

Atypical Mole (Dysplastic Nevus)

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Abstract

Atypical moles (Ams) represent a commonly acquired activated junctional nevus. They are fairly common with onset near puberty and they remain dynamic throughout adulthood. They rarely progress to melanoma and are considered primarily as markers of increased risk of developing it and no obligate precursor lesions of it. Development of atypical nevus is due to an interaction of genetic and environmental factors. There are no reliable clinical features that allow diagnosing with absolute certitude an atypical mole from a benign melanocytic nevus. An atypical mole, is a mole with a macular or macular and papular component showing at least three of the following criteria: irregular, poor-defined borders; asymmetric shape; irregular distributed pigmentation; a red peripheral hue and size larger than 5mm. Regarding familial atypical multiple mole-melanoma syndrome (FAMMM) diagnosis criteria are: occurrence of melanoma in one or more first conjugal degree relatives; presence of more than fifty nevus and presence of nevus(i) with atypical histologic features. Nowadays, no therapy is available to prevent the development of Ams. Individuals with AMs should be examined on a regular basis and educated to avoid extreme sun exposure. The frequency of follow-up depends on the risk of melanoma development (i.e. when there is a positive familial history for melanoma and AMs, the risk is higher).

Keywords

junctional nevus, familial atypical multiple mole-melanoma syndrome (FAMMM), macular papular component, white dysplastic nevus

Definition

Dysplastic nevus is usually an acquired atypical nevus characterized microscopically by a disorganized melanocytic proliferation associated with variable degrees of atypical cells.

Disease names and historical background

In 1820 Norris described the first English report; It was a case of cutaneous melanoma in two

members of a family while other family members had "many moles on various parts of their bodies"[1]. In 1974 Munro described an association of multiple active junctional nevi with familial history of malignant melanoma [2]. In 1978 Reimer and Clark coined the term "The B-K mole syndrome" to describe familial malignant melanomas stemming from heritable melanocytic moles with distinctive clinical and histological features [3,4]. Since then this lesion

A TSG denominated *CDKN2A* (chromosome 9p22-21) exerts a negative regulation on cell growth by inhibiting a cyclin dependent kinase through the synthesis of a protein (p16/INK 4a) [33,37]. There is evidence that multiple nevi, melanoma or pancreatic cancer may be inherited as autosomal dominant traits in families (FAMMM) known to carry *CDK2A* mutations [38]. Moreover, co-morbid uveal melanoma and cutaneous melanoma exist in patients with strong phenotypic expression of AMs, although *CDK2A* mutations have not been documented yet [39]. It has been premised that this protein allows the cell to repair the ultraviolet B radiation (UVB)-induced DNA damage before cell division. The presence of hereditary or acquired defects in this gene give rise to functional insufficiency and could permit the premature propagation of melanocytes with potentially carcinogenic DNA damage [36,40]. *CDK2A* mutations have been detected in 20% of families with [familial melanoma](#), and up to 78% in sporadic AMs [16,41]. A p16 alteration does not necessarily indicate melanoma, though [41]. Further studies suspect the existence of a novel TSG adjacent to the p16 locus that may co-segregate with *CDK2A* and increase the penetrance of the latter [37,15]. Another susceptible gene is *melastatin* in chromosome 15q13-q14. It is down-regulated with melanoma progression and inversely related to tumor thickness. In AMs there is diffuse *melastatin* mRNA expression although its exact role remains obscure [33].

The cyclin-dependent kinase gene *CDK4* (locus 12q14) is a proto-oncogene involved in the regulation of cellular senescence and could be implicated in the development of tumorigenic clones [42,43]. Recently, the mutational activation of the proto-oncogene *BRAF* (v-raf murine sarcoma viral oncogene homolog B1, chrom. 7q34) that participates in the Ras/Raf/MAPK (mitogen-activated protein kinase) signal transduction pathway has been incriminated to contribute to the initiation or progression of melanocytic neoplasia [44-46]. A peculiar finding is that *BRAF* mutation is more frequent in male than female subjects [45,47]. It is averred that all these gene mutations may occur prior to the establishment of distinct clinical or histological features [16,36]. Microsatellites are DNA repetitive sequences scattered throughout the human genome. The variation in microsatellite length is called microsatellite instability (MSI), and is associated with several familial and sporadic tumors. According to the level of instability, tumors with MSI were categorized in MSI-H (high instability) and MSI-L (low instability) [33]. In AMs MSI-L pattern was detected at 1p and 9p regions with an overall prevalence from 27 to 31% [48-50].

