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The dysplastic nevus: from historical perspective to management in the modern era:

I. Historical, histologic, and clinical aspects

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Abstract

Since its description in the 1970s, the dysplastic nevus has been a source of confusion, and whether it represents a precursor to melanoma remains a controversial subject. Although a Consensus Conference in 1992 recommended that the term “dysplastic nevus” no longer be used, the histologic diagnosis continues to present a therapeutic quandary for dermatologists and other physicians, and there remains significant variation in clinical management. In part I of this continuing medical education article, we will review the historical origins of the term, the evidence for its distinct histologic basis, and its clinical significance.

Keywords

nevus; melanoma; dysplasia; dysplastic nevus; common nevus

INTRODUCTION

The basis of the controversy

Key points

- The term “dysplastic nevus” is confusing and may have unintended meanings
- The terms “dysplastic nevus” and “atypical nevus” should not be interchangeable

Since the advent of the term in the late 1970s, “dysplastic nevi” (DN) have been a source of confusion and controversy. The heart of the matter is whether (and to what extent) DN represent premalignant lesions that will progress to melanoma.¹ There are those who view DN as a discreet entity of clinical significance,^{2–4} while others dismiss the concept entirely.⁵ DN were originally described in melanoma-prone families, with the implication that such lesions had a higher risk of transformation to melanoma than “non-dysplastic” nevi.^{6–8} This presumption has been promulgated over the years by multiple factors. First, the routine practice of grading nevus cytologic atypia as mild, moderate, or severe (see below) implies directed progression of DN towards melanoma. Similarly, the common reference to DN as “pre-melanoma” (or “pre-melanoma”) lesions suggests they are analogous to actinic keratoses or colon polyps which do evolve (albeit at very low rates)

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to carcinoma. Finally, dermatologists often refer to “non-dysplastic” nevi as “benign” or “normal” (rather than common or banal), which may carry the unintended implication that DN by contrast are not benign (i.e. may be malignant). To further muddy the waters, the terms “atypical nevus” and DN have been used interchangeably in the literature, which is inappropriate on two grounds. First, one represents a clinical finding (atypical nevus) while the other is a histologic description (DN); and second, the terms are not synonymous as lesions lacking clinical atypia may reveal dysplasia and some DN may not exhibit clinical atypia (see below). Given these considerations, this review will collectively refer to all non-dysplastic nevi as “common nevi” (CN) and give the most attention to studies based on histologically-defined lesions (i.e. confirmed DN).

Lack of consensus

Key points

- There is no consensus on terminology among dermatologists or dermatopathologists
- The term DN should not be abandoned

A Consensus Conference was held January 27–29, 1992 at the National Institutes of Health (NIH) to define, among other things, the histologic basis of “early” melanoma and the DN.^{9, 10} The panel recommended that the term DN be abandoned and a new nomenclature be adopted: “nevus with architectural disorder, accompanied by a statement describing the presence and degree of melanocyte atypia” (i.e. mild, moderate, or severe). No guidelines for clinical management of these lesions were issued. Over the years, a number of editorials appeared in the literature to weigh in on the controversy.^{11–15}

In 2005, Shapiro et al.¹⁶ surveyed all 856 active members of the American Society of Dermatopathology and 1100 (13%) active members of the American Academy of Dermatology and reported that the term DN continued to be favored (39% and 62%, respectively) by respondents of these groups. By comparison, the Consensus Conference-recommended terminology was the second most popular verbiage (25% and 15%, respectively).

Some dermatopathologists have promoted using the term “Clark’s nevus” instead of DN.⁵ Rather, we believe that the term DN, despite its problems, should not be abandoned – it has become too entrenched in our dermatologic language and practice. We argue that it represents a distinct histologic entity, and that a critical consideration of all the historical, clinical, and molecular aspects of this lesion type (parts I and II of this continuing medical education article) will lead to better understanding of its biologic significance and more rationale management by practitioners.

HISTORICAL AND CLINICAL ASPECTS

Origin of the concept

Key points

- The field can be traced back to three seminal papers published in the late 1970s
- Atypical nevi in melanoma-prone families were described, and given different “syndrome” names

Cawley¹⁷ in 1952 is credited with the first description of familial melanoma based on cases of cutaneous melanoma in a father and two of his three children. There were subsequent reports of melanoma-prone families in the 1960s and early 1970s.^{18, 19} However, the concept of the DN and its association with melanoma came from clinical observations of nevi in several melanoma-prone families in the late 1970s and early 1980s. First, the dermatopathologist Wallace H. Clark and colleagues at the University of Pennsylvania described distinctive nevi in 37 patients from six melanoma families with “B-K Mole syndrome” (B and K were the first letters of the names of two “unusually helpful” patients).⁶ Second, Henry T. Lynch at Creighton University and colleagues reported a similar nevus phenotype in a melanoma-prone family.²⁰ These phenotypic ‘syndromes’ were referred to respectively as B-K Mole syndrome and Familial Atypical Multiple-Mole Melanoma (FAMMM) syndrome. Third, David Elder and colleagues at the University of Pennsylvania coined the term ‘Dysplastic Nevus Syndrome’ (DNS), with familial and sporadic variants.²¹ Thus within a span of three years, three different names had been given to describe nevus phenotypes in melanoma-prone families. These three “syndromes” as described in these papers will be discussed in further detail since they represent the genesis of the concept of the DN and the origins of the controversy surrounding these lesions, and introduced the issues of nomenclature that have persisted from 1978 to the present.

