REVIEW

Melanocytic dysplastic naevi occupy the middle ground between benign melanocytic naevi and cutaneous malignant melanomas: emerging clues

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Although several studies have confirmed the aetiological importance of melanocytic dysplastic naevi (MDN) in the development of cutaneous malignant melanoma (CMM), the analysis of these lesions was directed mostly towards the study of melanomas. The underlying reasons include the relatively large size of CMMs, their direct lethal outcome, and the feasibility of establishing melanoma cell lines. In contrast, because of their relatively small size, questionable malignant potential, and the difficulty in establishing in vitro cultures, MDN have been studied less extensively. Hypothetically, transformed melanocytes can give rise to any lesion in the hierarchy of melanocytic tumours. Based on this hypothetical perspective, and on the epidemiological, morphological, immunohistochemical, and genetic characteristics of MDN, it is not surprising that these lesions occupy an intermediate position in the hierarchy of melanocytic lesions, and may be precursors of CMM. Although this argument appears to be straightforward, it is still controversial. This review explores the components of this argument and provides supporting evidence for this hypothesis.

entity, and his manuscript of 1812, reporting a case of disseminated melanoma, also marks the first published use of the word melanoma.¹

The incidence of melanoma has increased dramatically worldwide, posing a major threat to public health. For example, in the USA the incidence of melanoma is rising faster than that of any other cancer, with an estimated 20 000 to 40 000 cases of in situ CMM and 47 700 cases of invasive CMM diagnosed each year.²

Historical aspects of MDN

Although the concept of MDN was introduced only recently, these lesions were observed a long time ago. The observation was made in the context of melanoma in 1820 by William Norris, who arrived at the conclusion that melanoma is a hereditary disease associated with the development of moles. In 1829, Norris³ described a family in which two members developed melanomas and the other family members had many moles on various parts of their bodies. In 1974, Munro⁴ described macroscopic and microscopic pictures of what is now known as MDN. In 1978, Clark *et al* published the first report to advance MDN as a separate pathological entity associated with an increased risk of melanoma. The lesions were reported in two familial melanoma kindreds with multiple moles, and were named after the initials of the index families under the new designation of B-K mole.⁵ Later, they were referred to as large atypical naevi. In 1983, Lynch *et al* described a similar kindred and introduced the term “familial atypical multiple mole melanoma syndrome”.⁶ In 1980, Greene and his colleagues applied the term dysplastic naevi, because the lesions have clinical, architectural, and cytological atypical features.⁷

MDN and CMM

Although the exact cause of melanoma is unknown, numerous studies defined the presence of MDN as an important factor associated with an increased risk of melanoma. These dysplastic lesions are clinically different from common acquired naevi (table 1). Some patients may have many MDN and are at increased risk for the development of melanoma; a condition collectively known as the dysplastic naevus syndrome.⁶

Abbreviations: BN, benign naevi; CMM, cutaneous malignant melanoma; MDN, melanocytic dysplastic naevi; UVR, ultraviolet radiation

Although melanocytic dysplastic naevi (MDN) are aetiologically important in the development of cutaneous malignant melanoma (CMM), these lesions have not been studied extensively. Hypothetically, transformed melanocytes can give rise to any lesion in the hierarchy of melanocytic tumours. Based on this hypothesis, and on the epidemiological, morphological, immunohistochemical, and genetic characteristics of MDN, it is not surprising that these lesions occupy an intermediate position in the hierarchy of melanocytic lesions, and may be precursors of CMM. Although this argument appears to be straightforward, it is still controversial. This review will explore the components of this argument and provide supporting evidence for this hypothesis.

