Dysplastic Nevi
Morphology and Molecular and the Controversies In-between

Katharina Wiedemeyer, MD[a,b,1],
Wolfgang Hartschuh, MD[b,2],
Thomas Brenn, MD, PhD, FRCPath[a,c,*]

KEYWORDS

• Dysplastic nevus • Melanoma • Familial melanoma • Melanocytic • Neoplasm

Key points

- Dysplastic nevi (DN) show distinctive histopathologic features and are part of the spectrum of atypical nevi.
- DN are clinically, histopathologically, and genetically intermediate between common acquired nevi and melanoma.
- DN may be single or multiple, sporadic, or familial.
- DN are benign but rarely progress to melanoma.
- The presence of multiple DN or severely DN is associated with an increased overall melanoma risk.
- Complete excision of DN with clinically concerning features is advisable to allow for adequate histopathologic examination and diagnosis.

ABSTRACT

Dysplastic nevi are distinctive melanocytic lesions in the larger group of atypical nevi. They often are multiple and sporadic with genetic features intermediate between common acquired nevi and melanoma. Dysplastic nevi may be multiple, familial, and seen in patients with familial melanoma syndrome. Although their behavior is benign, they rarely represent a precursor to melanoma. If clinically suspicious, dysplastic nevi should be removed for adequate histopathologic examination and to exclude possibility of melanoma. Partial sampling should be avoided because reliable separation from melanoma requires visualization of the entire lesion to allow for examination of architectural histopathologic features and avoid sampling error.

OVERVIEW

Dysplastic nevi (DN) are benign melanocytic proliferations that initially were documented by Dr Wallace Clark and colleagues[1] in patients with the familial melanoma syndrome, also known as familial atypical multiple mole melanoma (FAMMM) syndrome. They belong to the broader group of

[a] Department of Pathology and Laboratory Medicine, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada; [b] Department of Dermatology, University Medical Center, Ruprecht-Karls-University, Heidelberg, Germany; [c] Arnie Charbonneau Cancer Institute, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada
[1]Present address: Diagnostic and Scientific Centre, 9-3535 Research Road NW, Calgary, AB, T2L 2K8, Canada.
[2]Present address: University Hospital Heidelberg, Im Neuenheimer Feld 440, 69120 Heidelberg, Germany
* Corresponding author. Diagnostic and Scientific Centre, Room IW-210, 9-3535 Research Road NW, Calgary, Alberta T2L 2K8, Canada,
E-mail address: thomas.brenn@ucalgary.ca

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atypical nevi and are intermediate between common acquired nevi and superficial spreading melanoma in terms of their clinical appearance, histopathologic features, and molecular genetics. DN may be solitary or multiple, and a majority are sporadic. They show atypical clinical presenting features and distinctive and reproducible histopathologic findings characterized by a combination of architectural and cytologic atypia. The clinical behavior is benign, but, similar to common acquired nevi, DN may be viewed as a melanoma precursor.[2] Ongoing controversies regarding DNs relate mainly to terminology, histopathologic grading, treatment, and surveillance. This review aims to provide an overview of current knowledge with a practical guide to the diagnosis and management of DN.

HISTORICAL BACKGROUND

The concept of atypical moles and their association with melanoma developed in the 1970s. In 1978, Clark and colleagues[1] documented a group of unique melanocytic nevi in patients with familial melanoma. The patients were found to have multiple (>10 to <100) of these nevi, ranging in size from 5 mm to 15 mm and showing irregular outlines with variegated appearances and a predilection for the upper trunk and extremities. Histopathologically, these nevi were found to be compound with an atypical junctional melanocytic hyperplasia composed of enlarged atypical epithelioid or spindled melanocytes, arranged singly and in irregular nests, but generally confined to the sides and tips of the rete. The melanocytes often contained finely dispersed, "dusty" cytoplasmic melanin pigment. Additional findings were delicate fibroplasia of the papillary dermis, lymphocytic infiltration, and prominent vessels of the superficial dermis. The investigators also mentioned that their use of the term, *atypical melanocytic hyperplasia*, is synonymous with *melanocytic dysplasia*, comparable to squamous dysplasia in actinic keratoses or of the cervical mucosa, and they were able to demonstrate transformation to melanoma of 2 such nevi with time. These distinctive nevi were termed, *B-K moles*, and the associated familial melanoma syndrome was termed, *B-K mole syndrome*, with B and K representing the first letters of 2 of the study patients' names.[1] A family with a similar clinical phenotype was documented in the same year by Dr Henry Lynch and colleagues,[3] who applied the term, FAMMM. Nevi with clinical and histologic features identical to the B-K mole subsequently also were identified in patients with nonfamilial melanoma, and remnants of these nevi were noted in the patients' melanoma. The investigators referred to these nevi as DN and to the clinical presentation as dysplastic nevus syndrome.[4]

TERMINOLOGY AND SYNONYMS

There has been significant controversy and debate regarding the terminology and the use of the term, *dysplastic nevus*. The term, *dysplasia*, as applied for epithelial proliferations, implies a premalignant condition with risk for progression to invasive carcinoma. Yet the concept of DN as a premalignant precursor necessary for the development of melanoma has never been proved, and it has been argued that the term, *dysplastic*, is used inappropriately in this setting.[5] To resolve issues around terminology, a 1992 consensus conference at the National Institutes of Health proposed replacing dysplastic nevus with *nevus with architectural disorder and cytologic atypia*.[6] Similar to atypical nevus, nevus with architectural disorder and cytologic atypia is a broad term and encompasses a wide spectrum of melanocytic lesions. The eponymous, *Clark nevus*, was proposed by Dr B Ackerman, but its definition lacks nuclear atypia, and, therefore, it is not synonymous with dysplastic nevus.[5] In the authors' opinion, dysplastic nevus remains the preferred terminology. Despite its flaws, it is of historic significance and most accurately refers to this unique subset of melanocytic nevi. In a 2004 survey, it also was found the preferred terminology by members of the American Society of Dermatopathology and the American Academy of Dermatology,[7] and it is the preferred terminology by the International Melanoma Pathology Study Group and the current fourth edition of the World Health Organization *Classification of Skin Tumors*.[8,9]

DYSPLASTIC NEVUS AND MELANOMA RISK

Early studies emphasized an increased melanoma risk in patients with DN and advocated to regard DN as premalignant conditions.[1,4,10] It now has become evident that DN are relatively common in the general population, and their prevalence vastly exceeds that of melanoma. A majority of DN remain stable or regress, and only a limited subset of DN shows potential to progress to invasive melanoma, with approximately 75% of melanomas arising de novo.[2,11–14] Furthermore, both common acquired nevi and DN are seen as benign melanoma precursors with approximately equal frequencies, and there does not appear to be a linear progression from common acquired nevi to

DN before transformation to outright melanoma occurs.[2,14] Although the risk of transformation to melanoma is low for individual DN, the presence of multiple clinically atypical or DN correlates with an overall increased melanoma risk.[8,15] The presence of greater than 10 clinically DN confers a 12-fold increased melanoma risk compared with a 2-fold increased melanoma risk in the presence of a solitary clinically dysplastic nevus. For comparison, increased numbers of small non-DN correlate with a 2-fold increased melanoma risk whereas large non-DN show a 4-fold increased melanoma risk.[16] The relative melanoma risk for individuals with dysplastic nevus syndrome is highest for individuals with greater than or equal to 2 family members diagnosed with melanoma and lowest for those with dysplastic nevus syndrome but no personal or family history of melanoma.[17]

CLINICAL FEATURES

Clinically, DN large are macular lesions, typically measuring greater than or equal to 5 mm in diameter. An additional central raised papular area represents the dermal growth component, giving rise to a fried egg or targetoid appearance (**Fig. 1**). Additional findings are irregular borders; variegated colors, ranging from light brown to dark brown and black; and peripheral erythema. DN typically present in adolescence and young adulthood with a decreasing prevalence with increasing age. They are most common in individuals of northern European descent with a prevalence of approximately 10% (range 7%–24%). They may be solitary or multiple and affect intermittently sun-exposed skin with a predilection for the back. DN also may be seen in patients with hereditary and nonfamilial melanoma and they are seen in up to 43% of patients with melanoma compared with 10% in the control group.[1,4,16] A majority of DN remain unchanged or regress over time, even in in melanoma-prone families.[18] The clinical presenting features also are summarized in **Table 1**.

