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

II. Molecular aspects and clinical management

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Abstract

The dysplastic nevus is a discreet histologic entity, which exhibits some clinical and histologic features overlapping with common nevi and melanoma. These overlapping features present a therapeutic challenge, and with a lack of accepted guidelines, the management of dysplastic nevi remains a controversial subject. Although some differences between dysplastic and common nevi can be detected at the molecular level, there are currently no established markers to predict biologic behavior. In part II of this continuing medical education article, we will review the molecular aspects of dysplastic nevi and their therapeutic implications. Our goal is to provide the clinician with an up-to-date understanding of this entity to facilitate clinical management of patients with nevi that demonstrate histologic dysplasia.

Keywords

nevus; melanoma; dysplasia; dysplastic nevus; common nevus

INTRODUCTION

Lack of predictive markers and guidelines for dysplastic nevi

Key points

- **Dysplastic nevi have overlapping features with common nevi and melanoma**
- **Lack of consensus or guidelines for management**

The dysplastic nevus (DN) is a distinct histologic entity (see part I of this continuing medical education article). Nevertheless, DN share some histologic features of non-dysplastic or “common” nevi (CN) which include presence of neoplastic nests of melanocytes, and features of melanoma such as cytologic atypia and dermal inflammatory response.[1] The benign lesions (DN, CN) cannot be distinguished from each other based on clinical examination alone,[2, 3] and DN often display some clinical features associated with melanoma such as irregular border and asymmetric distribution of pigmentation.[4, 5] Given these considerations, this review will focus on studies based on lesions that have been histologically-defined.

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A conference among melanoma thought leaders, convened at the National Institutes of Health in 1992, sought to define the histologic basis of "early" melanoma and the DN.[6] Changes in terminology were recommended – which have not been widely adopted – but guidelines for clinical management of DN lesions were never issued. Thus the "consensus conference" yielded no consensus.[7–11] A decade later there remained lack of consensus among dermatologists in the management of patients with DN and need for re-excision of DN following biopsy.[12] With the passing of yet another decade, it now seems timely to reassess the past collective clinical experience and incorporate new molecular insights concerning DN. It is our hope that an informative review of all the evidence may lead the way to a consensus regarding management of DN.

The promise of molecular analyses

Key points

- **Currently there are no validated markers in nevi to predict biologic behavior**
- **Molecular studies may identify differences between DN, CN, and melanoma**
- **Molecular-clinical correlations may identify predictive markers**

As indicated above, there are limits to histologic analysis in distinguishing DN from CN and melanoma. More importantly, histologic features are not always a reliable predictor of the biologic behavior of these lesions. The key questions in the clinician's mind relate to whether a given lesion is malignant or benign, and its likelihood of recurrence, transformation to melanoma, and/or clinical progression and metastasis. While various histologic features in melanoma (i.e. depth, ulceration) have been validated as predictors of recurrence and metastasis,[13] no such histologic markers predictive of biologic behavior have yet been validated for DN.

It is possible that molecular analyses of these melanocytic lesions will identify differences between DN, CN, and melanoma that may prove useful in predicting their biologic behavior. The first step is to characterize panels of lesions with defined histologic patterns at a molecular level to identify candidate markers. Second, candidate markers must be analyzed in panels of lesions with known clinical outcome in order to develop hypotheses regarding the predictive value of particular markers. Finally, a blinded trial is necessary to validate such clinical-molecular associations. Detection of specific chromosomal gains/losses by fluorescence-based in situ hybridization to differentiate Spitz[14, 15] and mitotically-active nevi[16] from melanoma is a paradigm for this approach.

MOLECULAR ASPECTS OF DN

A number of studies have investigated DN at a molecular level, and similarities and differences between DN, CN and melanoma are summarized in Table I.

Clonal origin of DN

Key point

- **Studies of clonality in DN are limited, but suggest DN like most CN are clonal**

Although several studies have demonstrated that most nevi are clonal neoplasms (i.e. arising from a single melanocyte) based on pattern of X chromosome inactivation in tissues from female patients, most were limited to study of CN and only one of these included DN. Robinson et al.[17] reported evidence for clonality in 81% of nevi – 25% of which were DN. They found no correlation between the presence or absence of dysplasia and clonality. Demonstration of clonality, however, may not be informative as to whether DN arise *de*

novo or from a pre-existing CN since in both circumstances all the cells would be expected to have arisen from a single progenitor cell. Given the heterogeneity of dysplasia observed within DN,[18] it seems possible that some DN may arise within CN.