However MSI was also detected in BMN (up to 25%) [49,50].

The mismatch repair system (MMR) is responsible for the repair of mismatched bases during DNA replication [33]. Mismatch repair proteins were widely expressed in AMs and melanomas but not in BMN [51,52]. Despite that fact, there was a lack of correlation between MMR expression and MMR function [51].

The telomeres (TTAGGG repeats at the end of chromosomes) decrease during successive cell divisions. It has been suggested that this process is responsible for the cellular senescence. The activation of the ribonucleoprotein telomerase appears to prevent the shortening of telomeres and therefore the programmed apoptosis in germ-line cells and cancer cells. It was found that the telomerase activity increases from benign melanocytic nevi to atypical nevi and further to melanoma [53].

So far, two models have been postulated to explain the origin of AM, both relying on the "two-hit" hypothesis of Kundson's (*ie*, two genetic events are required for the inactivation of tumor genes) [54,55]. The first one proposes that AM may arise by the inactivation of one allele of a specific melanoma-suppressor gene ("first hit"), and the subsequent loss of the second allele ("second hit") by a somatic mutation [56]. The second one premises that there are two independent genes. Mutations that occur in one of them ("first hit") may cause dysplasia in the melanocytes while in the other one may produce malignant transformation ("second hit") [57]. In contrast to TSGs, activated oncogenes such as *CDK4*, function dominantly in the cell and the "second hit" is needless on the other allele. Nonetheless, additional somatic mutations are required for the development of atypical melanocytes [55].

It is important to underline that there are multiple independent pathways of melanoma development because the penetrance of these genes is altered by other genetic or environmental factors [55,58,59].

Sun exposure appears to be the major environmental risk factor that substantially modifies the progress of atypical moles to melanoma [16,55,58,60-62]. In fact, UVB irradiation induces an increase in the number of melanocytes (increased mitotic activity) not only in exposed but also in covered skin. The size of the proliferative response is inversely correlated to the basal melanocyte number [63]. Moreover there is a higher, (up to 65%), DNA damage in melanocytes of AM than in cells of BMN [64]. In addition to that a recent study demonstrated that the elevated oxidative stress (which it may also be produced by UV exposure), can threaten the cellular integrity in AMs and may represent one

of the steps of the epigenetic mechanism, which causes the neoplastic transformation [65]. The final effect of ultraviolet radiation (UVR) depends on the dose (such as intermittent high-dose: sunburns) and the pattern of exposure (*i.e.* frequent or rare). A high-dose first exposure to the sun after a prolonged period of sun avoidance will induce a significant damage to DNA in melanocytes that have a low base-line capacity for DNA repair and low melanin content [62,66,67]. For example, the development and the final total number of BMN depends both on genetic predisposition and on infrequent intense sun exposure [68-70]. Of at least equal importance is the fact that melanocytes show resistance to UVB-induced apoptosis and are thus at high risk for incorporating UV-induced mutations [59,71]. These mutations affect not only susceptibility genes but also other genes implicated in the control of melanoma environment (such as immune surveillance, angiogenesis, growth factors). Hence, some "perturbed" cells may change their mitotic and/or their migrant behavior and progress to malignancy [62].

Age itself plays a major part in vulnerability to photo-induced carcinogenesis, to host response to injury and the capacity to repair DNA (inversely correlated) [72,73].

Histologically, a common acquired melanocytic nevus normally may transform to junctional, compound, dermal or regress completely. In case of a developmental error, (due to all the aforementioned factors), the nevus may show aberrant intraepidermal differentiation and growth, dermal alterations and random cytological atypia (*i.e.* melanocytic dysplasia). In this lesion, a malignant clone with potentially non-clinical features may emerge and develop to melanoma [74,75]. In conclusion, atypical mole may be defined as a monoclonal and genetically unstable melanocytic proliferation, distinct from BMN and malignant melanoma [50].