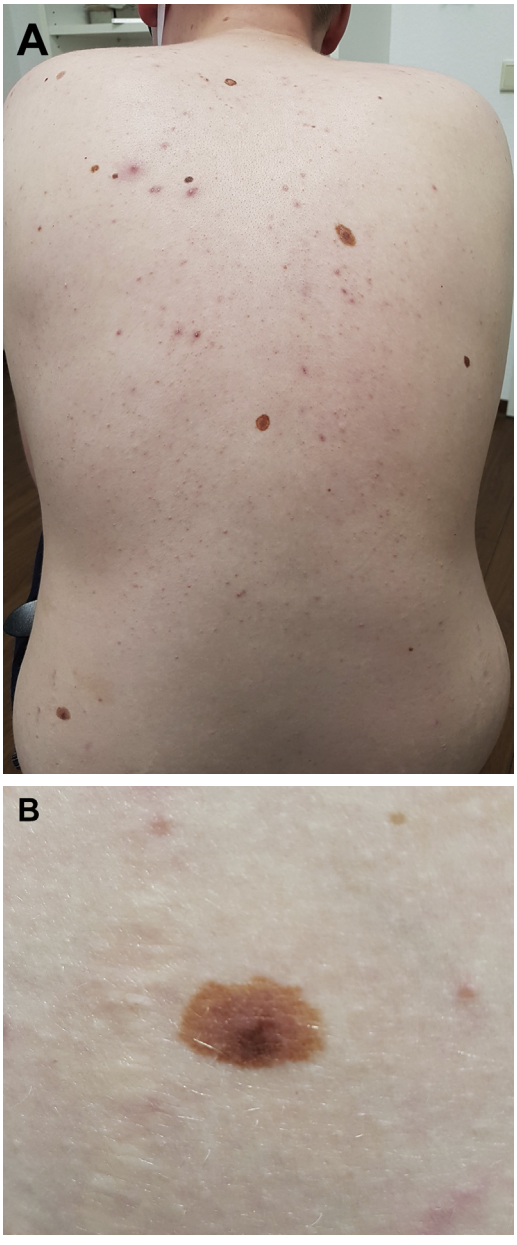


Fig. 1. This patient presents with multiple DN on the back (*A*). This dysplastic nevus is enlarged with irregular borders, color variegation, and a central raised area (*B*).

MICROSCOPIC FEATURES

The histologic criteria for a diagnosis of DN are based on the original description by Clark and colleagues[1] and require both architectural and cytologic changes.[19,20] Histopathologically, DN are intermediate between common acquired nevi and superficial spreading melanoma with atypical architectural and cytologic features not associated with common acquired nevi but insufficient for a diagnosis of superficial spreading melanoma. A diagnosis of DN is reproducible with excellent intraobserver and reasonable interobserver agreement when applying previously agreed-on histopathologic criteria.[21–23] DN may be junctional or compound. They are relatively circumscribed and symmetric but may show somewhat ill-defined radial borders with a trickling of single melanocytes toward their periphery (**Fig. 2**A, B). If present, the dermal component is shallow and centrally placed, and there is variable radial extension of the junctional component beyond the dermal

Table 1
Summary of the clinical presenting features of dysplastic nevi

Clinical Features of Dysplastic Nevi	
Sex	Equal gender distribution
Age	Adolescents, young adults
Site	Intermittently sun-exposed areas, in particular, the back
Size	≥5-mm diameter
Clinical appearance	Solitary or multiple Sporadic or familial Macular component representing junctional melanocytic proliferation Central papular growth representing the dermal melanocytic proliferation and giving rise to targetoid or fried-egg appearance Color variegation Ill-defined border Peripheral erythema
Associated syndromes	Dysplastic nevus syndrome, familial melanoma syndrome

growth (Fig. 2C). This phenomenon is regarded as shoulder formation. The junctional component is broad and composed of epithelioid to ovoid melanocytes in a lentiginous and nested growth pattern (Fig. 2D). The junctional melanocytic nests are irregularly shaped and distributed along the basilar epidermis mostly confined to the sides and tips of elongated rete, and there is fusion of junctional nests of adjacent and elongated rete ridges, referred to as *bridging* (Fig. 3A). In addition, there may be fusion of adjacent rete ridges (Fig. 3B). Focal suprabasal scatter of single melanocytes may be present, but it is confined to the lower levels of the epidermis and generally restricted to the lesional center (Fig. 3C). The melanocytes contain moderate amounts of cytoplasm, frequently with finely dispersed, dusty cytoplasmic melanin pigment (Fig. 4A). Cytologic atypia invariably is present and characterized by nuclear enlargement with variably prominent and occasionally multiple nucleoli, chromatin clumping, and nuclear hyperchromasia (Fig. 4B). The cytologic atypia is scattered and random rather than confluent and monotonous. Mitotic activity of the junctional component is rare. The involved epidermis shows a pronounced rete ridge pattern, and there is increased eosinophilic fibrous tissue surrounding the elongated rete ridges, known as *concentric eosinophilic fibroplasia* (Fig. 5A). A lamellar arrangement of connective tissue at the base of the rete ridges is referred to as *lamellar fibroplasia*. Other stromal and host response changes include a patchy lymphocytic infiltrate, increased vascularity in the superficial dermis, and pigmented melanophages (Fig. 5B).[20] The dermal component appears nevic and generally lacks cytologic atypia and mitotic activity (Fig. 6). Due to its shallow nature, it may be difficult to assess for maturation with depth.[19–21,24] DN may show varying degrees of cytologic and architectural atypia within a lesion, and they may be present in the background of an unequivocal melanoma (Fig. 7).

HISTOPATHOLOGIC GRADING

Controversy remains regarding the histopathologic grading of DN and interobserver reproducibility. Traditionally, the degree of atypia in DN has been divided into mild, moderate, and severe. The use of a 2-tier system using low-grade for mild and moderate atypia and high-grade for severe atypia also has been advocated.[25] Grading may be based solely on the degree of cytologic atypia or on a combination of architectural and cytologic features.[20,26] Mild melanocyte atypia has been defined as nuclear size similar to the nucleus of basal layer keratinocytes with condensed chromatin and inconspicuous nucleoli, whereas moderate atypia shows nuclear enlargement up to 1.5 times the size of the basal layer keratinocyte nucleus, and severe atypia is characterized by nuclear size twice or greater that of basal layer keratinocyte nuclei with nuclear hyperchromasia or vesicular nuclei with prominent nucleoli.[26] The degree of architectural disorder may be of equal importance to cytologic atypia when grading DN. Architectural features indicative of severe