Molecular profiling

Key point

- **Although many differences are apparent from molecular profiling, their clinical significance is unknown**

Scatolini et al.[19] isolated RNA from 18 CN, 11 DN, and 23 melanomas representing radial and vertical growth phase, and examined global gene expression using whole genome microarrays. Expression patterns among the DN were very similar with respect to genes involved in ectodermal development, while greater heterogeneity of expression was seen among genes involved in mitosis, apoptosis, and regulation of transcription. Many similarities were seen between DN and CN, in particular the expression of genes involved in mitosis, apoptosis and transcriptional regulation. Some proliferation genes, however, were expressed at higher levels in DN than in CN. Expression patterns of a group of genes involved in cellular detoxification, RNA processing, and antigen presentation allowed separation of DN into two subclasses: one more similar to radial growth melanoma and with expression levels higher than CN, and the other similar to vertical growth melanoma and with expression levels lower than CN.

Mutations in BRAF and Ras

Key point

- **DN harbor mutations in BRAF comparable to CN, but Ras mutations are rare**

Activation of the Ras-mitogen-activated protein kinase (MAPK) pathway is predominant in melanoma, and approximately 60% of tumors express a “driver mutation” in the BRAF kinase (most commonly V600E) which may potentiate Ras signaling[20] and appears to be a useful therapeutic target in metastatic melanoma.[21] The BRAF mutation is also predominant in nevi,[22] and several studies have examined its prevalence in DN. Wu et al.[23] examined a panel of 135 nevi and detected mutant BRAF in 81% of lesions representing a variety of nevus types: acquired, congenital, genital, CN, and DN. Similarly, Uribe et al.[24] reported comparable rates of BRAF mutation in DN (13/21, 62%) and CN (16/24, 67%). Although these authors found that DN tended to exhibit stronger BRAF staining than CN (particularly in the junctional component) and somewhat higher rates of phosphorylated Erk (downstream marker of MAPK pathway activation, 10/21 DN vs. 7/24 CN), there was not a general correlation between BRAF mutation and MAPK activation.[24] These studies indicate that the presence of BRAF mutation does not appear to be a molecular factor distinguishing DN from CN.

In contrast to congenital nevi which commonly harbor Ras mutations,[25] two studies performed by Papp and colleagues indicate that Ras mutations are rarely present in DN. They found activating N-ras mutations in only 1 of 19[26] and 1 of 18[27] DN examined.

Mutations and expression of tumor suppressor genes

Key points

- **Compared to CN, some DN exhibit alterations in p16 or p53 expression**
- **PTEN expression is lost in a fraction of DN and CN**

As noted above, the p16 tumor suppressor is a major melanoma predisposition gene that is commonly mutated in families with inherited melanoma. The p16 protein is a critical negative regulator of the cell cycle, and its functional loss is common in tumors.[28] A role for p16 in proliferative arrest of nevi is supported by the common finding of large atypical nevi in patients with germline p16 mutations.[29] No differences in clinical or histologic presentation of nevi, however, were noted in comparing individuals with different p16 mutations.[30] Several studies have investigated the presence of somatic p16 mutations in nevi, including DN. Wang et al.[31] found no p16 mutations in 20 nevi examined (6 of which were DN). Similarly, Papp et al.[26] found no p16 mutations among 19 DN. By contrast, Lee et al.[32] found four p16 mutations (3 missense, 1 intronic) in three of 12 DN. Interestingly, three of these mutations were C:T transitions at dipyrimidine sequences, characteristic of mutations directly induced by UV light.[33] Thus p16 mutations appear to be rare in nevi, but an insufficient number of nevi have been examined to ascertain whether the incidence is increased in DN compared to CN. On the other hand, p16 expression in some DN may be compromised by gene deletion (discussed below).

