small congenital nevi with an increased number of terminal hairs (Fig. 3). If investigated dermatoscopically, they show a combination of pattern of clods (globular pattern), reticular lines, and brown structureless areas (see Fig. 3). It is known that they are congenital (although most of them were not present at birth) because some of them present with terminal hairs, which identify them as hamartomas. Other nevi in the same patients have the same dermatoscopic pattern and, although they have no increase in the number of terminal hairs, it is likely that they are also congenital. The point thatis demonstrated by dermatoscopy is that at least some patients with the so-called dysplastic nevus syndrome actually have a congenital nevus syndrome. A high number of nevi of patients with the dysplastic nevus syndrome were monitored with digital dermatoscopy but practically none of them transformed into melanoma as suggested by the precursor hypothesis. Most if not all of the small number of melanomas detected during follow-up developed on normal skin and not in a preexisting nevus or were melanomas from the outset and showed no associated nevus histopathologically,[21,22] which is how digital dermatoscopy falsified the precursor hypothesis.

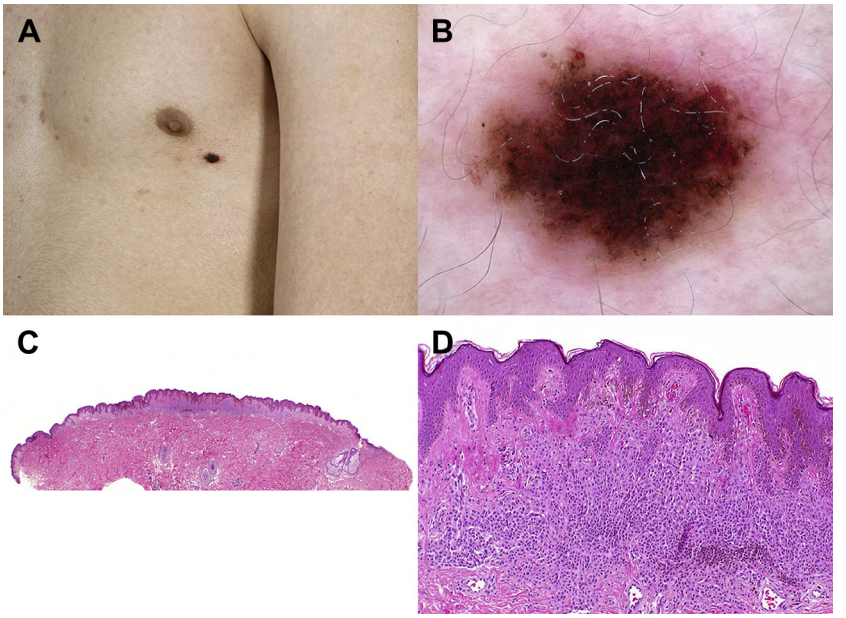

Fig. 2. Clinical (*A*) and dermatoscopic (*B*) image of clinically atypical lesion, histopathologically reported as dysplastic nevus. (*C*) and (*D*) Dermatopathologic images of the lesion, revealing a large but well-circumscribed proliferation of melanocytes within the dermis, corresponding to a brown structureless area in dermatoscopy (hematoxylin eosin, original magnification ×40). The clinical, dermatoscopic, and histopathologic appearance of this nevus is different from the lesions shown in **Fig. 1**. Integrating all information, the specific diagnosis should be superficial and deep congenital nevus and not dysplastic nevus.

THE CONFUSION OF DIAGNOSTIC UNCERTAINTY WITH BIOLOGIC UNCERTAINTY

The terms "dysplastic" and "atypical" nevus are often used by clinicians to express their diagnostic uncertainty. "Atypical" or "dysplastic" nevi share some clinical and dermatoscopic features with melanoma and are contrasted with so-called common nevi that are usually not confused with melanoma. This zone of morphologic overlap between nevi and melanoma has been interpreted