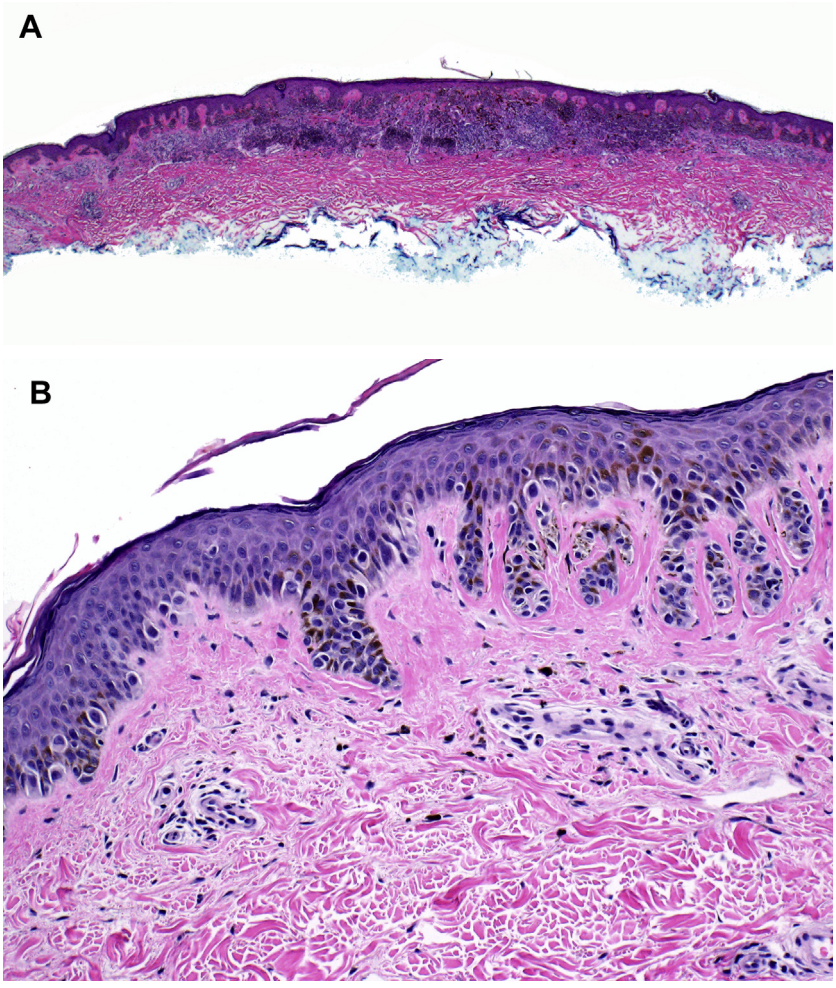


Fig. 2. This low-power overview is of a broad but relatively circumscribed and symmetric compound dysplastic nevus (hematoxylin-eosin, original magnification x10) (*A*). At the periphery there is a proliferation of single melanocytes (hematoxylin-eosin, original magnification x100) (*B*). The junctional melanocytic proliferation extends beyond the dermal component, also referred to as shoulder formation (hematoxylin-eosin, original magnification x100).

atypia include increased lesional diameter and lack of circumscription, asymmetry, an effaced rete ridge pattern, focally confluent growth of the junctional melanocytic proliferation, single cells predominating over nests, junctional mitotic activity, and low-level pagetoid spread.[20] The grading of DN is of particular importance to guide treatment because those with severe atypia show many overlapping histologic features with melanoma and may be difficult to reliably separate from early melanoma in individual challenging cases. In addition, the degree of atypia in DN correlates with a personal history of melanoma.[8] In 1 study, 19.7% of patients with severely DN were found to have a personal history of melanoma compared with 8.1% of patients with moderately DN and 5.7% with mildly DN.[27]

IMMUNOHISTOCHEMISTRY

The melanocytes in DN express S100, SOX10, Melan-A, microphthalmia-associated transcription factor (MITF), and tyrosinase (**Fig. 8**A). HMB45 staining typically is present only in the junctional and superficial dermal melanocytes but is lost in the deeper dermal component. The Ki-67 proliferative index of the dermal component is low, with less than 5% of melanocytes staining in a dermal hot spot.[28] P16 expression is preserved whereas there is lack or only focal expression of preferentially expressed antigen in melanoma (PRAME) (**Fig. 8**B).[29] Staining for Melan-A or SOX10 is of particular importance in routine daily practice to highlight confluent melanocyte growth and pagetoid spread.

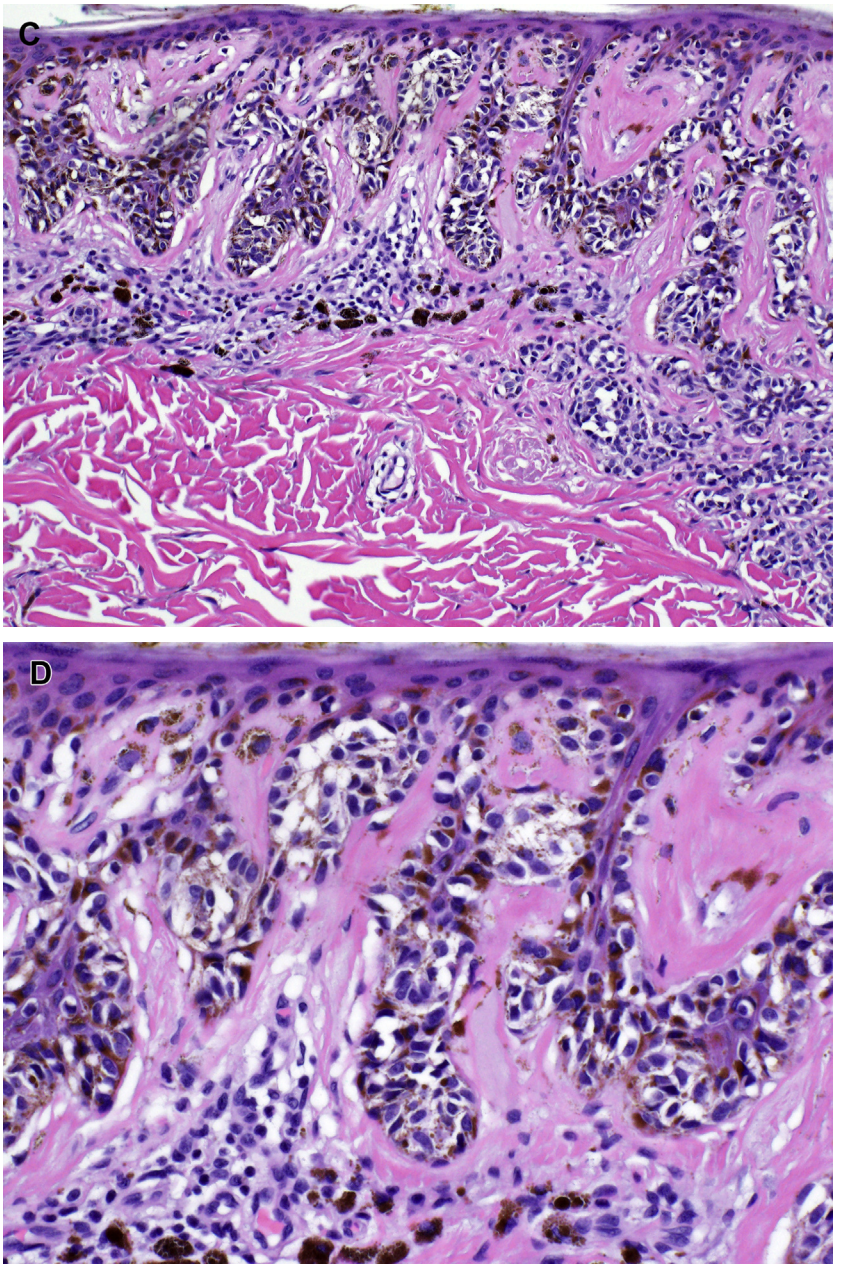


Fig. 2. (*continued*). (*C*). The rete ridges are elongated and there is a lentiginous and nested junctional melanocytic proliferation with disorderly arranged melanocytic nests (hematoxylin-eosin, original magnification x200) (*D*).

MOLECULAR AND GENETIC FEATURES

Over the past few years, knowledge of the molecular and genetic underpinnings of the various melanocytic proliferations has expanded significantly and several familial melanoma susceptibility genes now have been identified. A majority of melanoma prone families carry inherited mutations in *cyclin-dependent kinase 2A inhibitor* (*CDKN2A*). Other less frequently mutated genes in familial melanoma patients include *cyclin-dependent kinase 4* (*CDK4*), *BRCA1-associated protein-1* (*BAP1*), *MITF*, *telomerase reverse transcription* (*TERT*), and *protection of telomeres 1* (*POT1*).[30] Sporadic DN have recently been shown by several methods to be genetically intermediate between common