In Clark’s original report,⁶ the authors compiled six melanoma-prone families totaling 69 members in three or four generations, 25 of whom had cutaneous melanoma. Of these 25 patients, 17 were clinically examined and it was deemed that 15 of them had ‘B-K Mole syndrome.’ These patients were clinically defined as having less than 10 to greater than 100 nevi, exhibiting variability of size (from 5–15 mm in diameter), border, and color. Histologically, the nevi were defined as atypical melanocytic hyperplasias, with mesenchymal changes in the papillary dermis, and a lymphocytic infiltrate. It was stated that the term “atypical melanocytic hyperplasia is synonymous with melanocytic dysplasia”...defined as “individual melanocytes or small clusters of melanocytes that have some structural features of malignant melanocytes, but whose potential for development into obvious melanoma is obscure. The situation is precisely analogous to cervical dysplasia and senile keratoses: foci of squamous cells that have some structural features of malignancy, but may remain indolent, regress completely, or progress to obvious carcinoma.”

In Lynch’s report,²⁰ a single cancer and melanoma-prone family with five generations was described. Four individuals developed melanoma and three of these had atypical and numerous (>200) nevi. They proposed that “observation of melanoma in association with a distinguishing cutaneous phenotype characterized by multiple large moles, irregular in shape, colored reddish-brown to pink, with evidence of pigmentary leakage, and with an apparent autosomal dominant mode of inheritance, may constitute a new familial syndrome.” Referring to Clark’s paper which was published several months earlier, they added: “We believe that our more descriptive term ‘Familial Atypical Multiple Mole Melanoma’ syndrome...is a much more meaningful term than ‘B-K Mole’ syndrome. We believe that our term will provide physicians with a better basis for recognition and comprehension of the genetic significance of this newly described syndrome.”

Elder’s paper,²¹ as noted above, introduced the term DNS and postulated the existence of sporadic and familial variants. The authors reported on 79 patients with primary cutaneous melanoma but no family history of melanoma. Total body photographs that had been taken of these patients were reviewed retrospectively, and the patients were segregated into groups. Group I (five patients) had no other identifiable nevi or pigmented lesions, while Group IIA (eight patients) had a few small lesions on the buttocks that were <3 mm in diameter, and Group IIB (seven patients) had from 2–5

larger buttock lesions (0.5–1.5 cm). These patients also had lesions elsewhere, and the photographs suggested that many of them were suspicious, so that additional lesions were biopsied in all but one patient. It was estimated that these patients each had on average 26 nevi. Of the 13 additional biopsies performed, one showed a second primary melanoma, three were unremarkable melanocytic nevi, and nine demonstrated “microscopic atypia similar to that described in the familial B-K Mole syndrome.” Group III was the largest, composed of 59 patients that were deemed to have “normal” nevus patterns. No additional biopsies of these lesions were performed. Elder and colleagues also expanded upon the histologic features of DN, including “nuclear pleomorphism and hyperchromatism, with a lymphocytic inflammatory response and associated fibroplasia.” Two types of dysplasia were described: epithelioid-cell dysplasia and lentiginous melanocytic dysplasia. Epithelioid-cell dysplasia consisted of epithelioid cells with dusty pigment, prominent nucleoli, lateral fusion and pleomorphism of nests and nevus cells having small hyperchromatic nuclei located in the papillary dermis. Lentiginous melanocytic dysplasia was described as having prominent cytoplasmic retraction artifact, irregular (non-nested) basal melanocytic growth that was junctional without a dermal component. It was also purported in this paper that DN are precursors to melanoma, based on the dysplasia noted microscopically.

These three papers formed the backbone of the myriad studies that followed concerning DN, their role in the histogenesis of melanoma, and the controversy over their diagnosis and management.

Relationship to familial melanoma

Key points

- Numerous studies have documented relationship of DN to familial melanoma
- There have been multiple attempts to define DN-related syndromes

These early studies of melanoma kindreds suggested a close relationship with these clinically atypical and histologically DN. It was noted early on, however, that this nevus phenotype was not required for melanoma development in these kindreds, as Clark described two family members who developed melanoma without having clinically atypical or dysplastic nevi.⁶ An autosomal-dominant mode of inheritance of the nevus phenotype has been described in melanoma-prone families.²² It has been reported that up to 30–40% of these families harbor a mutation in the *CDKN2A* locus, which encodes the p16 and ARF tumor suppressor proteins.²³ Rare mutations have also been described in a several families in the proto-oncogene *CDK4*.²⁴ Bishop et al.²⁵ examined five families with known p16 mutations and characterized them phenotypically. They reported that p16 mutation-carriers were more likely to have 2 clinically atypical nevi (OR 3.1), presence of nevi on the buttocks (OR 4.4) or dorsal feet (OR 4.2), and total nevus number >100 (OR 3.4). In this study the histologic features of these nevi in patients with ‘atypical mole syndrome’ were not examined or discussed.

A case-control study²⁶ in the United Kingdom using these same criteria to define ‘atypical mole syndrome’ found that 40 of 266 (15%) patients with melanoma fulfilled these nevus criteria compared to only 7 of 305 (2%) controls. Of 32 families of these melanoma patients that were screened, 15 (47%) had members with the atypical mole syndrome phenotype although only one individual in the group had a history of melanoma. As in many such studies, the histology of these nevi was not examined.