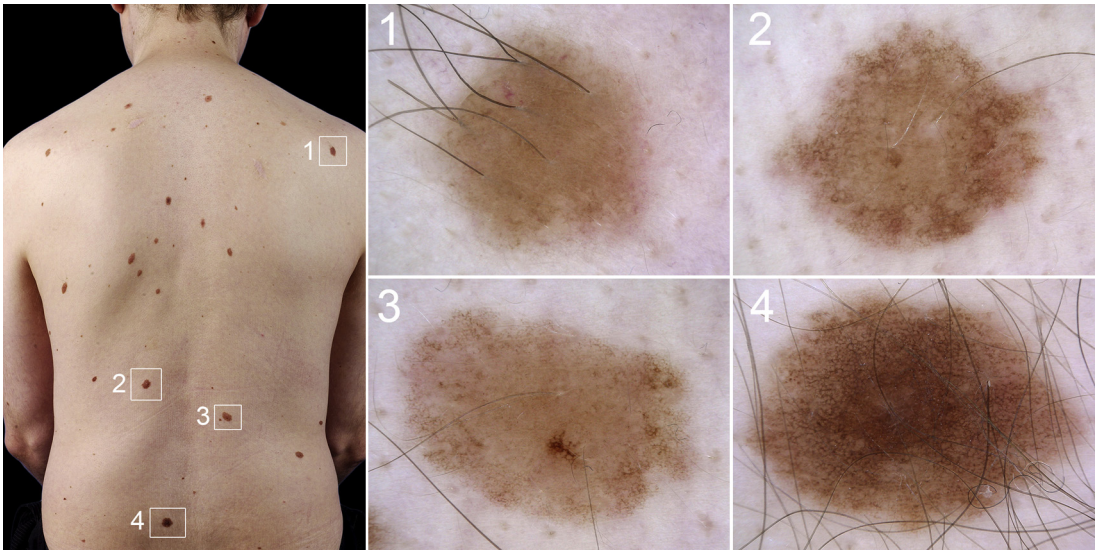

Fig. 3. Left: Clinical image of a patient with dysplastic nevus syndrome. Dermatoscopically (*1–4*) it can be seen that some of the large dysplastic nevi are congenital nevi by the presence of terminal hairs.

as biologic overlap. This analogy is a logical fallacy and not justified. A so-called dysplastic or atypical nevus has a higher chance to be a melanoma but not a higher chance to become a melanoma. Diagnostic uncertainty[23] must not be confused with biologic uncertainty. In **Fig. 4** dermatoscopy images of two nevi are shown. The left one is flat and has a reticular pattern and asymmetry of color; the right one is slightly raised, has a pattern of clods (globular pattern) and symmetry of pattern and color. Which one is more atypical/dysplastic? Most will say the left one because the probability that this lesion is a melanoma is higher. However, if this lesion is excised and the unequivocal diagnosis of nevus has been made, pathologically there is no justification to think that this lesion would have had a higher chance to transform into a melanoma than the lesion on the right. This is a logical fallacy. If a melanoma starts in a nevus, it most often starts in a nevus that looks like the nevus on the right (**Fig. 5**)![7,12,33]

Another example to demonstrate the fallacy that morphology predicts biologic behavior is given in **Fig. 6**. Here the baseline images of 4 pigmented lesions of the some patient with "dysplastic nevus syndrome" are shown. All 4 lesions were monitored with digital dermatoscopy. Only one turned out to be a melanoma. Can you predict which one will turn out to be the melanoma by morphology? The lesions that turned out to be a melanoma during follow-up did not appear more dysplastic or more atypical at baseline than the other nevi that did not change, at least from a dermatoscopic point of view (**Fig. 7**).

In analogy to the use of the term "atypical nevus" by clinicians and dermatoscopists, the term "dysplastic nevus" is used by some pathologists to express their diagnostic uncertainty. In this instance, the term "severe dysplasia" is used to capture the possibility that the lesion actually is a melanoma and not a nevus. For practical purposes, the lower grades of "dysplasia," like "moderate or minimal dysplasia," do not convey this meaning; in fact, their practical meaning (ie, their diagnostic or biologic significance) is completely unclear.

THE CONFUSION OF PORTIONS OF MELANOMA THAT LOOK LIKE NEVI WITH PORTIONS OF NEVI THAT LOOK LIKE MELANOMA

There are parts of a melanoma that may look like a nevus clinically, dermatoscopically, and histopathologically. Flat melanomas especially may have inconspicuous parts that may lack melanoma clues, which often led to the assumption that the inconspicuous part of the melanoma is a precursor nevus. This assumption is not justified. The realization of criteria used by dermatoscopists and dermatopathologists to diagnose melanomas may vary from classic over weak to absent. The absence of criteria in certain parts of the lesion does not eliminate the possibility that the whole lesion is a melanoma. The lesion shown in **Figs. 8** and **9** demonstrates this concept with regard to the example of the dermatoscopic feature of the pigment network ("reticular pattern"). An atypical or irregular pigment network like the one shown in the dermatoscopic image in **Fig. 9** is considered to be a strong clue to melanoma. The irregular network means that the network looks differently in different parts of the lesion. In some parts the lines are gray and thick and in others the lines are thin and light brown. One is tempted to assume that the thin and light brown parts correspond to a nevus and the thick and gray parts correspond to a melanoma. However, on dermatopathology (**Fig. 10**) it is evident that the entire lesion is a melanoma in situ. The misinterpretation of portions of melanoma as "dysplastic nevus" is not restricted to dermatoscopy; it is