Mutations in p53, which is upregulated by DNA damage signaling and promotes apoptosis, are found in over 50% of cancers and to a lesser extent in melanoma.[34] Several studies have investigated the presence of p53 mutations in DN. Lee et al.[32] found two p53 missense mutations in 12 DN examined. In another study, Levin et al.[35] detected p53 mutations in 2 of 5 DN and 2 of 11 CN. On the other hand, Papp et al.[26] failed to identify p53 mutations in 19 DN studied. Several groups have also examined p53 expression in DN by immunohistochemistry, as a method to detect p53 mutations that increase protein stability. The p53 protein has generally not been observed in CN or DN,[36, 37] although McGregor et al.[38] found p53 to be present in a minority of DN but not in CN. Similarly, two subsequent studies found that p53 protein expression was increased in DN compared to CN.[29, 39] These immunohistochemical-based studies, however, are problematic due to variance in sensitivity of detection and lack of direct confirmation of p53 mutations.

The phosphatase and tensin homolog (PTEN) phosphatase functions as a tumor suppressor through inhibition of the phosphatidylinositol kinase signaling, resulting in diminished activation of the survival kinase Akt, and is frequently lost in tumors.[40] Several studies have evaluated expression of PTEN in panels of melanomas and nevi. Expression of PTEN appears to be retained in most (approximately 60–70%) nevi and absent in most melanomas; significant differences between DN and CN were not observed.[41, 42]

Microsatellite instability and allelic loss of tumor suppressors

Key points

- **Microsatellite instability may be seen in some melanomas and DN, but not CN**
- **Some DN may harbor deletions in the p16-encoding chromosomal region 9p21**

It is important to note that lack of detection of mutations in a gene is not synonymous with presence of the gene and/or expression of wild-type protein. This is because deletions may occur in one allele (hemizygous deletion, referred to as loss of heterozygosity, LOH) that will not be detected by PCR-based sequencing methods. In the context of LOH, mutation or loss of the remaining allele results in loss of function or complete absence of the protein which in the case of a tumor suppressor may promote transformation. Historically, LOH of particular alleles was determined by assessing the presence or absence of markers (microsatellites) associated with particular genetic loci. Variation in microsatellites is referred to as microsatellite instability, often occurs in chromosomal regions containing tumor suppressor genes, and is a common feature of tumors (including melanoma). Hussein et al.[43] found microsatellite instability at chromosomal regions 1p and 9p in DN and

melanomas, but not in CN: the overall prevalence of microsatellite instability was 31% (7/22) in melanomas, 28% (17/60) in DN and 0% (0/30) in CN. This result is consistent with a prior report by Boni et al.[44] showing allelic losses at 1p in 3 of 9 DN and at 9q in 1 of 9 DN. Bale et al.[45] mapped a "DN locus" to a region on chromosome 1, and this was confirmed in subsequent linkage studies.[46, 47] A more recent genome-wide association study identified variants at 9p21 and 22q13 associated with nevus development,[48] although it is not clear if either set of variants favors development of DN over CN.

Multiple additional studies have documented LOH in melanomas involving the region 9p21[149, 150] that contains the *p16* gene locus,[49, 50] and some studies have shown increased LOH in DN compared to CN. Park et al.[51] reported LOH in 7 of 9 DN at one or more loci within 9p21, while LOH was not detected any of the 13 CN studied. Tran et al.[50] detected LOH in this region in approximately 40% (17/44) of melanoma tumors, 64% (9/14) of DN, and 50% (3/6) of CN. In this same study, homozygous deletion of 9p21 was found in 29% (4/14) of DN but in none of the CN. Similarly, Birindelli et al.[49] identified LOH at 9p21 in 15% (4/27) of melanomas and 9% (3/35) of DN examined, but in none of 26 CN. Park et al.[51] have also demonstrated LOH for the p53-containing locus in 43% (3/7) of DN; interestingly, these three lesions also revealed LOH for 9p21.

These early studies assessed the presence of the *p16*–containing locus using various microsatellite markers as noted above, which may account for some of the variability seen, and may overestimate loss of the *p16* gene. More recent studies have employed fluorescence in-situ hybridization using sequence-specific probes to directly detect loss of particular genes. Using this approach, Sini et al.[52] found hemizygous deletions within the 9p21 region in 10% (2/20) of CN, 55% (12/22) of DN, and 59% (19/32) of melanomas; specific probes for the *p16* gene, however, identified deletions in none of the CN (0/20), 9% (2/22) of DN, and 19% (6/32) of melanomas.