In perhaps the largest study to follow melanoma-prone families longitudinally, Tucker et al.²⁷ noted that the majority of clinically atypical nevi in 33 families remained stable or

regressed over a 25-year period. Although some melanomas were seen to arise in these nevi, melanoma also arose *de novo*, as well as in clinically typical nevi. It is possible that melanoma-prone families or those with known genetic mutations (such as in p16) have a greater risk of developing melanoma from nevi, although this is not the case in the majority of patients with sporadic atypical nevi (discussed below).

The current definition of 'DNS' remains confusing, especially with regards to the histologic entity DN, and various names (atypical mole syndrome, FAMMM syndrome, B-K mole syndrome) continue to be used in some quarters. According to the 1992 NIH Consensus statement⁹ alluded to above, a diagnosis of the FAMMM syndrome or DNS requires 1) melanoma in one or more first- or second-degree relatives, 2) the presence of a large number of nevi (>50) with many having atypical clinical features, and 3) nevi that demonstrate distinct histologic features. The Dutch Working Group proposed that DNS could be diagnosed in patients having a personal history of melanoma and one or more clinically atypical nevi.²⁸ A British group has proposed criteria that include 1) 100 or more nevi >2 mm (50 nevi if <20 years of age or >50 years of age), 2) two or more clinically atypical nevi (nevus >5 mm, irregular edge and pigmentation), 3) one or more nevi on the buttocks, and 4) 2 nevi on the dorsal feet.²⁵ It should be noted that the recommendations from the NIH Consensus conference⁹ are the only criteria among these early classifications of DNS that include histology as a defining feature of this syndrome, while other criteria do not incorporate histologic dysplasia in defining DNS. These criteria are summarized in Table I.

Clinical features of DN

Key points

- DN exhibit clinical features generally not associated with CN (Fig. 1)
- Many studies are problematic due to lack of histologic correlation

As noted above, Clark et al.⁶ reported that nevi in these families exhibited distinct characteristics base on size, border, and pigmentation. Many studies that followed serve to refine the clinical description of the atypical nevus,^{29, 30} however a shortcoming of most studies is lack of histologic correlation or confirmation (as noted above and discussed below).

These nevi are usually isolated, but rarely may be agminated.³¹ The clinical characteristics used by Tucker et al.³² in 1997 clinically defined the atypical nevus as being 5 mm in size and having flatness (being entirely flat or having a flat component). In addition, two of three characteristics were also necessary: 1) variable pigmentation, 2) irregular and asymmetric outline and 3) having indistinct borders (Fig 1). These were the criteria used in what is the largest case-control study studying melanoma risk and nevi discussed above. The Dutch Working Group has used the following criteria for atypical nevi: 1) 5 mm in diameter, 2) vague border, 3) asymmetric shape, 4) irregular pigmentation, and 5) red hue. Obviously, the most clinically relevant criteria would be those features most highly associated with melanoma risk. As mentioned above, Bishop et. al.²⁵ provided some data regarding nevus phenotype and melanoma risk.

While dermatoscopic criteria have also been developed by a number of groups^{33, 34} for evaluating melanocytic nevi, several studies were specifically designed to examine clinically atypical nevi. In a large study, Hofmann-Wellenhof et al.³⁵ classified atypical nevi into six dermoscopic types that were subclassified by pigmentation pattern. They reported that most patients had nevi with a predominant (i.e. signature) dermoscopic feature, and further noted that eccentric peripheral hyperpigmentation was a rare (7.5%)

finding in atypical nevi and recommended that such nevi be closely monitored or perhaps biopsied to rule out melanoma. Annessi et al.³⁶ studied 198 atypical macular melanocytic lesions that were histologically diagnosed as either DN or thin melanoma, and reported that diagnostic accuracy varied by method of analysis with the correct diagnosis rendered in 82.3%, 79.3%, and 71.2% of lesions using qualitative pattern analysis, ABCD rule, and 7-point checklist methods, respectively. The diagnostic accuracy for melanoma for the three methods was 70.8%, 67.8% and 57.7%, respectively. The presence of light brown structureless areas was highly associated with a diagnosis of melanoma (OR 27.9). Often under dermatoscopy, DN show a homogeneous pattern centrally with reticulated network³⁷ or dots^{38, 39} peripherally, with these heterogeneous regions thought to represent an active growth state. Finally, confocal microscopy has been used to study DN, which exhibit characteristics intermediate between CN and melanoma with respect to size and diameter of the dermal papillae and irregularity in cell size.⁴⁰

HISTOLOGIC FEATURES

Basic histopathology

Key points

- DN exhibit distinct histologic features (Fig 2) that are well described
- cytology and distribution, along with dermal characteristics, distinguish DN from CN

Although some melanocytic neoplasms may be difficult if not impossible to classify under conventional light microscopy, there is abundant literature describing the histologic nature of DN. In their original description of DN, Clark et al.⁶ enumerated four main features: 1) atypical melanocytic hyperplasia, 2) melanocytes with cytologic features characteristic of malignant melanocytes, 3) mesenchymal changes in the papillary dermis (eosinophilic fibroplasia) and 4) lymphocytic infiltrate as illustrated in Fig 2. While these criteria remain the basis for defining DN, at least four groups subsequently published additional criteria to help pathologists and dermatopathologists identify and categorize DN. These include groups representing the University of Pennsylvania (Table II),⁴¹ the World Health Organization (Table III),⁴² the European Organization for Research and Treatment of Cancer (Table IV),⁴³ and Duke University (Table V).⁴⁴ In addition Pozo et al.,⁴⁵ recognizing the pitfalls of categorizing atypia in a nevus, proposed an algorithm to segregate low from high grade dysplasia which was accomplished with a diagnostic accuracy of 99.5% in their study.