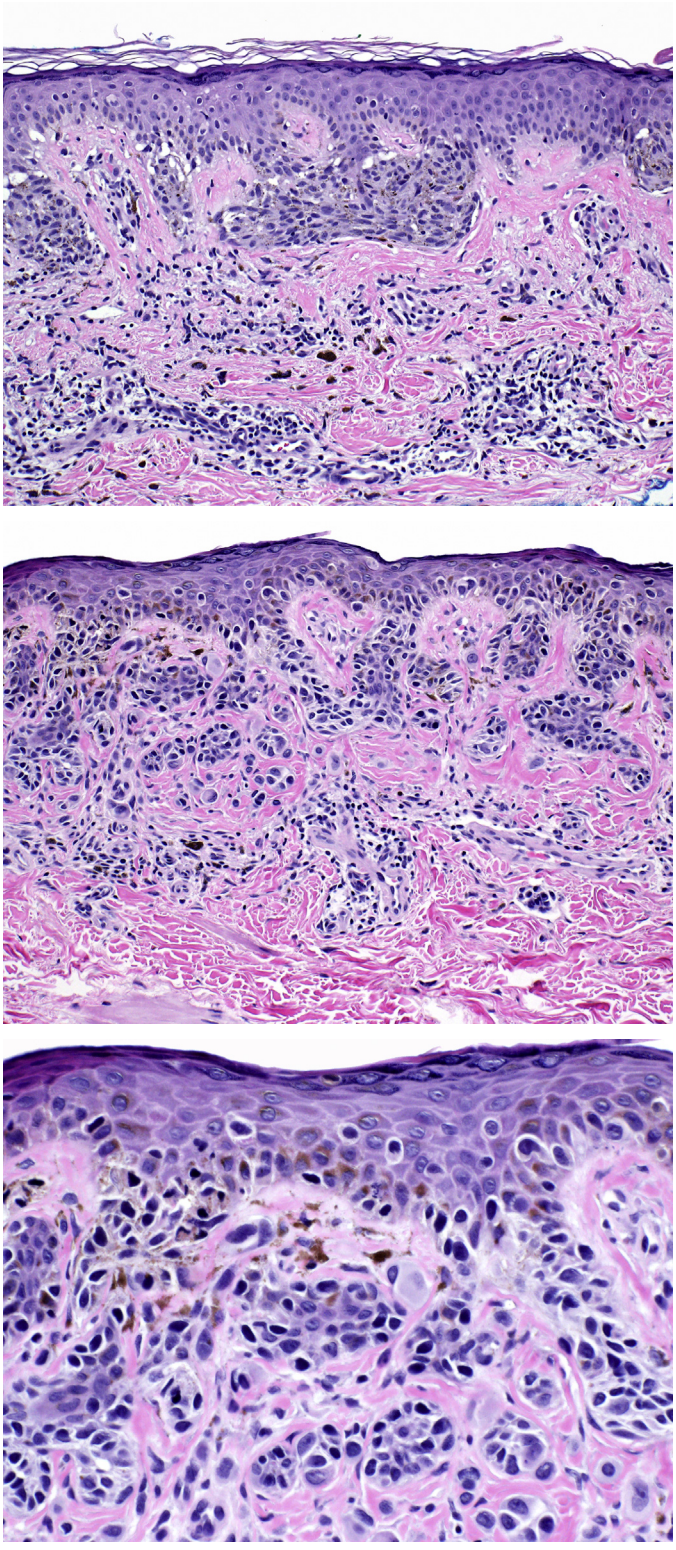


Fig. 3. Fusion of junctional melanocytic nests across elongated rete ridges is known as bridging. Also, note the patchy chronic inflammatory infiltrate within superficial dermis (hematoxylin-eosin, original magnification x40) (*A*). Fusion of adjacent rete ridges (hematoxylin-eosin, original magnification x40) (*B*). In the center of this dysplastic nevus, there is low-level intraepidermal ascent of single melanocytes (hematoxylin-eosin, original magnification x200) (*C*).

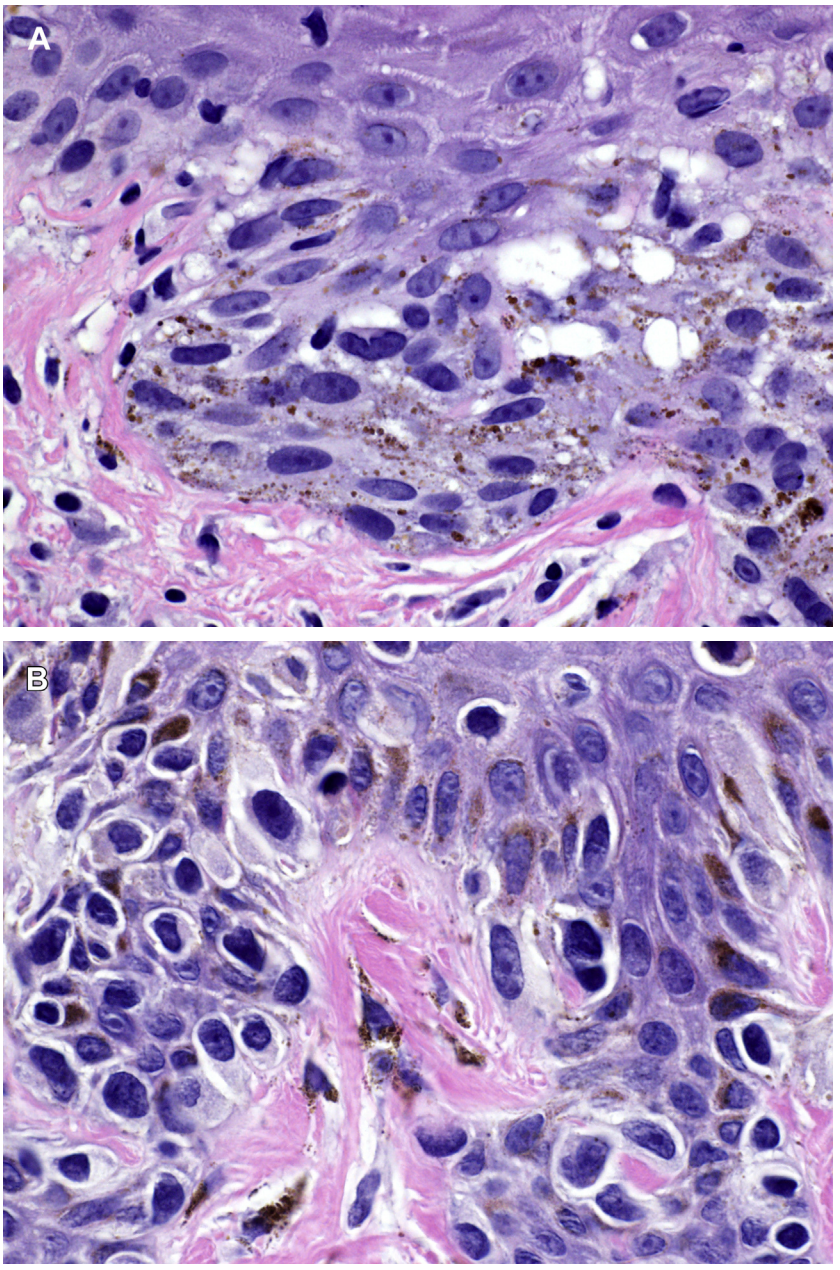


Fig. 4. Finely dispersed melanin pigment is seen in these atypical ovoid melanocytes giving rise to an olive-green, dusty appearance (hematoxylin-eosin, original magnification x400) (*A*). Marked cytologic atypia is appreciated in these melanocytes showing nuclear enlargement, nuclear hyperchromasia and prominent nucleoli (hematoxylin-eosin, original magnification x400) (*B*).

nevi and melanoma, further confirming the clinical and histopathologic impression.[31–33] Mutational analysis of melanomas and their benign precursors revealed single driver mutations in *BRAF*^{V600E} in common nevi whereas multiple driver mutations were observed in DN. Driver mutations resulting in activation of the *MAPK* signaling pathway, *TERT* promoter mutations and heterozygous abnormalities in *CDNK2A* were common. DN also show an overall mutational burden that is, higher compared with common nevi but lower than that observed in outright melanoma.[31–33] Similarly, studies on microRNA expression have confirmed the intermediate position of DN in the biologic spectrum form common nevi to melanoma.[34–36]