INTRODUCTION

Historical aspects and incidence of CMM

The term “black cancer” was first used to describe CMM by Hippocrates in the fifth century BC. In 1806, René Laennec provided the first description of melanoma as a disease

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Table 1 Summary of the morphological, immunohistochemical, and molecular features of melanocytic skin lesions

Feature	BN	MDN	Early CMM	Refs
Clinical				
Symmetry	Symmetrical	Asymmetrical	Asymmetrical	5–8, 9
Size	Small (<5 mm)	Larger (>5 mm)	Variable	5–8, 9
Border	Regular	Irregular	Irregular	5–8, 9
Colour	Uniform	Variegated	Variegated	5–8, 9
Histological				
Cytological atypia	Absent	Mild to severe	Severe	5–8, 9
Architectural atypia	Absent	Mild to severe	Severe	5–8, 9
Ultrastructural				
Melanosomes	Normal	Aberrant	Aberrant	10, 11
Golgi	Normal	Well developed	Well developed	10, 11
Mitochondria	Numerous	Abundant	Abundant	10, 11
Immunohistochemical				
MMR protein expression	Strong	Intermediate	Decreased	12
p53, HMB45 expression	Absent	Intermediate	Pronounced	13, 14
Proliferation marker expression	Low	Intermediate	High	15–17
Genetic				
MSI	Absent/Present	Present (+)	Present (+++)	18, 19
Allelic loss	Absent	Present (+)	Present (+++)	20–22
Loss of TSG (p16 and p53)	Absent	Present (+)	Present (+++)	23
Alterations of oncogenes (ras)	Absent	Present (+)	Present (+++)	24

BN, benign naevi; CMM, cutaneous malignant melanoma; MDN, melanocytic dysplastic naevi; MMR, mismatch repair; MSI, microsatellite instability; TSG, tumour suppressor gene.

SCOPE OF THIS REVIEW

Although many MDN are stable, some show atypical histological and cytological features, extending from mild to severe atypia that borders on CMM. Some groups have presented several examples of CMMs that have developed in pre-existing MDN,⁸ and consider MDN to be a precursor of CMM. Over the past few years, four lines of evidence have supported the concept of MDN as a major risk factor for, if not a direct precursor of, melanoma. These lines of evidence comprise the following: (1) epidemiological evidence, (2) morphological evidence, (3) immunohistochemical evidence, and (4) genetic evidence. Because available reviews about these issues are scarce, this review will analyse this evidence and concisely fill this gap in the literature.

The epidemiological evidence

MDN are relatively common lesions in the USA, where several million individuals have MDN but no family history of melanoma. In addition, it is estimated that approximately 32 000 people have the familial dysplastic naevus syndrome, which is seen in association with familial melanoma.²⁵ Four lines of evidence support the notion that MDN are a crucial marker for increased risk of CMM. First, MDN prevalence surveys performed in CMM studies found an increased risk of CMM in patients with MDN.^{26–29} In this regard, the prevalence of MDN in the general population and in patients with sporadic CMM has been estimated to be approximately 5% and 15%, respectively. Second, the presence of MDN is associated with almost 100% and 60% of cases of familial and sporadic CMM, respectively.^{30–31} Third, the presence of MDN carries an eightfold or greater risk for malignant melanoma.³⁰ For example, the presence of one MDN has been associated with a twofold risk, whereas 10 or more confer a 12 fold risk.³² Fourth, ultraviolet irradiation (UVR), an important aetiological factor in the development of CMM, seems to be involved in a similar way in the development of MDN.³³ In support of this, fibroblasts from patients with CMM/MDN are very sensitive to cell killing by UVR and the UVR mimetic carcinogen, 4-nitroquinoline-1-oxide.^{34–35} Moreover, shuttle vector studies have revealed that lymphoblastoid cell lines from patients with MDN have a reduced ability to handle UVR induced DNA damage,³⁶ and skin fibroblasts from these patients show more chromatid breaks after x ray irradiation.