The World Health Organization enumerated major and minor criteria for the histologic diagnosis of DN.⁴² The major criteria are: 1) basilar proliferation of atypical melanocytes which must extend at least three rete ridges or “pegs” beyond the dermal component and 2) organization of this proliferation in a lentiginous or epithelioid-cell pattern (Fig 2). The minor criteria include: 1) presence of lamellar fibrosis or concentric eosinophilic fibrosis, 2) neovascularization, 3) inflammatory response, and 4) fusion of rete ridges. Using these criteria, a diagnosis of DN requires both major criteria and at least two minor criteria. Using 20 different histologic features, the mean overall concordance of diagnosis reported for 1400 histologic specimens was 92%. The histologic specimens included CN, DN and radial growth phase melanomas, with 10 dermatopathologists participating.

These features may not be uniformly observed throughout individual nevus specimens. Barr et al.⁴⁶ examined 298 DN and found that 36% displayed heterogeneity with respect to atypical features. It has been reported that DN have deranged melanogenesis as indicated by reactivity with monoclonal antibody HMSA-2.⁴⁷ HMSA-reactivity is a

feature of melanocytes in DN and melanomas, but not CN.⁴⁸ Another distinction between CN and DN may be observed by immunohistochemical staining for type IV collagen. Lebe et al.⁴⁹ reported lack of staining in most CN, while 21 of 33 DN showed a continuous pattern of type IV collagen surrounding junctional nests in a concentric fashion while a discontinuous immunostaining pattern was observed in remaining cases.

On the other hand, there are those who believe that DN have never been fully characterized and do not constitute a specific entity. The most prolific proponent of this view was A. Bernard Ackerman. Dr. Ackerman criticized the usage and inconsistency of the term ‘dysplasia’ in pathology, and argued that features of the clinically atypical nevus and the histologic DN are essentially the same criteria that are used to distinguish a banal nevus from melanoma.^{5, 12} Ackerman maintained that all benign nevi could be classified as one of four types: 1) Unna’s nevus, with polypoid morphology and thickened papillary dermis, 2) Meisher’s nevus, dome-shaped with nevus cells arranged in a wedge configuration, 3) Spitz’s nevus, characterized by a benign silhouette of epithelioid or spindled cells having large nuclei with abundant cytoplasm, and 4) Clark’s (or dysplastic) nevus.

The problem with ‘dysplasia’

Key points

- Use of the term “dysplasia” connotes a cytologic change towards neoplasia
- DN may not be akin to epithelial dysplasias in other tissues

One criticism, leveled by Ackerman and others, is use of the term ‘dysplasia’ in describing the histological characteristics of DN. Elder² noted that “the term is not without ambiguity, but...firmly entrenched and widely understood by physicians of most specialties.” While the term dysplasia is entrenched, we feel it is poorly understood by most clinicians and not rigorously defined or applied by most pathologists. ‘Dysplasia’ literally is translated from the Greek *dys-* (bad or malfunction) and *-plasia* (growth, development or change), thus connoting a change in cytology towards neoplasia or malignancy. The original descriptions of DN, and in particular their histologic features, suggested that these lesions may indeed be akin to epithelial dysplasia noted in actinic keratoses, colon polyps, and cervical intraepithelial dysplasia, which are all known to be potential precursor lesions of carcinoma. Evidence that DN are true precursor lesions of melanoma is not convincing from the published literature, as discussed below. A new consensus must be approached so that medical students, residents, dermatologists and those in other specialties taking care of patients with clinically atypical nevi have a clearer message regarding the potential (or lack thereof) for melanoma arising in these nevi.

The NIH Consensus Conference^{9, 10} and subsequent commentaries^{12–14} have endorsed changes in the nomenclature, recommending the phrase ‘nevus with architectural disorder.’ Ackerman and others have advocated the term ‘Clark’s nevus’ both in honor of its initial descriptor as well as to reinforce the notion that it is a nevus variant. However, both these terms have had little support in the dermatology and dermatopathology communities as evidenced by multiple surveys conducted.^{16, 50, 51} As noted above, dermatopathologists and dermatologists favor the term ‘dysplastic nevus’ to the NIH-recommended ‘nevus with architectural disorder’.¹⁶ However those with dual training in dermatology and dermatopathology prefer the phrase ‘nevus with architectural disorder.’

Inter-pathologist correlations

Key points

- Most studies show good intra-observer reproducibility but poor inter-observer correlation
- There are many overlapping histologic features of CN and DN
- The main difficulty with DN relates to stratification of melanocytic dysplasia

Many studies have been undertaken to characterize the intra- and inter-observer reproducibility of diagnosing DN, as well as grading the ‘dysplasia’ present in nevi. There are obviously major difficulties inherent in performing such studies, namely variation in histological criteria as well as the observers themselves. Some of these studies will be specifically discussed below, although most appear to demonstrate good intra-observer reproducibility but poor inter-observer correlation.