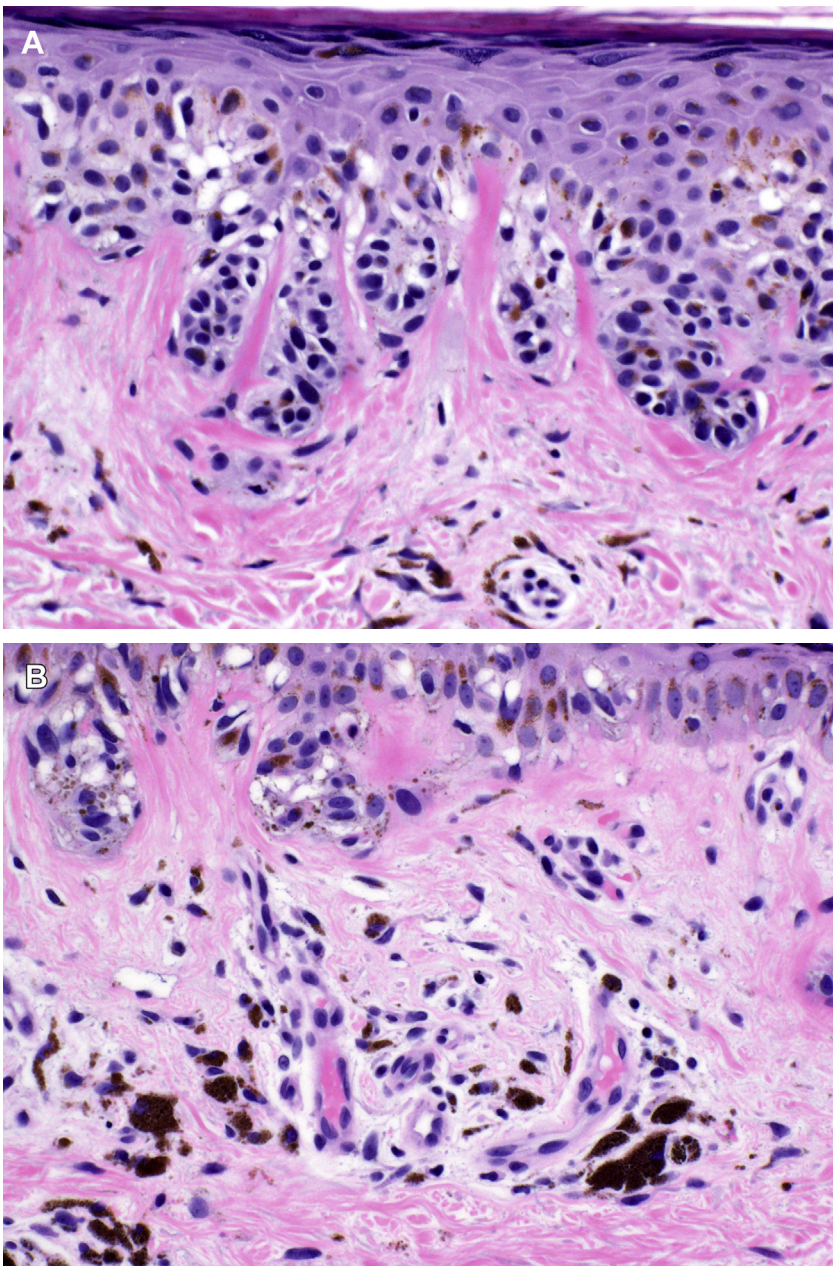


Fig. 5. Eosinophilic fibroplasia surrounds these rete ridges (hematoxylin-eosin, original magnification x200) (*A*). Pigment incontinence and prominent vessels are seen in the superficial dermis (hematoxylin-eosin, original magnification x200) (*B*).

TREATMENT

DN and clinically atypical nevi require regular clinical monitoring and should be removed by excision, preferably with a 1-mm to 3-mm clinical margin, to exclude melanoma in the presence of clinically concerning findings, such as a history of recent growth, change in shape or color, increasing erythema, and itching sensation.[37,38]

It is important to avoid partial and fragmented sampling using superficial shave biopsies, small punch biopsies through the lesional center, or sampling by curettage.[39] These procedures do not allow for adequate histopathologic assessment of important architectural features necessary to separate DN from superficial spreading melanoma, such as lesional symmetry and circumscription and maturation of the dermal component with depth. Partial samples also are

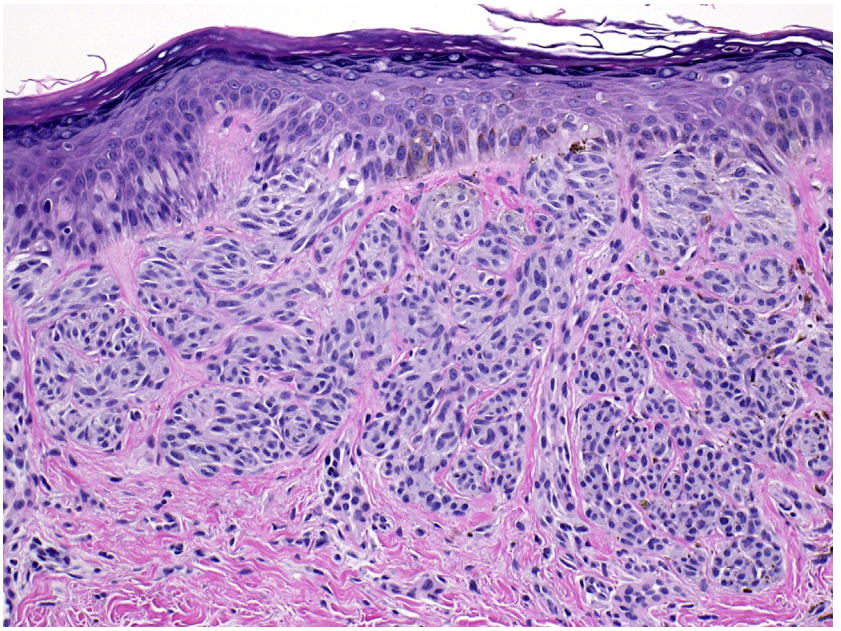


Fig. 6. The dermal component is bland and devoid of cytologic atypia or mitotic activity. Maturation with depth is preserved (hematoxylin-eosin, original magnification x40).

prone to sampling error because more concerning or outright melanomatous areas may not be represented in the original biopsy.[37] Furthermore, subsequent excisional biopsies of previously partially sampled melanocytic lesions often are difficult to assess due to distortion by the presence of a scar and the concerning features of recurrent nevus phenomenon, leading to potential for overdiagnosis as melanoma. Complete excision of clinically atypical nevi, even with narrow margins, allows for a more confident initial diagnosis and reduces the number of surgical procedures for the patient by avoiding frequent repeat biopsies and excisions of partially sampled DN. Furthermore, there is little argument for performing formal re-excisions of completely excised DN, even if severely atypical.[40] Similarly, there is no good evidence to suggest re-excisions of mildly or moderately DN even if tissue edges are only focally involved as long as the lesion is adequately sampled and represented in the biopsy and there is no evidence of residual pigmented lesion clinically.[41–43]

DIFFERENTIAL DIAGNOSES

DN can be separated from lentiginous junctional and lentiginous compound nevi by the presence of architectural and cytologic atypia.

Nevi of special sites show considerable histologic overlap with DN and reliable separation may be challenging. Nevi of special sites frequently present at anatomic sites where DN are rare, for example, acral and genital skin. Although acral nevi show worrisome architectural features, including a lentiginous junctional growth and upward scatter of single melanocytes within the epidermal layers, there is little, if any, cytologic atypia and a minimal host response in the form of fibrosis or a lymphohistiocytic inflammatory infiltrate.[44,45] Similarly, genital nevi show significant architectural atypia with a disorderly nested growth of the junctional component and focal pagetoid spread.[46] In contrast to DN, however, there is no prominent junctional lentiginous growth component, and the cytologic atypia is confluent rather than scattered and random. Genital nevi also lack the host response typical of DN. Despite their concerning histologic features, nevi of special sites are benign. They do not appear to be melanoma precursors, and they are not associated with an overall increased melanoma risk.

Most important and challenging is the separation of DN from early superficial spreading melanoma. DN show architectural and cytologic features overlapping with those of superficial spreading melanoma, and the distinction is based on the overall constellation of features and the severity of changes. It is important to understand that the border between severely DN and early melanoma may be blurred and not sharply defined; moreover, there is poor interobserver