Clinical description and diagnosis criteria

There are no reliable clinical features that allow diagnosing with absolute certitude an atypical mole from a benign melanocytic nevus. However, the atypical mole may have some particular attributes, which differentiate the aforementioned entities.

An atypical mole, (see also Fig. 1 and 2), is a mole with a macular (flat) or macular and papular (raised) component, (it may appear as "fried egg") [18], showing at least three of the following criteria:

- irregular, poor-defined borders that tend to fade into adjacent normal skin
- asymmetric shape



Fig 1: Two Atypical Moles, one with macular and a central papular component (the upper one) and one with only macular component. Presence of irregular distributed pigmentation, borders that tend to fade into the adjacent normal skin and a red peripheral hue (at the upper one).



Fig 2: Atypical Mole, with a macular component, asymmetric shape, ill-defined borders and irregular distributed pigmentation with haphazard mixture of colours.

- irregular distributed pigmentation with haphazard mixture of colours from pink to red to brown to black,
- a red peripheral hue (it seems like background erythema),
- size larger than 5mm [15].

Small nevi exhibiting atypical features only on histological examination should also be considered as atypical ones regardless of their diameter (even smaller than 3mm) [25,32]. Some believe that it is impossible to differentiate atypical moles from early malignant melanoma, since the same clinical criteria (A: Asymmetry, B: Border irregularity, C: Colour variegation, D: Diameter greater than 6mm) have been advocated for the diagnosis of the latter [76]. There is no predilection site on the body, but most frequently they may occur on the back, the chest, the buttocks, the breasts, and the scalp. Lesions can be found in sun-exposed and sun-protected areas. In addition to that, melanomas of the trunk appear to be more frequently associated with melanocyte proliferation of a pre-existing nevus [77].

Regarding FAMMM syndrome, the NIH consensus paper has proposed the following criteria:

- 1- occurrence of melanoma in one or more first conjugal degree relatives,
- 2- presence of more than fifty nevus,
- 3- presence of nevus(i) with atypical histologic features [12].

In 1997 the Dutch Working Group inferred that FAMMM should be considered when a patient and at least one more relative have melanoma with or without atypical nevi, while one or several (other) relatives have atypical nevi [78].

A clinical variant of the atypical nevus is the white dysplastic nevus. Clinically it appears as non-pigmented white to pale-red macule with slightly accentuated skin markings and a silvery, shiny appearance on its surface under tangential light (the latter may serve also as a clue for the diagnosis) [54,79].

Histopathological features

To diagnose an atypical mole both architectural and cytologic atypia should be present, combined with the presence of a host response (see Table 2 and Figures 3,4) [29,80].

Cytologic atypia may extend focally and randomly in the nevus. It may be distinguished in low grade when at least 10% of the melanocytes are atypical and in high grade when more than 90% are atypical throughout the nevus. Cytologic atypia may be presented as:

- large nuclei (equal or slightly larger than that of basal layer keratinocyte nuclei) ,
- hyperchromatic nuclei,

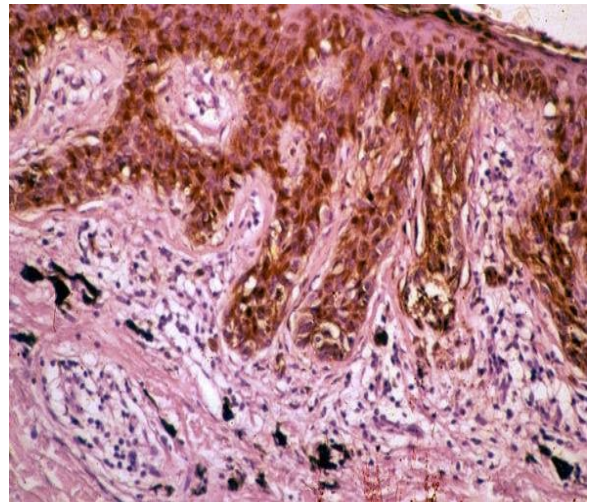


Fig 3 (Courtesy of Dr. Olympia Tzaida, Pathologist): Presence of melanocytes with large, hyperchromatic nuclei Presence of "BRIDGING" and "DISTORTION" of the rete ridges. Presence of the "SHOULDER" phenomenon. Melanophages and mild I Lymphohistiocytic infiltrate in the papillary dermis.