In summary, it appears that a subset of DN harbor genetic aberrations generally not seen in CN, which include LOH of regions that may contain the gene encoding p16. Whether hemizygous loss of p16 is compensated by the remaining allele, or results in decreased p16 protein levels in nevus cells, remains an open question. One study found lower levels of p16 with nuclear localization by immunohistochemistry in DN compared to CN,[29] although an earlier study found comparable levels of p16 in DN and CN.[53]

Proliferation markers

Key point

- **DN may exhibit higher proliferative rates than CN, but lower than melanoma**

The observation of dark dots by dermoscopy at the periphery of some DN, as noted above, suggests that these nevi may be in the process of active proliferation.[54] Several studies have investigated whether DN have higher rates of proliferation compared to CN. Lebe et al.[55] examined a panel of melanomas and nevi by immunohistochemistry using antibodies against cyclin D1 and Ki-67 to identify proliferating cells. While melanomas exhibited much higher rates of proliferation than nevi, analysis of 42 DN and 21 CN revealed comparable rates of cyclin D1 expression but significantly higher rates of Ki-67 positivity in DN compared to CN. In a related study examining expression of cyclins D1 and D3, Alekseenko et al.[56] found significant differences between DN and CN. They reported mean rates of 8% for melanoma (n=14), 5% for DN (n=24) and 0.3% for CN (n=10) for cyclin D1, and rates of 18% for melanoma, 6% for DN, and 2% for CN for cyclin D3. Such findings are consistent with higher expression of proliferative genes in DN compared to CN, as reported by Scatolini et al.[19] On the other hand, Nasr et al.[57] did not observe positive staining for Ki-67 or phosphorylated histone-H3 in any lesions among a panel of 20 DN and 20 CN. These

studies are limited by sensitivity of the staining and the markers examined, but taken together, it appears that DN may be associated with higher rates of proliferation than CN, although all nevi are generally less proliferative than melanomas.

Apoptosis markers

Key point

- **Lack of evidence that DN cells are more resistant to apoptosis than those in CN**

One explanation for long-term persistence of nevi is that nevomelanocytes are more resistant to apoptosis than non-nevus-associated melanocytes, and this has been demonstrated *in vitro*.[58] There is no evidence, however, that cells comprising DN are more resistant to apoptosis than cells of CN based on expression of apoptotic regulatory molecules. Expression of the prototypic apoptosis inhibitor Bcl-2 did not appear significantly different between DN and CN in two studies,[39, 59] although Tron et al.[60] reported Bcl-2 expression in CN (5/7) but not DN (0/6). The inhibitor of apoptosis protein Survivin is broadly expressed in nevi, with no significant differences noted between DN and CN.[61, 62] Similarly, expression of various death receptors that trigger extrinsic apoptotic pathways was comparable in DN and CN.[63] Finally, Zhang et al.[64] reported that the tumor suppressor RUNX3, a regulator of apoptosis and proliferation, is expressed in equal proportions of DN (34/63, 54%) and CN (14/25, 56%).

Increased ROS in DN

Key point

- **DN may display higher levels of oxidative stress than CN**

Pavel et al.[65] analyzed melanocytes from DN and found elevated levels of reactive oxygen species compared to CN. Similarly, Smit et al.[66] isolated melanocytes from DN lesions and adjacent skin, and found that DN-associated melanocytes exhibited higher levels of reactive oxygen species and oxidative DNA damage than normal melanocytes from the same patients. The role of oxidative stress in the development and potential progression of DN has not been investigated.

Markers of senescence

Key points

- **It is unknown if DN have increased resistance to oncogene-induced senescence**
- **Most markers of senescence have not been examined in DN**

A current model to explain nevus development and transformation to melanoma invokes the concept of senescence, or terminal growth arrest.[67] It is thought that nevi initially result from melanocyte proliferation that is followed by a senescent state; failure of some cells within a nevus to achieve (or escape of some cells from) senescence may lead to melanoma. In this model, the initial hyperproliferation and subsequent induction of senescence is mediated by activation of an oncogene (such as mutant BRAF), and the senescent state is maintained by expression of p16 which is sufficient to mediate senescence in some tumor cells in culture.[68] Consistent with this model, expression of mutant (V600E) BRAF in human melanocytes triggers cell growth followed by growth arrest, and some nevi express markers of senescence such as p16 and acidic beta-galactosidase.[29, 69] It has been debated, however, whether acidic beta-galactosidase represents a reliable marker of senescence and whether nevi are truly senescent since nevus-derived cells can proliferate *in vitro*.[70–73] There are obviously additional limitations to the senescence model given that some nevi

don't express mutant BRAF, and the majority of melanomas do not arise directly from nevi (see below). Nevertheless, it would be interesting to investigate the expression of senescence markers in DN compared to CN. Bennett[74] initially proposed that DN might represent escape from p16-dependent senescence, and her group subsequently showed that p16 expression was reduced in DN,[29] but studies[29, 69] examining other senescence-associated markers in nevi did not include DN.