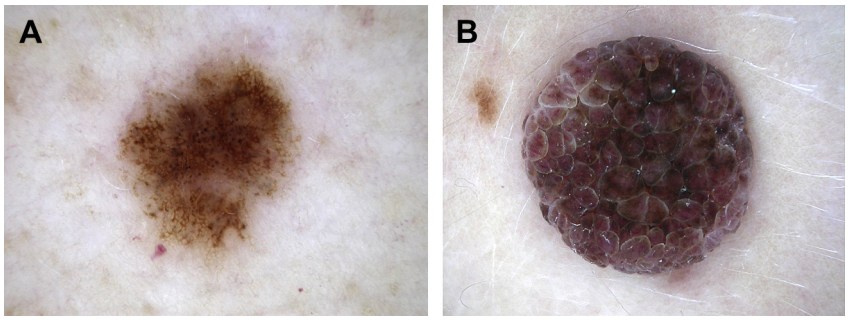

Fig. 4. Dermatoscopic images of 2 melanocytic nevi. (*A*) A flat Clark's nevus showing brown reticular lines and clods, with patterns and colors arranged asymmetrically. (*B*) A slightly raised dermal nevus (Unna nevus) dermatoscopically showing a pattern of clods with symmetrically arranged pattern and color.

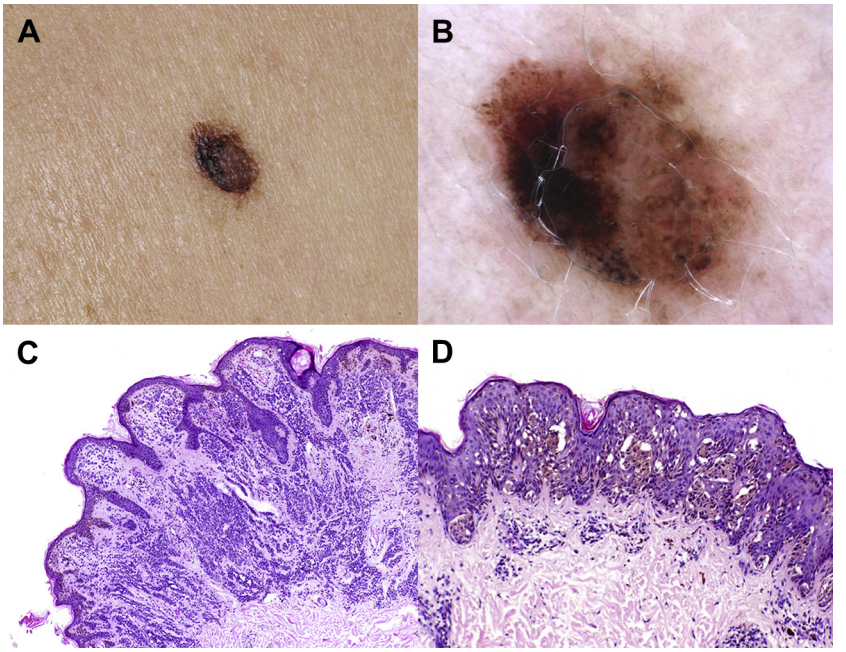

Fig. 5. Clinical (*A*), dermatoscopic (*B*), and histopathologic (*C, D*) images of a melanoma (*D*) arising within an otherwise inconspicuous dermal nevus with a pattern of clods (*C*) (hematoxylin eosin, original magnification ×100).

also common in dermatopathology. Parts of a melanoma may resemble a nevus on dermatopathology. This phenomenon is well known by dermatopathologists under the term "nevoid" melanoma, which is a melanoma that as a whole looks like nevus.