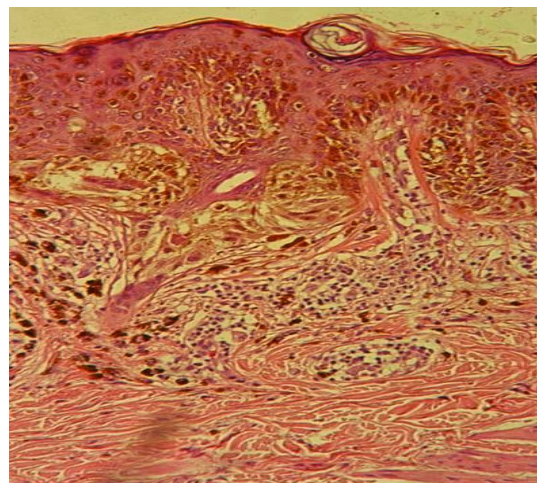


Fig 4 (Courtesy of Dr. Olympia Tzaida, Pathologist): Presence of suprabasilar melanocytes single or in nests, with hyperchromatic nuclei. We may also observe "DISTORTION" of the rete ridges and the dermo-epidermal junction. Characteristic presence of nested melanocytes in the basal layer. Melanophages, intense lymphohistiocytic infiltrate and lamellar fibroplasia in the papillary dermis.

- pleiomorphic nuclei (irregular, often polyhedral),
- pale eosinophilic cytoplasm, or
- conspicuous cytoplasm with finely particulate and diffusely distributed melanin,
- a densely hyperchromatic chromatin pattern,
- nucleolus prominence (in more than 50% of cells),

- cell enlargement (diameter more than twice that of basal layer keratinocyte nuclei [15,75,80-82]

Architectural atypia may appear as:

- Lentiginous melanocytic hyperplasia; elongated nests of varied size and shape (spindle or epithelioid) melanocytes which form bridges between adjacent rete ridges “*bridging*” [18,29]. However another study suggests that it is more important to search for the “*distortion*” of rete ridges instead of bridging as differentiating criterion of architectural disorder [25].
- Proliferation of single or nested melanocytes in the basal layer that extends beyond the main dermal component for three or more rete ridges “*shoulder phenomenon*” [18,29,75,83].
- The presence of a bad overall symmetry and absence of circumscription (a diffuse single-cell pattern of proliferation in at least one edge).
- The absence of cohesion (less than 50% of junctional nests compact and cohesive) [80].
- Suprabasilar melanocytes (single or nested melanocytes located above the epidermal basal layer either in more than two high-power fields or at the edge of the lesion [80].

It should be emphasized that *pagetoid growth* should only sporadically be found in an AM. However, in case of an epithelioid and/or spindle cell melanocytic proliferation with *mitotic figures* (which are *highly unusual in AM*), a diagnosis of junctional Spitz nevus should also be considered [82]

The host response (which commonly is most prominent in the “shoulder” of the nevus) [75] may be evident as:

- concentric or lamellar fibroplasia (characteristic collagen deposition and concentric eosinophilic fibrosis),
- prominent, proliferating vessels in the papillary dermis (neoangiogenesis),
- patchy lymphohistiocytic infiltrates in the papillary dermis,
- presence of melanophages [29,75].

It is verified that occasional atypical melanocytes may be detected in many BMN [84,85]. It has been postulated that the atypia seen in AM may represent the histologic pattern of an active proliferating nevus which originates initially as a lentigo, evolves later to a junctional and a compound one [29,84]. Furthermore, all the histopathologic criteria for the diagnosis of AM may also be seen in melanoma [13]. Additionally, AMs may comprise several distinct cytologic subtypes of lesions and the acral ones may frequently show even aberrant architecture [86-88]. For all these reasons several scoring systems have been proposed in order to facilitate the diagnosis of AMs by utilizing the cytologic, histologic and host response features.