Furthermore, both major and minor structural and numerical abnormalities, reflecting general chromosomal instability, were seen in patients with MDN.³⁷

Morphological evidence

Histological features

Dysplastic naevi are considered to be naevi with variable mild architectural and cytological atypia to severe atypia bordering on melanoma in situ (fig 1; table 1).³² Dysplastic naevus cells are usually arranged along the basal cell layer or extending downwards into the upper dermis. Cell nests are confined to the thickened papillary dermis and are scattered at unequal distances from each other. Cytologically, dysplastic naevus cells have small oval nuclei, surrounded by abundant amounts of faintly stained cytoplasm. Five lines of histological evidences support the notion that MDN fill the gap between benign naevi (BN) and CMM. (1) Some of dysplastic naevus cells exhibit “random mild to severe cytological atypia” and mitotic figures similar to early melanomas.³ In this regard, these atypical naevus cells have a size 1.3 to 1.5 times larger than the reference melanocytes. Their nuclei vary from 8 to 24 µm in diameter, they have relatively abundant cytoplasm, and contain hyperchromatic nuclei with occasional visible nucleoli and delicate chromatin strands. The nuclear membrane may be folded or deeply indented. (2) Early photographic documentation revealed the transformation of some of these lesions into melanoma. (3) The presence of residual MDN in some excised melanomas.⁹ (4) A quantitative light microscopic study with DOPA staining revealed that the number and mean diameter of melanocytes in MDN is similar to that seen in superficial spreading melanomas.¹⁰ (5) Some research groups have presented several examples of CMMs that developed in pre-existing MDN.³⁸

Ultrastructural features

Electron microscopic studies revealed that MDN with severe dysplasia share several features with radial growth phase melanomas, including: (1) the large size of the dysplastic naevus cells, (2) bizarre shaped and pleomorphic nuclei, (3) well developed Golgi, (4) abundant and deranged mitochondria, and (5) aberrant melanosomes with deranged structures and irregular melanisation.¹¹ Moreover, the atypical intra-epidermal melanocytes of MDN contain a much higher

Figure 1 Histological appearance of a melanocytic dysplastic naevus (A, original magnification, $\times 100$; B, original magnification, $\times 400$).

proportion of abnormal melanosomes than those in BN, similar to that seen in CMM.³⁹ The complete absence of these features in BN and their presence in MDN emphasises the middle ground that MDN occupy among benign and malignant melanocytic lesions (table 1).

Immunohistochemical evidence

Several experimental observations support the notion that MDN represent intermediate lesional steps in a progression leading to CMM (table 1).¹² These observations include: (1) proliferation marker (proliferating cell nuclear antigen/cyclin) studies revealed that the reactivity of MDN is intermediate between BN and CMM^{15–17}; (2) analysis of the expression patterns of mismatch repair proteins revealed that expression in MDN was intermediate between BN and CMM¹²; (3) the cell cycle protein p53 accumulates in MDN,¹³ but at much lower overall frequency than in malignant melanoma⁴⁰; (4) histocompatibility locus antigen class I abnormalities are similar in both CMM and dysplastic naevus cells⁴¹; and (5) dysplastic naevus cells mildly to moderately express HMB45, a protein that is expressed by melanoma cells, but not by dermal naevus cells within BN.¹⁴

Genetic evidence

The finding of genetic changes in MDN similar to those found in CMM suggests that some of these dysplastic lesions are intermediate transitional stages in the course of melanoma tumorigenesis.^{12 18 20 21} These changes include: (1) flow cytometry studies have found an increased frequency of abnormal DNA content in MDN⁴²; (2) linkage analysis studies have suggested that CMM and MDN may be pleiotropic manifestations of the same melanoma susceptibility genes at the 1p and 9p regions⁴³; (3) the similar allelic losses at the 1p, 9p, and 17p regions^{20–23} in MDN and CMM support the existence of a biological continuum between some MDN and CMM⁴⁴; (4) the same microsatellite instability (MSI) pattern is present in MDN at a frequency that is intermediate between BN and CMM^{18 19}; (5) TP53 and ras gene mutations occur in MDN at a much lower frequency than in melanomas; and (6) DNA abnormalities in MDN and superficial spreading melanomas are similar.²⁴