It is clear that there are many overlapping histologic features of CN and DN. In a study restricted to clinically typical acquired melanocytic nevi, Klein et al.⁵² examined 58 nevi and found at least one histologic feature of DN present in 88% of lesions. Additionally, it was noted that two or more histologic features of DN were present in 69% of specimens and three histologic features were found in 29%. Several studies address inter-observer agreement in distinguishing DN from CN or melanoma. Duncan et al.⁵³ showed an overall concordance of 77% (κ values 0.55–0.84) in a study involving five dermatopathologists. Similarly, Piepkorn et al.⁵⁴ found that while intra-observer reproducibility was substantial, inter-observer concordance was only fair, among six pathologists reviewing 149 melanocytic lesions despite differences in criteria. Moreover, the WHO melanoma program showed a 92% mean overall concordance in distinguishing CN, DN, and radial growth phase melanomas based on their criteria.⁴² By contrast, there is typically less concordance seen in grading nevi (i.e. classifying mild, moderate, or severe atypia). The previously cited study indicated that experience of the dermatopathologist may be important, as more experienced dermatopathologists demonstrated a grading concordance ranging from 35–58% (κ values 0.38–0.47) while less experienced dermatopathologists showed a concordance between 16 and 65% (κ values 0.05–0.24).⁵³ Thus the main difficulty with the DN does not necessarily seem to be its histologic diagnosis per se, but rather the stratification of melanocytic dysplasia. One study found, however, that given a set of rigid criteria (with a 1 to 5 scoring system) these discrepancies improved but were not entirely eliminated, as a panel of five dermatopathologists and two melanoma specialists were within one grade of the mean on 88% of the cases and in only 3% of the cases did they differ by two or more grades.⁵⁵

Another difficulty in the histological evaluation of these nevi is the apparent heterogeneity with respect to atypical features within individual nevi,⁴⁶ as noted above. Such heterogeneity within lesions is not only problematic for scoring degrees of dysplasia in a nevus, but also may lead to missing a diagnosis of melanoma arising within the nevus in some cases. Of course the main clinical concern is distinguishing severe dysplasia from melanoma. Studies have shown that there is difficulty in distinguishing ‘severe cytologic dysplasia’ in the junctional component of melanocytic proliferations from melanoma-in-situ and superficial dermal invasion. For example, Cook et al.⁵⁶ found that 17% of previously diagnosed melanomas were re-classified as benign lesions with atypia whereas 2% of lesions previously diagnosed as benign were reclassified as melanoma, upon further review by a panel of eight pathologists. It is important to mention that most studies were performed with “expert dermatopathologists” and as such may not generalize to those with general anatomic pathology training or dermatologists who read their own slides. In one study, 17.6% of pathologists offered a false positive

diagnosis of melanoma-in-situ for lesions diagnosed as DN by a panel of expert pathologists.⁵⁷ It is likely that the disparity in the diagnosis of benign versus malignant melanocytic neoplasms that occurs in the real world is likely to be underestimated in the literature.

Correlation of nevus dysplasia and melanoma risk

Key point

- Development of DN is associated with increased melanoma risk

Most prior studies attempting to correlate nevi and melanoma risk were based on patients' clinical phenotype (i.e. clinically atypical nevi) rather than histologic examination of their nevi. Very few studies have attempted to correlate the presence of DN, as defined histologically, with melanoma risk. Arumi-Uria et al.⁵⁸ retrospectively reviewed 6275 cases of "nevus with architectural disorder", which were then grouped based on presence of mild (40%), moderate (26%), and severe (5%) cytologic atypia. A history of melanoma diagnosis in these patients with nevi showing mild, moderate, and severe atypia was 5.7%, 8.1% and 19.7%, respectively. The authors concluded that melanoma risk is higher for persons with DN having higher grades of histologic atypia.

Another study tried to assess the degree of nevus atypia in three groups: patients with past history of melanoma, those with DN and positive family history of melanoma, and unrelated spouses without family history of melanoma. Nevi were evaluated using guidelines from the NIH Consensus Conference guidelines,^{9, 10} and a trend in more severe dysplasia increasing from the low risk groups to those with a history of past melanoma was noted.⁵⁹ Although studies are few in number, it appears that patients who develop more severe cytologically atypical nevi may have a higher likelihood of developing subsequent melanoma.

Is clinical atypia synonymous with histologic dysplasia?

Key points

- Atypical nevus is a clinical term, while DN is a histologic term
- While atypical clinical features may correlate with histologic dysplasia, this is not always the case

In the original descriptions of DNS, it was posited that diagnosis of atypical nevus based on clinical features and that of DN based on histologic grounds, were synonymous. While this assumption was supported in some earlier studies,⁶⁰⁻⁶² others have shown this not necessarily to be the case. In melanoma patients in which the most clinically atypical lesion was removed, Grob et al.⁶³ found that correlation of histologic dysplasia with clinical atypia increased with the number of atypical features. On the other hand, Klein et al.⁵² prospectively analyzed 58 clinically benign lesions (<5 mm in diameter, symmetric, uniformly pigmented, with distinct margins and no erythema) and found that 88% had at least one histologic feature of DN, while 69% had two features and 29% had three features.

Another study by Meyer et al.⁶⁴ was performed with family members in multiple melanoma kindreds, in which 100 pigmented lesions were clinically photographed and evaluated histologically. The overall concordance between clinical and histologic atypia was fair, as the presence of macularity and color variegation correlated somewhat with

higher grades of histological atypia. Similarly, Annessi et al.⁶⁵ found very poor correlation between nevi that were clinically atypical and histologically dysplastic. In this study, 940 acquired nevi were clinically assessed by five dermatologists, and then blindly examined histologically by a single experienced dermatopathologist. Poor correlation between clinical atypia and histologic dysplasia was evidenced by a κ value of 0.17 (sensitivity 58.4%, specificity 66.6%). In particular, many nevi that were 3 to 5 mm in size and not thought to be clinically atypical were found to exhibit histological dysplasia.