Mutant active BRAF induces senescence by up-regulating the tumor suppressor IGFBP7, which acts through autocrine/paracrine pathways to inhibit MAPK signaling, and IGFBP7 is frequently lost in melanoma.[75, 76] Several studies have examined the link between mutant BRAF and IGFBP7 in DN. Decarlo et al.[77] analyzed a panel of DN, and detected IGFBP7 expression in 48% (12/25) of DN expressing wild-type BRAF and in 56% (5/9) of DN expressing mutant BRAF. In another study of genital nevi, Nguyen et al.[78] found IGFBP7 expression in 80% (8/10) of DN with wild-type BRAF and 67% (2/3) DN with mutant BRAF; similarly, IGFBP7 was expressed in 100% (4/4) of CN with wild-type BRAF and 67% (2/3) CN with mutant BRAF. While the absence of IGFBP7 in some mutant BRAF-expressing DN suggests that this putative senescence pathway may not be intact in a subset of DN, a similar dissociation between mutant BRAF and IGFBP7 was observed in CN.

MANAGEMENT OF DN

Variation in management of DN by dermatologists

Key points

- **Significant variation in practice indicated by survey**
- **Lack of evidence supporting routine ophthalmologic exams for patients with DN**

As noted above, no guidelines regarding management of DN emanated from the NIH conference in 1992,[6, 79] and none have been forthcoming since. In a survey of fellows of the American Academy of Dermatology regarding management of patients with history of histologically-confirmed DN, Tripp et al.[12] found significant variation in physician practices. While 99% of the dermatologists recommended that these patients perform self-skin examinations, 75% performed total body skin exams on follow-up visits, 60% recommended ophthalmologic exams for some patients, 49% obtained baseline total body skin photography for most patients, and 23% routinely used dermoscopy.[12] Regarding follow-up visits for their patients with DN, 58% recommended exams every 12 months and 33% recommended exams every 6 months in most patients. Variation in surgical management of DN is discussed below.

While there is clear evidence that use of photography and dermoscopy can enhance early melanoma detection, their use is largely dependent on physician familiarity and training in these techniques as well as economic feasibility of their incorporation into individual practices.[80] Is there evidence to inform as to the indication for ophthalmologic exams – notably, does patient history of DN portend future risk of developing ocular melanoma? Vink et al.[81] described five melanoma kindreds, each with a single member affected by ocular melanoma, suggesting an association between cutaneous and ocular melanoma. On the other hand, Molven et al.[82] described a family with inherited melanoma based on CDK4 (R24H) mutation and a single member who developed ocular melanoma, but the patient was not a mutation carrier, suggesting a different etiology for the ocular and cutaneous melanomas in this family. In a more definitive study, Taylor et al.[83] found no association among 44 patients between uveal melanoma and cutaneous melanoma and/or DN. They found a 4.5% prevalence of DN in patients with uveal melanoma, compared to 41%

prevalence of DN in patients with cutaneous melanoma.[83] Thus patients with DN do not appear to have an increased risk for ocular melanoma, and ophthalmologic screening in the absence of ocular symptoms may not be indicated.

Therapeutics

Key points

- **Multiple therapeutic modalities have been studied in DN, including imiquimod, 5-fluorouracil, tretinoin, isotretinoin, and laser ablation**
- **No therapeutic treatment appears efficacious in eliminating DN**

Several pharmacologic agents have been tried in patients with DN. These include therapies that have been efficacious for actinic keratoses, perhaps reflecting a view that if DN are precursor lesions to melanoma they might respond like precursor lesions to squamous cell carcinoma.