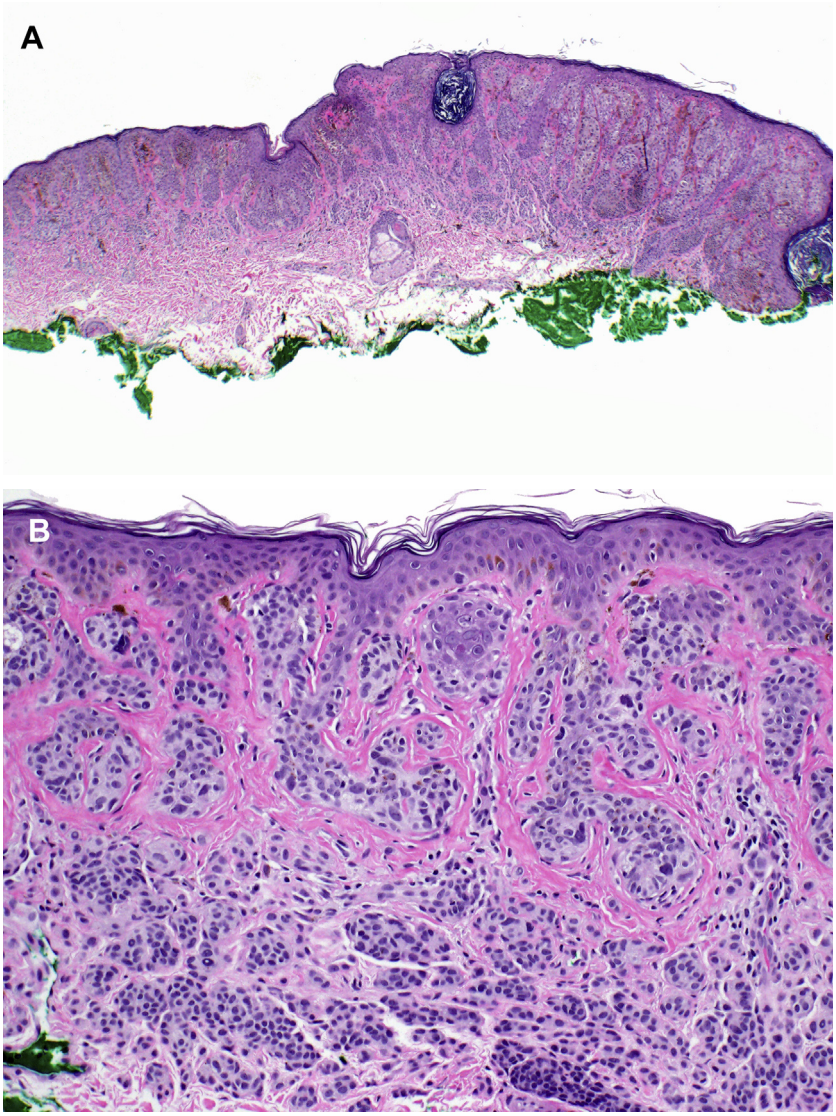
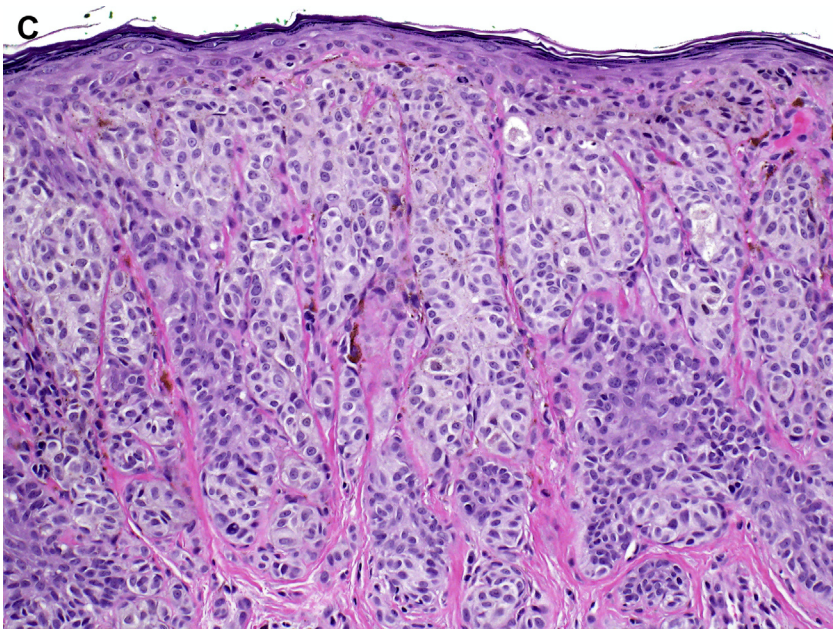


Fig. 7. There is marked lesional asymmetry in this melanoma (*right*) arising in a background of a dysplastic nevus (hematoxylin-eosin, original magnification x10) (*left*) (*A*). Higher magnification of the dysplastic nevus component shows architectural disorder and scattered cytologic atypia of the junctional component and a bland, nevi dermal component (hematoxylin-eosin, original magnification x40) (*B*). The adjacent melanoma shows marked and confluent cytologic atypia.

agreement in this diagnostic setting. Features in favor of a diagnosis of melanoma are large lesional size with marked asymmetry and poor circumscription and significant architectural disorder of the junctional component, resulting in contiguous growth of melanocytes with effacement and atrophy of the overlying epidermis and diffuse pagetoid spread across the lesion. Melanoma shows severe and confluent rather than scattered and random cytologic atypia and there is cytologic atypia with loss of maturation of the invasive dermal component and mitotic activity. Areas of regression, especially when present in different stages, also are indicative of melanoma. Increased Ki-67 proliferative index greater than 5%, loss of p16 expression, and diffuse PRAME expression of the dermal components are immunohistochemical findings in support of a diagnosis of invasive melanoma.

An additional significant diagnostic dilemma is lesions variably referred to as *lentiginous DN in the elderly* or *lentiginous melanoma*.[47–50] These neoplasms show elongated rete ridges and a diffuse proliferation of epithelioid melanocytes in a disorderly single cell and nested pattern reminiscent of DN. Cytologic atypia is limited but focal



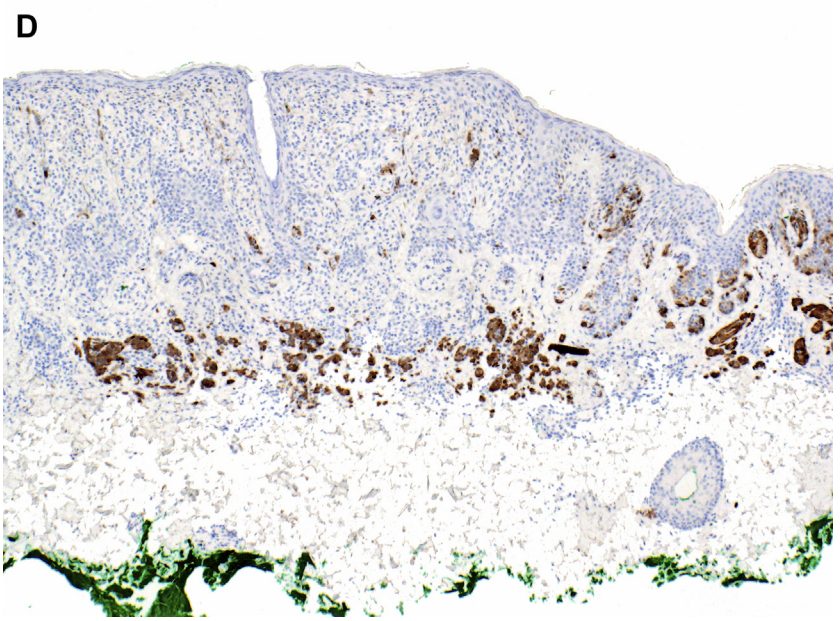


Fig. 7. (*continued*). (hematoxylin-eosin, original magnification x100) (*C*). P16 staining highlights the background dysplastic nevus whereas there is lack of p16 expression in the melanoma (p16, original magnification x20) (*D*).

pagetoid spread may be present. Clinically, these melanocytic tumors often are large, measuring approximately 1 cm in diameter. They present on sun-damaged skin of elderly patients in their 50s and 60s, with a predilection for the upper back, shoulder, and head and neck area. They are best regarded as early melanoma or at least a significant precursor lesion to melanoma. Familiarity with this clinicopathologic entity is important to avoid underdiagnosis as dysplastic nevus, particularly on partial samples. The histologic features of DN in contrast to those of common acquired nevi and superficial spreading melanoma are summarized in **Table 2**.