THE TERM "DYSPLASTIC NEVUS," ALTHOUGH INADEQUATE, SERVED CLINICIANS, PATHOLOGISTS, AND PATIENTS WELL

Although inadequate, the term "dysplastic nevus" served dermatologists and dermatopathologists

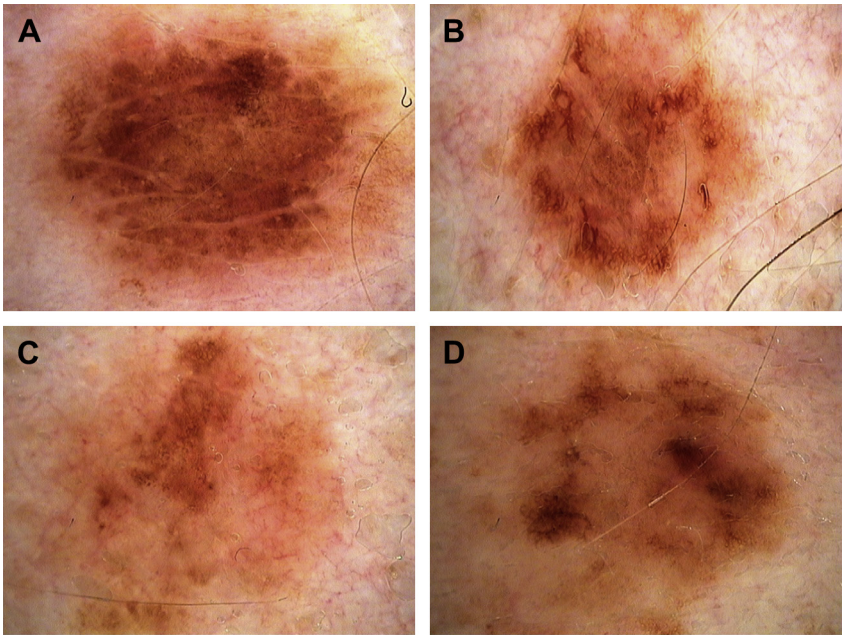

Fig. 6. (*A–D*) Four atypical melanocytic lesions on the same patient, documented by dermatoscopic follow-up. Although all lesions show atypia, only the lesion on the lower right (*D*) was a melanoma.

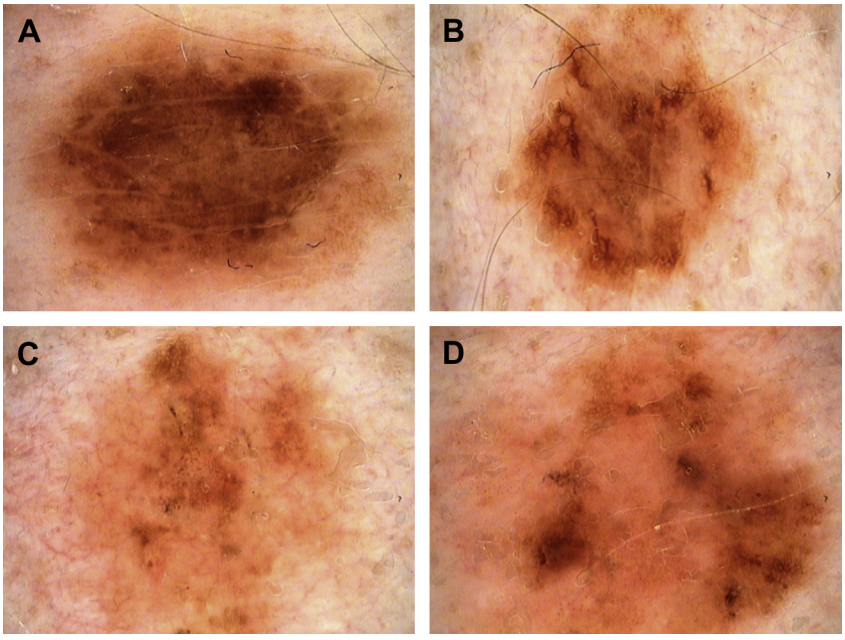

Fig. 7. Dermatoscopic follow-up images of lesions corresponding to those shown in **Fig. 6**, imaged 6 months after baseline. Only the melanoma (*D*) changed significantly; the other atypical nevi (*A*–*C*) did not change during follow-up.