Dusza et al.[84] treated 14 DN in 10 patients with 5% imiquimod cream 3 times per week for 16 weeks. There were no obvious clinical changes in the size and morphology of the study nevi, but 4 of 14 treated nevi and none of 14 untreated nevi showed significant reduction of junctional and intraepidermal nevomelanocytes and papillary dermal fibrosis with variable inflammation suggestive of partial regression. Somani et al.[85] conducted a more limited trial of 5% imiquimod in which three patients applied drug to a single clinically-atypical nevus 5 nights per week for 12 weeks. The nevi were biopsied at the outset, and then excised following the treatment period. None of the lesions cleared; two proved to be DN and developed an inflammatory reaction, while the third lesion was a CN that demonstrated minimal inflammation. The authors were concerned that the two DN appeared to display more severe histologic atypia following imiquimod treatment.[85]

Although systemic 5-FU has been associated with eruptive DN (see above), topical application of 5-FU has been investigated as a potential therapeutic for DN. Bondi et al.[86] treated six DN in a 37-year-old female with 5% 5-FU cream twice daily for 5 weeks; four CN from unrelated individuals were also treated. All six DN responded with inflammation, ulceration, and subsequent (clinical) disappearance of the lesion, while the four control CN remained unchanged.[86] Subsequent patch tests and intradermal skin testing in the patient who responded showed no evidence of contact sensitivity to fluorouracil.[86] The authors noted that an additional four DN lesions in this patient responded to 5-FU, while those in additional patients did not. It does not appear that the response of DN to 5-FU has been evaluated in any subsequent studies in the literature.

The effect of topical tretinoin under occlusion with and without topical steroid was investigated by Stam-Posthuma et al.[87] in a prospective randomized double-blind study. Three clinically-atypical nevi in 30 patients were treated under Actiderm occlusion (replaced weekly) either with placebo, 0.1% tretinoin, or tretinoin in combination with 1% hydrocortisone, and for 4 months. Lesions were monitored by photography throughout the study period and histologically at the end, revealing that although about 40% of lesions treated with tretinoin or tretinoin plus hydrocortisone were reduced in size, they remained clinically atypical and retained histologic atypia.[87]

Edwards et al.[88] treated eight patients with DNS with oral isotretinoin, 40 mg twice a day for 4 months. At completion of therapy, at least three previously identified and photographed clinically atypical lesions were re-photographed and removed for histologic evaluation. There were no clinical or histologic changes observed in the lesions which were

confirmed to be DN in these patients. Thus oral isotretinoin does not appear to have a significant biologic effect on DN.

Finally, laser ablation has been attempted for removal of DN. Duke et al.[89] treated 31 nevi (including DN) with a Q-switched ruby laser (694 nm, 40–60 nanoseconds, 7.5–8.0 J per cm^2) and reported that although 16 (52%) of the nevi showed a clinically visible decrease in pigment at the 4-week follow-up visit, no lesion demonstrated complete histologic removal of all nevomelanocytes. A potential concern is that laser treatment of nevi may increase the risk of malignancy by eliminating the protective pigment, thereby leaving the remaining cells more vulnerable to UV radiation as well as potentially obscuring the ability to detect morphologic changes over time. However, to our knowledge, there have been no reports of malignancies arising in laser-treated nevi.[90]

Prophylactic surgical removal

Key point

- **Prophylactic removal of clinically atypical nevi unlikely to prevent melanoma, but unclear if reduces risk**

In patients with numerous or clinically atypical nevi, there may be a tendency to remove lesions in a “prophylactic” manner. Such practice of nevus removal may be sought by the patient to reduce their melanoma risk, or promulgated by the physician out of fear of missing a melanoma. It is clear that complete removal of a patient’s nevi will not prevent melanoma, which (as discussed above) is more likely to arise from isolated epidermal melanocytes in the skin than from pre-existing nevi. However, it is unclear to what extent “molectomy”, however impractical this might be, would reduce long-term melanoma risk in high-risk patients. A report of one such case in a patient with history of multiple prior melanomas described removal of 117 clinically-atypical lesions over a 1-year period, and the patient developed no subsequent melanomas,[91] but to our knowledge this approach has not been formally studied.