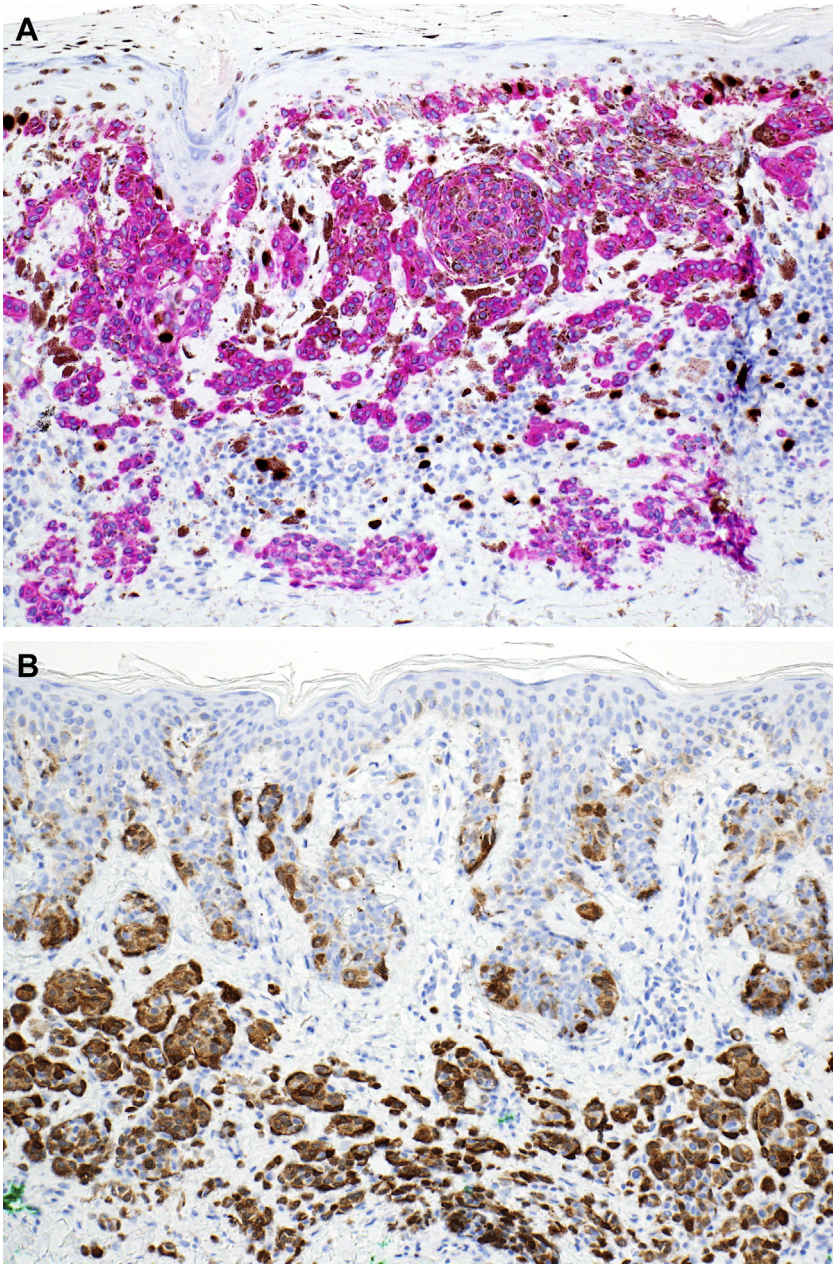


Fig. 8. Melan-A staining (*red*) highlights junctional and dermal melanocytes. The mib-1 (*brown*) proliferative index in melanocytes is low (Melan A, original magnification x40) (*A*). There is preserved p16 expression in dermal melanocytes (p16, original magnification x40) (*B*).

Table 2
Summary of the histopathologic findings of dysplastic nevi in comparison to common acquired nevi and superficial spreading melanoma

	Common Acquired Nevus	Dysplastic Nevus	Superficial Spreading Melanoma
Overall architecture			
Size	Small	Large (≥0.5 cm)	Large (>0.5 cm)
Symmetry	Symmetric	Mainly symmetric	Asymmetric
Circumscription	Circumscribed	Relatively circumscribed	Ill-defined
Junctional component			
Growth pattern	Mainly nested	Lentiginous and nested	Variably lentiginous and nested
Nest arrangement	Base of rete ridges	Disorderly arranged with bridging of nests	Disordered arrangement with fusion of nests
Intraepidermal ascent of melanocytes (pagetoid spread)	No intraepidermal ascent of melanocytes	Focal low-level intraepidermal ascent of melanocytes in lesional center	Prominent intraepidermal ascent of melanocytes into granular cell layer and across the entire lesion
Cytologic atypia	Absent	Scattered	Confluent
Epidermal changes	Preserved epidermal architecture	Pronounced rete ridge pattern	Epidermal atrophy with consumption of the epidermis
Dermal component (if present)			
Junctional shoulder	Absent	Present	Extensive
Cytologic atypia	Absent	Absent	Present
Maturation with depth	Preserved	Preserved	Absent
Mitotic activity	Rare	Rare	Variable
Mesenchymal changes			
Inflammation	Variable	Patchy	Variable
Fibrosis	Absent	Concentric eosinophilic and lamellar surrounding rete ridges	Diffuse

SUMMARY

DN are a distinctive clinicopathologic entity with clinical, histopathologic, and molecular features intermediate between common acquired nevi and superficial spreading melanoma. Although initially reported in patients with familial melanoma and thought to represent an important melanoma precursor, a majority of DN occur in the sporadic setting. They are benign and transformation of DN to melanoma is a rare event. The overall count of DN and increasing degrees of atypia are of importance, however, because they correlate positively with an increased overall melanoma risk in a given patient. If clinically concerning due to recent change, DN should be removed, preferably by excision, to allow adequate histopathologic examination with visualization of the entire lesion. Histopathologic grading should take into account both cytologic and architectural features. DN with severe atypia pose the main diagnostic challenge, and reliable separation from early melanoma may be difficult in individual cases. The histopathologic findings also need to be interpreted in a patient's individual clinical background, including age, extent of sun damage, localization, and medical history; and a close interaction between the treating clinician and the pathologist/dermatopathologist is necessary to guide appropriate treatment.

CLINICS CARE POINTS

When reporting DN, the following should be considered:

- Appropriate clinical information available at time of biopsy: age, anatomic site, gender, clinical and dermoscopic findings, lesional size, level of clinical concern, type of biopsy, and incisional versus excisional biopsy
- Using preferred nomenclature: lentiginous junctional/compound dysplastic nevus with mild/moderate/severe atypia
- Grading of atypia, taking into account both cytologic and architectural features
- Reporting status of margins and adequacy of excision
- Immunohistochemistry for Melan-A/SOX10, which is helpful to highlight lesional architecture of the junctional component
- Immunohistochemistry for p16, PRAME, and Ki-67, which may be useful to exclude melanoma in challenging and severely atypical tumors, but adequate interpretation relies on the presence of a significant dermal component
- Liaising with treating clinician/dermatologist to gain insight into local clinical practice and expectations and to issue treatment recommendations accordingly
- Avoiding treatment recommendations, which, in general, are not necessary for mildly DN and moderately DN
- For small, superficial, and fragmented partial samples, alerting clinician to possibility of sampling error
- Expressing level of concern and ambiguity in challenging lesions because distinction of severely DN from early melanoma is notoriously challenging

DISCLOSURE

The authors have nothing to disclose.