These studies support the notion that a clinically atypical nevus does not equate to a nevus with histologic dysplasia and vice versa. This again brings into question the clinical usefulness of a histologic diagnosis of DN. What the clinician would mainly like to know is whether the pathologist thinks there is some probability that a given lesion represents melanoma or is not sampled adequately to exclude that possibility.

EPIDEMIOLOGY AND NATURAL HISTORY

How common are DN?

Key points

- The prevalence of DN is unclear, since most studies did not include histologic confirmation
- DN may be less common than CN in the general population, but more common than CN in “high-risk” patients

The prevalence of DN in the general population is unknown, as most epidemiologic studies have been based on clinical examination without histologic confirmation of dysplasia. A study by Steijlen et al.⁶⁶ based on autopsy cases estimated the prevalence of DN to be 10%, while Piepkorn et al.⁶⁷ estimated their prevalence in Caucasians to be as high as 50%. Lee et al.⁶⁸ reported that among 874 new dermatology patients, 2.4% had biopsies demonstrating DN (compared with 5.8% demonstrating CN) on the first visit, suggesting that DN are less common than CN. One study found the number of DN in individuals correlates with total number of melanocytic lesions,⁶⁷ independent of personal or family history of melanoma.⁶⁹ However, a Swedish case-control study found rates of histologically-diagnosed DN of 40% in patients with history of melanoma versus 8% in controls.⁷⁰ DN tend to be more prevalent in younger adults, although this may partly reflect the disappearance of nevi over time and a tendency towards larger numbers of nevi among more recent birth cohorts.⁷¹ They usually appear in childhood, become readily apparent by puberty, and continue to appear throughout adulthood.⁷¹ Given the importance of genetic determinants in nevus formation and phenotype (discussed in part II of this continuing medical education article), it seems likely that individual patients will be predisposed to forming CN or DN. Thus while DN may be less common than CN in the general population, they may be more prevalent than CN in “high-risk” patients who have prior history of melanoma and/or clinically-atypical nevi.

Eruptive DN

Key points

- Many conditions associated with eruptive CN have also been associated with rapid development of DN

- Eruptive DN may occur after exposure to chemotherapy, melanotropic peptides, or HIV infection

Various factors have been associated with eruptive CN, such as blistering diseases and immunosuppression secondary to cancer, chemotherapy, or human immunodeficiency virus infection. Many of these conditions have also been associated with rapid development of DN. For example, increased numbers of DN have been documented in organ transplant patients within five years of onset of immunosuppression.⁷² Induction of multiple atypical melanocytic lesions has frequently been reported in children with malignant hematological diseases and chemotherapy-induced immunosuppression. Most cases described are of patients with acute lymphoblastic leukemia who developed DN following completion of chemotherapy.^{73, 74} Similar cases have been described in adults, most commonly occurring while receiving 5-fluorouracil (5-FU) for metastatic solid tumors,^{75, 76} but also may occur *following* exposure to 5-FU⁷⁷ or prior to chemotherapy exposure in patients with chronic myelogenous leukemia.⁷⁸

There have also been recent reports of patients developing DN following administration of melanotropic peptides for the purpose of tanning. Cardones and Grichnik⁷⁹ described a 40-year-old male who developed multiple new DN following self administration of α -melanocyte-stimulating hormone. Similarly, Langan et al.⁸⁰ reported two patients presenting with new and rapidly changing DN following subcutaneous injection of melanotan I and II.

Finally, eruptive DN have been described in patients with human immunodeficiency virus infection. Duvic et al.⁸¹ reported seven patients presenting with new nevi demonstrating histologic dysplasia, which arose as they became symptomatic from human immunodeficiency virus infection.

Role of UV exposure

Key point

- UV exposure may promote development of DN

A role for UV radiation in the development of nevi is somewhat controversial, with some studies showing no relationship between patterns of sun exposure and numbers of nevi in patients,⁸² while others report significantly increased numbers of nevi on intermittently and chronically sun-exposed areas⁸³ and in children living in sunnier climates.⁸⁴ Most studies purporting to examine the role of UV in promoting the development of DN (compared to CN), however, are difficult to interpret since identification of DN was based on clinical examination alone.^{83–86} Stierner et al.⁸⁷ found that patients with DNS had larger differences in nevus counts between sun-exposed and sun-protected areas than control subjects, suggesting heightened sensitivity to “nevogenic” effects of UV. This finding is consistent with studies showing that nevi in patients undergoing UVB phototherapy develop more irregular macroscopic and dermoscopic features over time,⁸⁸ but histologic correlates have not been described.