Re-excision controversy

Key points

- **Decision to re-excise relates to physician perception of DN and their risk of transformation to melanoma**
- **Some physicians re-excise DN to prevent recurrence and potential pseudomelanoma phenomenon**
- **Lesions with severe dysplasia should be re-excised given difficulty in distinguishing from melanoma**
- **DN that do not resemble melanoma, including DN with positive histologic margins, do not need to be re-excised and may be observed like CN**

Regarding surgical management, the survey by Tripp et al.[12] found that 86% of dermatologists intend on biopsy to remove DN completely, 75% use margins of ≥2 mm, and 67% would re-excise DN with positive histologic margins. Although the NIH Consensus Conference[6, 79] established margin guidelines (2–5 mm) for re-excision of DN, *indications* for re-excision were not specified. Because DN often consist of melanocytes that extend beyond the clinical lesion, it is common for biopsies (even when physician intent is to completely remove the lesion) to demonstrate positive margins. The decision to re-excise vs. observe likely relates to variation in physician perception of DN and the risk of transformation to melanoma.

A recent study[92] surveyed 101 dermatologists in the Chicago area regarding the role of histologic grade and margin status documented in the pathology report in their decision to re-excise vs. observe DN following biopsy. Positive margin status was correlated with higher rates of decision to re-excise for all grades of nevi but was most marked for lesions diagnosed with "moderate" dysplasia. While 81% of respondents indicated they would re-excise nevi with moderate dysplasia and positive margins on biopsy, only 9% of respondents favored re-excision of moderately dysplastic lesions with negative margins.

There appear to be three primary reasons for re-excising DN. First, there may be concern that a particular lesion is melanoma, based on physician- or patient-related factors or the histology. As noted above, there is discordance among dermatopathologists as to identification of dysplasia and cytologic atypia,[93–95] and thus lesions with severe dysplasia could represent melanoma. Thus it is recommended that lesions demonstrating severe histologic atypia be re-excised. Lesions demonstrating only mild or moderate histologic atypia are a source of much greater controversy. A second reason to re-excise DN is to prevent their recurrence. This reason may in part be seated in a fear that the lesion may recur as melanoma (thinking that if DN are precursors of melanoma then they should be completely removed). However, given that the risk of melanoma arising in DN may be no greater than in CN (discussed in part I of this article), following this course may lead one to re-excise *all* nevi with positive margins. Additionally, one may want to avoid lesions recurring as "pseudomelanoma" – a benign histologic simulator of melanoma[96] that can be problematic for the pathologist. Another potential concern is overdiagnosis of a recurrent DN as melanoma if the pathologist signing out the recurrent lesion has no knowledge of the previous pathology. Re-excising DN for these reasons may represent a form of defensive medicine driven by medico-legal concerns, but there also may be an implicit financial incentive to perform additional procedures. What may be perceived as an increasing tendency to over-biopsy and over-treat DN has been referred to in the lay press as the "nevomelanocytic industrial complex".[97] The risks and benefits of re-excising DN are summarized in Table II.

Some of these concerns have been informed by two recent studies. First, King et al.[98] analyzed clinical findings and histologic changes in 357 cases (28% were DN) of recurrent nevus phenomenon which were compared with 34 cases of melanoma with regression. Most recurrences were in patients under age 40, and located on the back, with a median recurrence time of five months. Many cases revealed only pigment, and residual nevus was present in only 33% of cases, often associated with deeper adnexal structures. While many recurrent nevi shared some histologic similarities (i.e. pseudomelanoma) with primary melanoma with scar/fibrosis, the vast majority of recurrent nevi were readily identifiable.[98]

Second, Goodson et al.[99] studied the rate of clinical recurrence and factors associated with recurrence of DN following biopsy. Of 195 DN with greater than two years of follow-up, 7 (3.6%) demonstrated recurrence on clinical examination. In all, 98 DN had a follow-up period of at least four years with no clinical recurrence. Of 61 CN biopsy sites examined, clinical recurrence was observed in two (3.3%). For all nevi studied, recurrence was significantly associated with shave biopsy technique but not with nevus dysplasia or subtype, or the presence of positive margin or congenital features. This study suggests that re-excision of nevi, including mildly to moderately DN with a positive histologic margin, may not be necessary.