well in the past for various reasons. First, the concept of stepwise tumor progression is appealing and plausible and the dysplastic nevus fills the gap between a benign lesion and a malignant lesion. When melanomas are small and flat, they are difficult to diagnose clinically and dermatoscopically. They look like nevi. From a dermatologist's point of view it is appealing to assume that the phase when melanoma is still inconspicuous is a benign precursor stage of malignancy but not yet malignant. This averts to confess the inability to diagnose small and flat melanoma with certainty. The same limits that pertain to clinicians and dermatoscopists pertain to dermatopathologists. Melanomas are rarely diagnosed when they are smaller than 5 mm, although they exist. Second, there is a certain fear of doctors that diagnostic uncertainty will be misinterpreted as incompetence. From the point of view of a dermatopathologist, it may be easier to call a lesion a severely dysplastic nevus than to admit that he does not know for sure whether this lesion is a melanoma in situ or a Clark nevus. There is an understandable need to paraphrase diagnostic uncertainty. The terms "dysplastic nevus" and "atypical nevus" fulfill this purpose. Third, removal of a nevus for diagnostic reasons is associated with morbidity and is not a pleasure to the patients. It costs them time and money; it may leave scars, and there may be complications including bleeding and infection. If the removed nevus turns out to be just an "ordinary" nevus, patients may view the efforts and risks taken into account to have it removed under a different light as compared with

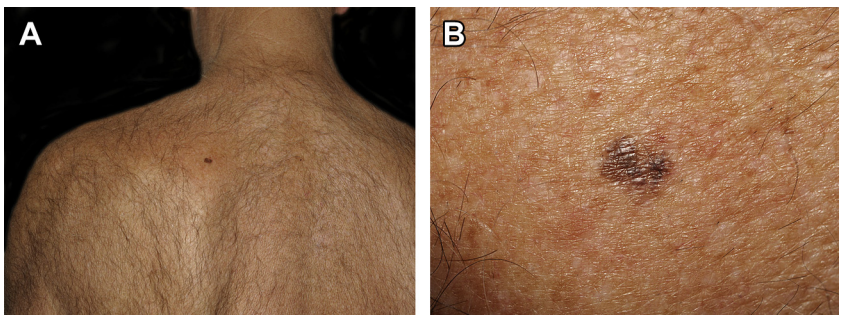

Fig. 8. Clinical overview (*A*) and macro (*B*) image of a melanoma shown in **Figs. 9** and **10**.

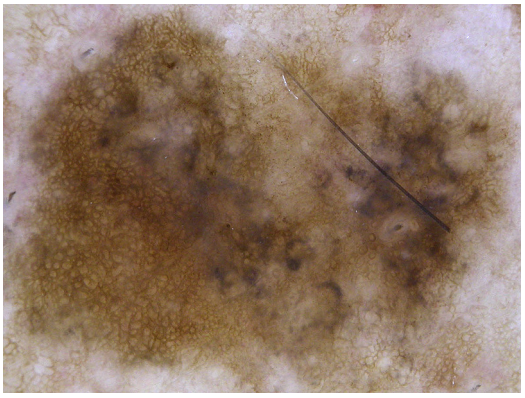

Fig. 9. Dermatoscopic image of the melanoma shown in Fig. 8. Inconspicuous reticular lines on the lower left coexist with an atypical pigment network within the rest of the lesion.

the situation if the removed nevus turns out to be a more "dangerous " dysplastic nevus. By mentioning that "it was good to have this nevus removed because it might have been on the way to something malignant" it sanctifies our decisions in retrospect. Last, it has to be admitted that the phenotype of multiple large nevi commonly known as "dysplastic nevus syndrome" is associated with an increased risk to develop melanoma. Although the fate of a single lesion cannot be predicted, neither by clinical nor by dermatoscopic examination, it is known that these patients need lifelong surveillance of their skin by skilled dermatologists to detect melanomas as early as possible and to remove them when they are still small and flat so that the patient is cured by simple excision.

TWO DIFFERENT CAMPS: BELIEVERS AND NONBELIEVERS

Unfortunately, some disputes in dermatology and dermatopathology are not solved by arguments. Arguments are replaced by beliefs and critique is not tolerated or ignored. Sometimes 2 or more camps are forming that are centered on charismatic persons and the camp with more followers and more visibility prevails. The camp of the critics of the "dysplastic nevus" was led by A Bernard Ackerman, one of the most distinguished and charismatic figures in dermatology and dermatopathology of the last century. He was the first to express significant doubts with regard to the existence and relevance of the dysplastic nevus and refuted the precursor hypothesis.[34] During the past years the controversy of the dysplastic nevus has not been solved. The positions of believers and critics of the dysplastic nevus eventually become so entrenched, especially in dermatopathology, that any open and critical discussions stopped. This is where dermatoscopy comes into play. Dermatoscopy may create a new momentum and supply the dermatologic community with new arguments that may lead to fresh and surprising