We believe that the use of these systems is unnecessary because the aim of the histologic evaluation should be not to confirm the diagnosis of an AM but to exclude melanoma [15].

CYTOLOGIC ATYPIA	ARCHITECTURAL ATYPIA	HOST RESPONSE
1-Large nuclei	1-Lentiginous melanocytic hyperplasia	1-Concentric or lamellar fibroplasia in the dermis
2-Hyperchromatic nuclei	2-"BRIDGING" or "DISTORTION" of the rete ridges	2-New Proliferating blood vessels in the papillary dermis
3-Pleiomorphic nuclei	2-"SHOULDER" phenomenon	3-Lymphohistiocytic infiltrate in the papillary dermis
4-Pale eosinophilic cytoplasm	3-Asymmetry and absence of circumscription	4-Melanophages
5-Dusty-like cytoplasm	4-Absence of cohesion	
6-Hyperchromatic chromatin pattern	5-Suprabasilar melanocytes	
7-Nucleolus prominence		
8-Cell enlargement		

Table 2: Histopathological features of the Atypical mole

Diagnosis methods

The best way to diagnose an atypical mole is a combined clinical-instrumental methodology [89]. *Firstly*, it is pivotal to give the outmost importance to all clinical information (*i.e.* historical background including the aforementioned environmental factors and any potential morphologic changes over time of the lesion). *Secondly*, the subject’s entire skin surface (including the intertriginous areas and the scalp), should be examined carefully. The research for the “*ugly duckling*” sign (*i.e.* nevi that do not fit into the common profile of the most nevi in a given patient) and the use of a Wood’s lamp for AMs with ill-demarcated outlines may result helpful [90,24]. *Thirdly*, all the suspicious lesions should be scrutinized by dermatoscopy (epiluninescence microscopy-ELM-) [15,91,92]. It is asserted that a trained dermatologist in ELM may improve the diagnostic accuracy by 15% [93,94]. By using pattern analysis as the diagnostic algorithm, dermoscopy may achieve a 84% of sensitivity and 83% of specificity regarding the differentiation between BMN and melanoma [95]. However, the management of a clinically doubtful lesion that otherwise would be excised should not be influenced by the absence of classic ELM features for AM [15,91]. A new, noninvasive, diagnostic technique is near infrared spectroscopy. It performs a spectrophotometric assessment of pigmented skin lesions and appears to have a diagnostic accuracy of 97% between AMs and BMN, 92% between AMs and lentigines and up to 84% specificity for melanoma [96,97].

The use of conventional total body photography is under discussion for subjects with FAMMM syndrome because photographing multiple AMs may lead to unnecessary surgical excisions of BMN. Nevertheless, it may prove to be most helpful for patients with sporadic AMs, because these individuals do not develop normally new nevi later in life [18]. Finally, the usefulness of computerized imaging systems remains to be elucidated. In some studies it seems to improve the detection of suspected lesions by 16% while in a quantitative meta-analysis the diagnostic accuracy achieved was not statistically different from a human one [30,98,99].

Differential diagnosis

An atypical mole must be differentiated from (see Table 3):

ATYPICAL MOLE	ATYPICAL MOLE	WHITE MOLE
Melanoma <i>in situ</i>	Post-inflammatory hypopigmentation	
Pigmented basal cell carcinoma	Hypomelanosis	
Pigmented varieties of Bowen's disease	Vitiligo	
Pigmented spindle cell and/or epithelioid cell nevus	Pityriasis alba	
	Lichen sclerosus et atrophicus	
	Superficial morphea	
Pigmented varieties of nevocellular nevus	Hansen's disease	
Blue nevus	Idiopathic guttate flat warts	
Combined melanocytic nevus-blue nevus	Hypopigmented mycosis fungoides	
Coccardiform nevus	Anetoderma	
Seborrheic keratosis		
Pigmented actinic keratosis		
Darkly pigmented solar lentigo		
Traumatic hematoma		
Pyogenic granuloma		
Dermatofibroma		

Table 3: Differential diagnosis of the Atypical Mole

- melanoma *in situ*,
- pigmented basal cell carcinoma,
- pigmented varieties of Bowen's disease,
- pigmented spindle cell and/or epithelioid cell nevus,
- darkly pigmented varieties of lentiginous nevocellular nevus without significant cellular atypia,
- blue nevus,
- combined melanocytic nevus-blue nevus,
- coccardiform nevus,
- seborrheic keratosis,
- pigmented actinic keratosis,
- darkly pigmented solar lentigo,
- traumatic hematoma,
- pyogenic granuloma and
- dermatofibroma [24].