CONCLUSIONS AND RECOMMENDATIONS

There is considerable variation among physicians in their clinical approach to patients with DN, which likely stems from different interpretations of the DN and its relative risk of

transformation to melanoma. Studies in recent years have identified some biologic and molecular similarities between DN and CN, as well as differences (Table I). Despite these distinctions, including increased proliferative rate, genomic instability and loss of p16 in some DN, in general DN are far more similar to CN than to melanoma (Table III). We look forward to future studies that may identify subsets of DN, based on molecular markers, which could be associated with higher risk. At present, however, there is no clinical evidence that DN as a group behave more aggressively (i.e. tendency towards melanoma transformation) than CN and no markers have been validated to identify those lesions (either DN or CN) that may be more predisposed to melanoma transformation and/or metastasis.

If individual DN lesions can be distinguished from melanoma histologically, then such lesions appear to represent a variant of melanocytic nevus, and given their prevalence could be considered a normal nevus variant (such as blue nevus, Spitz nevus, etc.). Just as DN represent a particular nevus subtype to which particular individuals are predisposed, similar findings have more recently been extended to patients with distinct subtypes of CN.[100, 101] These observations support a broader concept of melanocytic tumor formation, in which all melanocytes within an individual are genetically similar and the nevi that ultimately are formed are a product of a specific set of genetic defects and environmental exposures.

Given all these considerations, we suggest that most DN can be managed clinically like CN. That is to say, any clinically suspicious lesions should be removed and those patients with clinically atypical or numerous nevi should be carefully monitored given their increased melanoma risk. A complete summary of our recommendations for management of DN is provided in Table IV.

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Abbreviations used

5-FU	5-fluorouracil
CN	common nevus
DN	dysplastic nevus
DNS	dysplastic nevus syndrome
LOH	loss of heterozygosity
MAPK	mitogen-activated protein kinase
PTEN	phosphatase and tensin homolog

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Learning objectives

At the conclusion of this learning activity, participants should: 1) understand molecular aspects shared by dysplastic and common nevi; 2) be familiar with the molecular aspects of dysplastic nevi that may differ from common nevi; and 3) be aware of the controversies and evidence pertaining to management of dysplastic nevi.

CAPSULE SUMMARY

- Some dysplastic nevi (DN) exhibit molecular characteristics distinct from “common” nevi (CN).
- These include distinct gene expression patterns, higher proliferation index, mutation or altered expression of p16 and p53, and increased microsatellite instability.
- Dysplastic nevi are similar to common nevi with respect to clonality, markers of senescence, rate of BRAF mutation, and rate of recurrence following biopsy.
- There are currently no markers that have been shown to predict biologic behavior of DN.
- DN may be considered variants of melanocytic nevi that can be managed like CN.

Table I

Differences and similarities between DN and CN

Differences (DN vs. CN)	Similarities
Distinct histologic features	Clonality
Marker of greater melanoma risk	Expression of apoptosis regulators
Higher proliferation index	Senescence markers
Distinct gene expression patterns	BRAF mutation rate
Mutation / deletion of *p16* gene *	Loss of PTEN expression
Altered expression of p53 *	Risk of transformation to melanoma
Increased microsatellite instability	Rate of recurrence after biopsy

CN, common nevus; DN, dysplastic nevus

* Reported in some but not all studies

Table II

Potential advantages/disadvantages of re-excising DN

Advantages	Disadvantages
Diagnostic confirmation (if partial biopsy)	Potential over-treatment:
Decrease risk of lesion recurrence	Cost
May prevent “pseudomelanoma”	Risks of skin surgery
Medicolegal (defensive medicine)	

DN, dysplastic nevus

Table III

Molecular features distinguishing DN, compared to CN and melanoma

	DN	CN	Melanoma
Proliferation index	+	0	+++
BRAF mutation rate	++	++	++
Mutation / deletion of *p16* gene	+	0	+++
Altered expression of p53	+	+	++
Loss of PTEN expression	++	++	+++
Microsatellite instability	+	0	+++

CN, common nevus; DN, dysplastic nevus

0, absent; +, low rate; ++, detectable with some frequency; +++, high rate or frequency

Table IV

Recommendations for management of DN

Any clinically suspicious nevus should be removed
DN should be regarded as histologic variants of CN
Beyond histologic examination, no tests currently available to predict biologic behavior of nevi
Most DN do not need to be re-excised following biopsy
DN showing severe histologic dysplasia or that cannot be distinguished from melanoma should be re-excised
Patients with clinically atypical or numerous nevi, or previous biopsies of DN, should be recognized as having increased melanoma risk
Patients at increased risk for melanoma should be carefully monitored

CN, common nevus; DN, dysplastic nevus