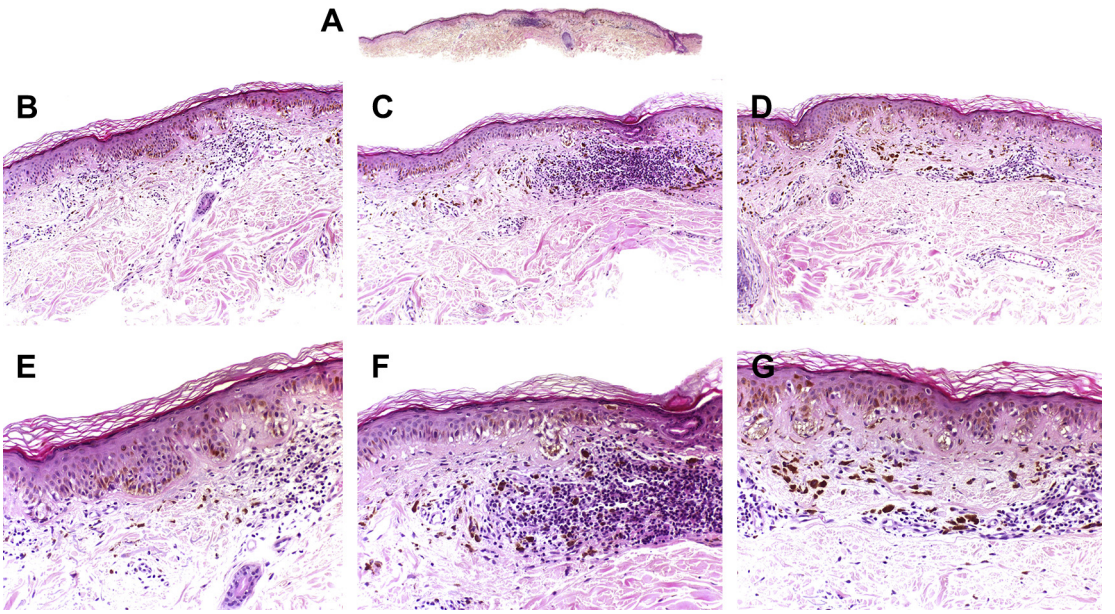

Fig. 10. Overview (*A*) and close-up (*B–G*) histopathologic images of the melanoma shown in Fig. 9. Nests of melanocytes confined to the rete ridges (*D, G*) coexist with confluent single melanocytes at the dermoepidermal junction (*C, F*) (hematoxylin eosin, original magnification ×100).

solutions of an old problem. The problem of the dysplastic nevus in particular and the unsolved problem of the classification of nevi cannot be solved by pathology alone but only by clinical-dermatoscopic-biologic-pathologic correlation.

SUMMARY

The term “dysplastic nevus” is a misnomer and should be abandoned. The generic term “dysplastic nevus” is not just a name, it is the root of the concept that histomorphology (or any morphologic examination including dermatoscopy) is able to predict the fate of a benign melanocytic proliferation. There is no evidence that this hypothesis is true but there are observations that falsify it. This does not necessarily mean that the concept of stepwise tumor progression is not valid; it means that the accumulation of mutations that is necessary to induce malignancy does not express itself as a morphologic spectrum that spans from common nevus over dysplastic nevus to melanoma in situ.

From a dermatoscopic point, the diagnosis of atypia or dysplasia describes diagnostic uncertainty and not an entity (ie, a specific type of nevus). In contrast to the histomorphologic criteria of dysplasia, the patterns observed by dermatoscopy are reproducible and robust and can be used to classify nevi without the need to excise them except when there is diagnostic uncertainty. The use of the generic terms ”dysplastic nevus” and “atypical nevus” for nevi with chaotic arrangement of colors or patterns (morphologic characteristics that are correlated with diagnostic uncertainty) is discouraged. Preferably a specific diagnosis should be made based on dermatoscopic pattern (for example, Spitz nevus, Reed nevus, Clark nevus, or congenital nevus) and if this is not possible on clinical or dermatoscopic grounds alone the term “nevus, not otherwise specified” should be used.

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