As far as white AM is concerned, its clinical differential diagnosis should encompass:

- a) post-inflammatory hypopigmentation,
- b) hypomelanosis,
- c) vitiligo,
- e) lichen sclerosus et atrophicus, f) superficial morphea,
- g) Hansen's disease,
- h) idiopathic guttate flat warts,
- i) hypopigmented mycosis fungoides,
- j) anetoderma [54].

Treatment, prognosis and preventional measures

Nowadays, no therapy is available to prevent the development of AMs [23]. Individuals with AMs should be examined on a regular basis and educated to avoid extreme sun exposure [75,15]. The frequency of follow-up depends on the risk of melanoma development (*i.e.* when there is a positive familial history for melanoma and AMs, the risk is higher) [15]. The vast majority of AMs either remains relatively stable or differentiate to dermal nevi or regress and completely disappear over time (most commonly over 50 years old)[16]. The cases of regression and complete disappearance seem to be associated with continual sun protection [16].

Prophylactic excision of a clinically AM is unnecessary because it does not provide sufficient risk-reduction to justify the cost and morbidity related to this procedure [100,101]. Nonetheless, the biopsy of a suspicious lesion for AM should be performed when:

- a) it is extremely atypical by clinical evaluation,
 - b) it is referred to be changing, (even in the case of an asymmetric involution), or new onset,
 - c) an individual presents sporadic (one or two) lesions,
 - d) the lesions are located in difficult sites (hairy scalp, perianal area) to monitor,
 - e) the compliance of the patient is insufficient,
 - f) a patient has an associated immune suppressive disease[16,24,102,103].
- The excision margin should be extended up to the papillary or upper reticular dermis [24]. Regarding FAMMM-prone families, the current guidelines comprise:
- monthly self or parental total body nevus examination,
 - skin evaluation by a dermatologist initially every 3 to 6 months until both the patient and the physician are comfortable and then annually,
 - early biopsy of nevi showing atypical changes with clinical features suggestive melanoma,
 - clinical examination to all 1st degree relatives and selected 2nd degree,
 - ophthalmologic follow-up for early detection of uveal melanoma,
 - meticulous sun protection and

- rigorous avoidance of sunburn [15,23,39,104,105].

The children should be examined for the first time before 10 years of age because the earliest invasive melanoma occurred at that age in these families [104]. At present there is no need for genetic counseling, (except for research purposes), because the outcome will not change the prognosis of the patient [106].

It is imperative that sun protection, (especially against intermittent and intense sun exposure), initiate in early childhood. This could reduce the potential genomic damage at a time of maximal cell vulnerability and thus diminish the risk of malignant transformation [62].

Sun protection measures should encompass reflective surfaces such as umbrellas and canopies, cotton clothing, broad-brimmed hats or with bills, sunglasses that block 99 to 100% of the full UV spectrum and certainly sun avoidance between 10 AM and 4 PM [107]. As far as sunscreens are concerned, their protective efficacy for the prevention of skin cancer is controversial [108,109]. In reality, in actual use the sun protection factor (SPF) is lower than expected because the amount used is less than 50% of the recommended amount. Nevertheless, it appears that when sunscreen with SPF 15 or greater (15+) is applied, there is a strong and significant protection [67].

Alternative treatments have been advocated for the elimination of AMs with rather subtle results; topical 5% fluorouracil [110], topical tretinoin (0.05 and 0.1%) with or without occlusion and combined or not with hydrocortisone [111-113], oral isotretinoin [114] and laser ablation with the Ruby Laser [115,116]. In particular, the 810nm pulsed-Diode Laser, utilized for hair removal, may prompt an otherwise BMN to present atypical and histological characteristics in the treated areas [117].

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