Although sunscreen use can decrease total nevus numbers,⁸⁹ whether this also holds for DN specifically is not known. One study found cells from DN (compared to cells from CN) have increased sensitivity to UVB-induced DNA damage.⁹⁰

Marker of melanoma risk

Key point

- Presence of DN are associated with increased melanoma risk in individuals

There is substantial evidence that patients with DN are at increased risk for developing melanoma. This association was first appreciated in melanoma kindreds as members of these families appeared to have increased numbers of DN,⁹¹ although some family members with melanoma did not have DN.⁹² Subsequent studies found that the presence of DN did not necessarily correlate with p16 mutations in individuals in these high-risk families.^{93, 94} In addition to familial factors, DN increase melanoma risk when associated with increased absolute numbers of nevi.⁹⁵

A number of studies have reported increased risk of sporadic (non-familial) melanoma, ranging from 4 to 15-fold, in patients with DN.^{70, 95–98} Interestingly, one study examining new cases of first primary non-familial melanoma comprising 61 patients with superficial spreading and 19 patients with nodular subtypes showed that DN occur nearly four times more frequently among patients with a prior diagnosis of superficial spreading melanoma relative to nodular melanoma.⁹⁹ Finally, several studies have also implicated DN as an independent risk factor for developing multiple primary melanomas.^{92, 100}

Thus while the presence of DN are associated with increased melanoma risk in individuals, the finding of CN-derived melanomas in such patients raises the question of whether in fact individual DN lesions are more likely than CN to progress to melanoma (discussed below).

DN progression to melanoma

Key points

- There are no ideal models for studying nevus transformation to melanoma in real time
- Most DN do not progress to melanoma
- Studies of nevus-derived melanomas reveal similar incidence of melanomas arising in DN and CN
- Assessing the rate of individual DN vs. CN transforming to melanoma depends on the relative prevalence of these nevus types

Although it is clear that DN represent a marker of melanoma risk, there is little direct evidence that individual DN lesions progress to melanoma at any higher rate than CN. Indeed, the heart of the controversy lies in the question of whether DN represents a premalignant lesion. This question of natural history, however, is problematic because it is not possible to identify a lesion as DN without biopsy, and the process of biopsying precludes long-term monitoring of the lesion. Moreover, there is no established animal model for DN in which lesions develop *in situ* and can be monitored long-term for transformation to melanoma. Thus there is no ideal model for studying nevus transformation to melanoma in real time.

Meyer et al.¹⁰¹ transplanted histologically-confirmed DN to athymic (nude) mice and found that while over 90% of the xenografts survived transplantation, most developed an inflammatory response and 30% regressed over a 16-week observation period.

Approximately 20% of nevi developed junctional intraepidermal melanocytic hyperplasia in a lentiginous pattern, with cytologic hypertrophy, dendritic morphology and hypermelanization, but none of the transplanted lesions transformed to melanoma, either spontaneously or following UV irradiation.¹⁰¹ More recent mouse models based on transgenic melanocyte expression of various oncogenes including NRas,¹⁰² mutant CDK4,¹⁰² mutant BRAF^{103, 104} and KRas,¹⁰⁵ or following repeated topical application of dimethylbenzanthracene¹⁰⁶ all develop “nevus-like” cutaneous lesions. In some cases, these lesions may progress to invasive melanoma,^{102–105} however they appear to arise in the dermis without an epidermal or junctional component,^{102–105} or consist predominantly of perifollicular melanocytes,¹⁰⁶ and thus do not represent good histologic correlates of DN.

Clark’s early description of DN was in the context of evolution to melanoma, but he acknowledged that most individual DN lesions never progress to melanoma.¹⁰⁷ As noted above, subsequent studies by Tucker et al.²⁷ confirmed that most DN in melanoma kindreds regressed or were stable, and only rarely developed into melanoma. Numerous studies, on the other hand, of familial and sporadic melanomas have shown that DN can serve as precursors to melanoma, based on the histologic finding of DN in association with melanoma.^{95, 108, 109} Assuming that the minimal number of nevi transforming to melanoma per year is roughly equivalent to the number of melanomas diagnosed each year with associated nevic components, Tsao et al.¹¹⁰ estimated the lifetime risk of individual nevi (including DN) transforming to melanoma is extremely low, on the order of 1/10,000. Based on the literature, it appears that 20–30% of melanomas appear to arise from nevi.^{111–113} Two studies similarly found that approximately 20% of melanomas had an histologically-associated DN,^{114, 115} while another found DN remnants in association with only 7% (34/512) of melanoma cases.¹¹⁶

The question of whether a DN is more commonly found than CN in association with melanoma has been addressed in multiple studies. Although Black et al.¹¹⁷ reported higher rates of DN (32%) vs. CN (10%) underlying 500 cases of invasive melanoma, more recent studies have *not* shown a predominance of DN-derived melanoma. Of 1126 nevus-derived melanomas reviewed by Sagebiel et al.,¹¹⁵ 79% were associated with CN and 21% with DN. In another study of 147 melanomas arising from nevi, Skender-Kalnenas et al.¹¹⁸ found 56% were DN and 44% were CN. Bevona et al.¹¹⁹ reported that of 1606 nevus-associated melanomas, 43% arose from DN and 57% from CN. In a review of melanomas diagnosed in an academic group practice over 10 years, Goodson et al.¹²⁰ reported that 66 melanomas arose from CN versus 45 from DN. Similarly, in several studies of patients with nevi monitored by photography, nevus-derived melanomas appear to arise from DN and CN in roughly equivalent proportions.^{29, 121–123}

There is potential error in interpreting nevus origin from histological specimens. The possibility of a collision event (melanoma and nevus arising in adjacent sites) could yield an overestimate of nevus-derived melanomas, or this proportion could be underestimated due to cases where melanoma destroys the nevus precursor and there is no histologic remnant of nevus. More importantly, the question of whether the rate of melanoma transformation is greater for individual DN vs. CN hinges on the relative prevalence of these nevus types. For example, equivalent numbers of DN- and CN-derived melanomas in a patient population in which CN are predominant would suggest that DN have higher rates of transformation to melanoma than CN. On the other hand, similar data in a patient population in which DN predominate would lead to the opposite conclusion. As described above, numerous studies have attempted to assess the prevalence of DN in various patient groups, but many were confounded by lack of histologic confirmation. Nevertheless, it would seem that the relative likelihood of nevus transformation to melanoma depends upon the clinical context, as noted above.