REFERENCES

1. Clark WH Jr, Reimer RR, Greene M, et al. Origin of familial malignant melanomas from heritable melanocytic lesions. 'The B-K mole syndrome. Arch Dermatol 1978;114(5):732–8.
2. Martin-Gorgojo A, Requena C, Garcia-Casado Z, et al. Dysplastic vs. Common Naevus-associated vs. De novo Melanomas: an observational retrospective study of 1,021 patients. Acta Derm Venereol 2018;98(6):556–62.
3. Lynch HT, Frichot BC 3rd, Lynch JF. Familial atypical multiple mole-melanoma syndrome. J Med Genet 1978;15(5):352–6.
4. Elder DE, Goldman LI, Goldman SC, et al. Dysplastic nevus syndrome: a phenotypic association of sporadic cutaneous melanoma. Cancer 1980;46(8):1787–94.
5. Ackerman AB, Magana-Garcia M. Naming acquired melanocytic nevi. Unna's, Miescher's, Spitz's Clark's. Am J Dermatopathol 1990;12(2):193–209.
6. NIH Consensus conference. Diagnosis and treatment of early melanoma. JAMA 1992;268(10):1314–9.
7. Shapiro M, Chren MM, Levy RM, et al. Variability in nomenclature used for nevi with architectural disorder and cytologic atypia (microscopically dysplastic nevi) by dermatologists and dermatopathologists. J Cutan Pathol 2004;31(8):523–30.
8. Shors AR, Kim S, White E, et al. Dysplastic naevi with moderate to severe histological dysplasia: a risk factor for melanoma. Br J Dermatol 2006;155(5):988–93.
9. Xiong MY, Rabkin MS, Piepkorn MW, et al. Diameter of dysplastic nevi is a more robust biomarker of increased melanoma risk than degree of histologic dysplasia: a case-control study. J Am Acad Dermatol 2014;71(6):1257–1258 e1254.
10. Reimer RR, Clark WH Jr, Greene MH, et al. Precursor lesions in familial melanoma. A new genetic preneoplastic syndrome. JAMA 1978;239(8):744–6.
11. Elder DE. Precursors to melanoma and their mimics: nevi of special sites. Mod Pathol 2006;19(Suppl 2):S4–20.
12. Halpern AC, Guerry Dt, Elder DE, et al. Natural history of dysplastic nevi. J Am Acad Dermatol 1993;29(1):51–7.
13. Tucker MA, Fraser MC, Goldstein AM, et al. A natural history of melanomas and dysplastic nevi: an atlas of lesions in melanoma-prone families. Cancer 2002;94(12):3192–209.
14. Bevona C, Goggins W, Quinn T, et al. Cutaneous melanomas associated with nevi. Arch Dermatol 2003;139(12):1620–4, [discussion 1624].
15. Halpern AC, Guerry Dt, Elder DE, et al. Dysplastic nevi as risk markers of sporadic (nonfamilial) melanoma. A case-control study. Arch Dermatol 1991;127(7):995–9.
16. Tucker MA, Halpern A, Holly EA, et al. Clinically recognized dysplastic nevi. A central risk factor for cutaneous melanoma. JAMA 1997;277(18):1439–44.
17. Slade J, Marghoob AA, Salopek TG, et al. Atypical mole syndrome: risk factor for cutaneous malignant

melanoma and implications for management. J Am Acad Dermatol 1995;32(3):479–94.
18. Bishop JA, Wachsmuth RC, Harland M, et al. Genotype/phenotype and penetrance studies in melanoma families with germline CDKN2A mutations. J Invest Dermatol 2000;114(1):28–33.
19. Clemente C, Cochran AJ, Elder DE, et al. Histopathologic diagnosis of dysplastic nevi: concordance among pathologists convened by the World health organization melanoma programme. Hum Pathol 1991;22(4):313–9.
20. Elder DE. Dysplastic naevi: an update. Histopathology 2010;56(1):112–20.
21. de Wit PE, van't Hof-Grootenboer B, Ruiter DJ, et al. Validity of the histopathological criteria used for diagnosing dysplastic naevi. An interobserver study by the pathology subgroup of the EORTC Malignant Melanoma Cooperative Group. Eur J Cancer 1993;29A(6):831–9.
22. Piepkorn MW, Barnhill RL, Cannon-Albright LA, et al. A multiobserver, population-based analysis of histologic dysplasia in melanocytic nevi. J Am Acad Dermatol 1994;30(5 Pt 1):707–14.
23. Rhodes AR, Mihm MC Jr, Weinstock MA. Dysplastic melanocytic nevi: a reproducible histologic definition emphasizing cellular morphology. Mod Pathol 1989;2(4):306–19.
24. Shea CR, Vollmer RT, Prieto VG. Correlating architectural disorder and cytologic atypia in Clark (dysplastic) melanocytic nevi. Hum Pathol 1999;30(5):500–5.
25. Duffy KL, Mann DJ, Petronic-Rosic V, et al. Clinical decision making based on histopathologic grading and margin status of dysplastic nevi. Arch Dermatol 2012;148(2):259–60.
26. Weinstock MA, Barnhill RL, Rhodes AR, et al. Reliability of the histopathologic diagnosis of melanocytic dysplasia. The dysplastic nevus panel. Arch Dermatol 1997;133(8):953–8.
27. Arumi-Uria M, McNutt NS, Finnerty B. Grading of atypia in nevi: correlation with melanoma risk. Mod Pathol 2003;16(8):764–71.
28. Vyas NS, Charifa A, Desman GT, et al. Observational study examining the diagnostic practice of Ki67 staining for melanocytic lesions. Am J Dermatopathol 2019;41(7):488–91.
29. Lezcano C, Jungbluth AA, Nehal KS, et al. PRAME expression in melanocytic tumors. Am J Surg Pathol 2018;42(11):1456–65.
30. Aoude LG, Wadt KA, Pritchard AL, et al. Genetics of familial melanoma: 20 years after CDKN2A. Pigment Cell Melanoma Res 2015;28(2):148–60.
31. Shain AH, Bastian BC. From melanocytes to melanomas. Nat Rev Cancer 2016;16(6):345–58.
32. Shain AH, Joseph NM, Yu R, et al. Genomic and transcriptomic analysis reveals incremental disruption of key signaling pathways during melanoma evolution. Cancer Cell 2018;34(1):45–55 e44.
33. Shain AH, Yeh I, Kovalyshyn I, et al. The genetic evolution of melanoma from precursor lesions. N Engl J Med 2015;373(20):1926–36.
34. Quiohilag K, Caie P, Oniscu A, et al. The differential expression of micro-RNAs 21, 200c, 204, 205, and 211 in benign, dysplastic and malignant melanocytic lesions and critical evaluation of their role as diagnostic biomarkers. Virchows Arch 2020;477(1):121–30.
35. Torres R, Lang UE, Hejna M, et al. MicroRNA ratios distinguish melanomas from nevi. J Invest Dermatol 2020;140(1):164–173 e167.
36. Xu Y, Brenn T, Brown ER, et al. Differential expression of microRNAs during melanoma progression: miR-200c, miR-205 and miR-211 are downregulated in melanoma and act as tumour suppressors. Br J Cancer 2012;106(3):553–61.
37. Fleming NH, Shaub AR, Bailey E, et al. Outcomes of surgical re-excision versus observation of severely dysplastic nevi: a single-institution, retrospective cohort study. J Am Acad Dermatol 2020;82(1):238–40.
38. Terushkin V, Ng E, Stein JA, et al. A prospective study evaluating the utility of a 2-mm biopsy margin for complete removal of histologically atypical (dysplastic) nevi. J Am Acad Dermatol 2017;77(6):1096–9.
39. Elston DM, Stratman EJ, Miller SJ. Skin biopsy: biopsy issues in specific diseases. J Am Acad Dermatol 2016;74(1):1–16, quiz 17–8.
40. Engeln K, Peters K, Ho J, et al. Dysplastic nevi with severe atypia: long-term outcomes in patients with and without re-excision. J Am Acad Dermatol 2017;76(2):244–9.
41. Goodson AG, Florell SR, Boucher KM, et al. Low rates of clinical recurrence after biopsy of benign to moderately dysplastic melanocytic nevi. J Am Acad Dermatol 2010;62(4):591–6.
42. Hiscox B, Hardin MR, Orengo IF, et al. Recurrence of moderately dysplastic nevi with positive histologic margins. J Am Acad Dermatol 2017;76(3):527–30.
43. Dickman JS, Haddad RM, Racette A. Predictive value of positive margins in diagnostic biopsies of dysplastic nevi. Dermatol Res Pract 2020;2020:6716145.
44. Clemente C, Zurrida S, Bartoli C, et al. Acral-lentiginous naevus of plantar skin. Histopathology 1995;27(6):549–55.
45. Kerl H, Trau H, Ackerman AB. Differentiation of melanocytic nevi from malignant melanomas in palms, soles, and nail beds solely by signs in the cornified layer of the epidermis. Am J Dermatopathol 1984;6(Suppl):159–60.

46. Gleason BC, Hirsch MS, Nucci MR, et al. Atypical genital nevi. A clinicopathologic analysis of 56 cases. Am J Surg Pathol 2008;32(1):51–7.
47. King R, Page RN, Googe PB, et al. Lentiginous melanoma: a histologic pattern of melanoma to be distinguished from lentiginous nevus. Mod Pathol 2005;18(10):1397–401.
48. Kossard S. Atypical lentiginous junctional naevi of the elderly and melanoma. Australas J Dermatol 2002;43(2):93–101.
49. Kossard S, Commens C, Symons M, et al. Lentiginous dysplastic naevi in the elderly: a potential precursor for malignant melanoma. Australas J Dermatol 1991;32(1):27–37.
50. King R. Lentiginous melanoma. Arch Pathol Lab Med 2011;135(3):337–41.