THE CLINICAL RELEVANCE OF DYSPLASTIC NAEVI

The clinical relevance of MDN lies in their association with an increased risk of CMM. Cohort and case-control studies have shown that this increased risk occurs in several clinical settings. First, patients with numerous MDN are at a higher risk of developing CMM than those individuals with a single or only a few MDN. Second, patients with a personal or family history of CMM have an increased incidence of MDN. In this regard, there is a 100 fold increase in the incidence of MDN in patients who have previously had CMM, a 200 fold increase in those with at least two family members with CMM, and a more than 1200 fold increase in those with both a personal and a family history of melanoma.^{26–29 45}

THE HEATED CONTROVERSY ABOUT DYSPLASTIC NAEVI

To date, the “dysplastic naevus” remains a controversial issue and contrary views about its existence are reported repeatedly in the literature. Part of the problem with these lesions is the lack of a precise definition. Some investigators such as Clark and co-workers considered MDN as: (1) lesions with aberrant melanocytic differentiation, and (2) premalignant lesions that can develop into CMM. Alternatively, other investigators such as Ackerman and co-workers considered MDN as: (1) wholly benign lesions, (2) variants of common acquired naevi, (3) the most common melanocytic naevus in humans, and (4) naevi of no clinical importance.

Ackerman proposed several reasons to explain why Clark and co-workers have been “led astray” about the issue of MDN. First, Clark and colleagues had the preconceived idea of the evolutionary nature of the lesions from benignancy (BN), to intermediacy (pre-malignant lesions), to malignancy (CMM). Accordingly, they thought that MDN would be the

Take home messages

- Several lines of evidence suggest that melanocytic dysplastic naevi (MDN) are aetiologically important in the development of cutaneous malignant melanoma (CMM)
- MDN are epidemiologically associated with the occurrence of CMM: there is an increased risk of CMM in patients with MDN; MDN are found in almost 100% and 60% of familial and sporadic CMMs, respectively; the presence of MDN carries an eightfold or greater risk for malignant melanoma; and ultraviolet irradiation is involved in the development of both MDN and CMM
- MDN share some morphological features with CMM and appear to fill the gap between benign naevi (BN) and CMM
- Immunohistochemistry has shown that the expression of proliferation markers, mismatch repair proteins, p53, and HMB-45 is intermediate between BN and CMM, and that both lesions show abnormalities in histocompatibility class I expression
- Molecular studies have revealed genetic aberrations in MDN that are intermediate between those found in BN and CMM, including abnormalities of DNA content, allelic losses, p53 and ras gene mutations, and microsatellite instability
- Thus, MDN appear to represent intermediates in the pathway of melanomagenesis and may be precursors of CMM, although this idea is still controversial, and more work is required to prove it

intermediate lesional step in the hierarchy of melanocytic neoplasms. Second, what is now known about MDN, because Clark's naevi were biopsied only rarely in those days. Third, Clark and co-workers biopsied only large and unusual naevi in their patients with familial melanoma, but not smaller ones of more conventional appearance—that is, the appearance of BN. Therefore, they did not recognise that the histopathological features described as being typical of MDN were common to both MDN and BN. In addition, they failed to realise that the MDN were merely larger variants of BN. Fourth, Clark and co-workers did not have consistent criteria for the recognition of MDN; therefore, they were carried away by speculations that supported their preconceived idea. For instance, the mutagenic effects of UVR in the initiation, promotion, and progression of melanocytic lesions.^{5 8 38 46 47}

CONCLUSIONS

Some MDN are not a “genetic dead end” but rather legitimate precursors of malignant melanoma. In this regard, MDN deserve this legitimacy because they almost fulfil the four requirements of precursor cells: (1) they are epidemiologically associated with the occurrence of CMM; (2) they share some morphological features with CMM; (3) they have immunohistochemical and (4) genetic characteristics that are intermediate between BN and CMM. Although current knowledge suggests that MDN do represent intermediates in the pathway of melanomagenesis, our current understanding of both the changes in MDN and the nature of these lesions is rudimentary, and much effort will be required to improve it.

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