CONCLUSIONS AND RECOMMENDATIONS

Over the past 30 years, clinicians have struggled with the diagnosis of DN. The terminology has contributed to confusion over understanding how they differ from CN, and predicting their biological behavior. Many of the early clinical studies were flawed because clinically atypical nevi were often assumed to be DN without histologic confirmation. While the terminology is still debated, there appears to be sufficient evidence to substantiate DN as an histologic entity distinct from CN, although the two cannot be reliably distinguished on clinical examination. There is no evidence that individual DN will inevitably progress through sequentially higher grades of dysplasia, although some of the past terminology and interpretations of the literature have suggested this may be a viable pathway of melanoma development. There is substantial clinical evidence indicating that melanoma most commonly develops *de novo*, i.e. from isolated melanocytes rather than from nevi. Less commonly, melanoma arises from pre-existing nevi which may be either CN or DN. Despite the problems inherent in its terminology, the DN has become entrenched in our dermatologic language and practice. It represents a distinct histologic entity, whose biologic significance appears to be more as a marker of melanoma risk rather than a precursor to melanoma. These considerations will be further addressed in part II of this continuing medical education article, which reviews molecular aspects and clinical management of DN.

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Abbreviations used

CN	common nevus
DN	dysplastic nevus
DNS	dysplastic nevus syndrome
FAMMM	familial atypical multiple-mole melanoma

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Figure 1. Clinical features of atypical nevi. Indistinct borders are evident in lesions (A), (B), and (C). Variable pigmentation is seen in these lesions as well as lesions (D), (E), and (F). Irregular borders are present in many of these lesions.

Figure 2.

Histologic features of dysplastic nevi. (A) Architectural disorder demonstrated by lateral asymmetry and “shouldering” (original magnification x40). (B) Lentiginous melanocytic hyperplasia with bridging of rete ridges (original magnification x200) and (C) cellular atypia (original magnification x200). (D) Patchy lymphocytic host response (original magnification x100). (E) Prominent eosinophilic fibroplasias (original magnification x200). (F) Variable and “random” cytologic atypia and mitotic junctional activity (original magnification x600).

Table I**Proposed definitions for Dysplastic Nevus Syndrome (DNS)****NIH consensus criteria** (ref. 9)

- Occurrence of melanoma in 1 1st or 2nd degree relatives
- Large number of nevi (often >50), some of which are clinically atypical
- Nevi demonstrating certain distinct histologic features

Dutch working group criteria (ref. 28)

Sporadic DNS

- Melanoma and 1 severely clinically atypical nevi

Familial DNS

- 2 close relatives with melanoma (with or without atypical nevi)
- 1 relative with atypical nevi

Revised (British group) DNS score (ref. 25)

100 nevi of size >2mm (50 or more if under 20 or over 50 years of age)	1 point
2 atypical nevi	1 point
1 nevus on buttocks	1 point
2 nevi on dorsal feet	1 point

(Total score >2 = DNS)

Table II

Histologic criteria proposed by Clark, Elder, and colleagues (ref. 41)

Architecture	Nests bridge rete
	Nests at the side of rete
	Single cells between nests, nests predominating
	Lentiginous elongation of rete
	Anastomosis of rete
	Little or no pagetoid spread
Host response	Patchy lymphocytic infiltrate
	Eosinophilic fibroplasia
	Lamellar fibroplasia
	Prominent vessels
Cytology	Variable slight to moderate atypia
	Few (if any) mitoses
	Occasional macronuclei
	Scattered epithelioid nevus cells
	Scattered cells with finely granular melanin

Table III**WHO Criteria for diagnosis of DN (ref. 42)**

Major criteria *	Basilar proliferation of atypical melanocytes, extending at least three rete ridges beyond dermal component
	Organization of proliferation in lentiginous or epithelioid-cell pattern
Minor criteria *	Lamellar or concentric eosinophilic fibrosis
	Neovascularization
	Inflammatory response
	Fusion of rete ridges

* Diagnosis of DN requires fulfillment of both major criteria as well as 2 minor criteria

Table IV

EORTC Cooperative Group criteria (ref. 43)

CN [*]	<2 features noted below for DN [*]
DN	3 of the following features: Marked junctional proliferation Irregular nevus nests Large nuclei Lymphohistiocytic infiltrate
Melanoma-in-situ	Pagetoid growth Continuous junctional proliferation

^{*} CN, common nevus; DN, dysplastic nevus

Table V**Duke University grading system for DN (ref. 44)**

Architectural disorder	Junctional component nested at both edges
	Overall symmetry
	>5% of nests cohesive
	Suprabasal spread (prominent or at edge)
	>50 % confluence of proliferation
	Single cell proliferation absent or focal
(mild: 0–1 criteria; moderate: 2–3 criteria; severe: 4–6 criteria)	
Cytologic atypia	Nuclei round or oval, and euchromatic
	Nuclei larger than those of basal keratinocytes
	Nucleoli prominent
	Cell diameter twice that of basal keratinocytes
	(mild: 0–1 criteria; moderate: 2 criteria; severe: 3–4 criteria)