Dysplastic nevus: the eye of the hurricane

Dysplastic nevi were generally recognized, thanks to the contributions of Clark et al. in 1978. These lesions were described in a familial context, which was called the 'B-K mole syndrome'. However, it is worth noting that this was not the first time that these nevi had been described in the literature. If we look back in history, we can find that in 1820, Norris had already described some very similarly pigmented lesions, also in a familial context, just as Cawley subsequently did in 1952. Clark coined the term of dysplastic nevi for lesions presenting in patients with personal and family histories of malignant melanoma, having from 10 to 100 nevus lesions of a certain size, irregular shape and variable pigmentation of more than 5 mm. In addition, he pointed out that histologically, such lesions were principally characterized by the presence of atypical melanocytic hyperplasia.


Historical background

Dysplastic nevus is another field of Dermatopathology in which Dr McNutt has contributed to the body of knowledge. Dysplastic nevi were generally recognized, thanks to the contributions of Clark et al. in 1978. These lesions were described in a familial context, which was called the 'B-K mole syndrome'. However, it is worth noting that this was not the first time that these nevi had been described in the literature. If we look back in history, we can find that in 1820, Norris had already described some very similarly pigmented lesions, also in a familial context, just as Cawley subsequently did in 1952. Clark coined the term of dysplastic nevi for lesions presenting in patients with personal and family histories of malignant melanoma, having from 10 to 100 nevus lesions of a certain size, irregular shape and variable pigmentation of more than 5 mm. In addition, he pointed out that histologically, such lesions were principally characterized by the presence of atypical melanocytic hyperplasia. The context in which they were described implied that dysplastic nevi probably lesions precursor to melanoma. In a parallel study, Lynch et al. also described them in a familial context that was designated 'familial atypical multiple mole melanoma syndrome'. Later, in 1980, Elder et al. described dysplastic nevi in a nonfamilial context, termed 'sporadic dysplastic nevus syndrome'. This description implied that dysplastic nevi were not only a group of lesions to be encountered in the reduced familial group that had been described as precursor to melanoma but that these lesions could also occur as sporadic lesions.

Since its initial description by Clark, the dysplastic nevus has been considered 'in the eye of the hurricane' for distinct reasons, whether because of the utilized criteria for its clinical and histological description or to its relationship to melanoma. As far as nomenclature is concerned, in addition to dysplastic nevus, this type of lesion has also been referred to as Clark nevus or atypical nevus. Histologically, Clark spoke of the presence of atypical melanocytic hyperplasia as synonymous to melanocytic dysplasia because of the presence of melanocytes in isolated units or in the form of small groups that presented some of the cytological characteristics of malignant melanocytes as well as mesenchymal changes in the papillary dermis (eosinophilic fibroplasia) and lymphocytic infiltrate. The use of the term dysplasia was the subject of much dispute because according to some
authors, there is no single definition of dysplasia in pathology and its utilization could result in confusion.6–9 In this context, multiple studies were conducted to analyze the histological characteristics of the same and to look for reproducible histological criteria. Some groups put greater emphasis on architectural characteristics, while others felt that cytological criteria should be more important.10–13

Given the existing differences among the different groups, two consensus conferences were convened by the National Institutes of Health. The first was held in 198414 and determined that the histological criteria that defined the lesions were principally architectural. However, given that the controversy continued, a second conference was held in 199215 during which dysplastic nevus syndrome was defined as the appearance of melanoma in one or more of the identified families, in first and second degree relatives, and also in the presence of a great number of nevi (more than 50), some of which were atypical with some histologically distinctive characteristics. Patients displaying these criteria, if they lived for more than 70 years, presented a 100% risk of melanoma within their lifetimes. Likewise, it was determined that there were also individuals displaying this type of lesion outside of the familial context who presented a greater risk of melanoma than the general population, although lesser than in the familial cases. Then, it was recommended that the term atypical nevus be utilized for its clinical description, and histologically, emphasis was placed on its architectural as well as its cytological characteristics. Thus, the term ‘nevus with architectural disorder and cytological atypia of melanocytes’ was suggested along with an estimate of the grade of atypia. This last point, the grade of atypia, became another subject of dispute regarding what specific criteria should be considered, as well as their possible reproducibility.12,13

### Epidemiological aspects

The presence of nevus with architectural disorder (NAD) and cytological atypia of melanocytes in individuals outside of the familial context required that studies be conducted on its incidence in the general population. The results presented in the literature vary between 1.8% and 18%.16–18 Among these studies, the results presented by Crutcher and Sagebiel19 stand out. They observed a prevalence of 4.9% in the population of Napa Valley (California) in cases with histological confirmation, unlike the other studies conducted, which based their results solely on clinical data.

NADs have been defined as precursors to melanoma, but not all cases of NAD give rise to melanoma. Many studies have been conducted to determine the risk per se. The relative risk (RR) has been determined to vary between 3.9% and 8.8%.16,20–22 These figures were based principally on clinical observations, except the study conducted by Titus-Ernstoff et al.,23 which reported an RR of 6.2% in patients with NAD along with a histological correlation. This last factor, the clinical-pathological correlation of this type of NAD, is a factor to keep in mind, above all in studies predating digital dermoscopy, before which some lesions clinically classified as atypical nevus were not histologically confirmed and vice versa. Other noteworthy research included studies of the presence of residual NAD associated with melanoma, reporting a NAD in 20–40% of the melanomas studied.24,25

### Histological characteristics and grading of atypia

NADs present a series of histological criteria that allow us to classify them, equally in the cases of junctional or compound lesions, by identifying elongation and distortion of rete ridges, dermal eosinophilic fibrosis, presence of nevus nests arranged along the sides and on the tip of the rete ridges, and, in the case of compound lesions, extension of the junctional component three epidermal rete ridges beyond the dermal component.

When Clark described NADs, he did not classify them into different grades of atypia, although other authors did. Histological grading has served as an attempt to relate the grade of atypia to the risk of an individual developing malignant melanoma, which has been limited by a certain amount of subjectivity. There exist many examples in the literature dealing with the histological grading of lesions in multiple localizations, such as the uterine cervix and its relation to the risk of developing squamous carcinoma of the cervix,26 dysplasias of the gastric mucosa in relation to adenocarcinoma of the stomach,27 etc. In the field of NADs, there appears to be a spectrum of morphological changes, architectural as well as cytological. In one study, directed by Dr McNutt,28 we attempted to evaluate whether the grade of the histological atypia of NADs had any relationship to the risk of the individual developing melanoma; we observed that the greater the grade of atypia, the greater the likelihood for that patient to have a personal history of melanoma.

In particular, those patients with NAD displaying severe atypia had 4.08 (2.91–5.7) times greater risk of suffering melanoma than those patients with NAD with mild atypia and 2.81 (2–3.95) times greater risk than those patients with moderate atypia. Likewise, patients with NAD with moderate atypia presented...
1.45 (1.13–1.87) times greater risk of suffering melanoma than those patients with NAD displaying mild atypia. These results stressed the importance of grading NADs in order to help to determine the individual risk of developing melanoma.

In that study, the grading was based on architectural (lateral circumscription, symmetry, intensity of rete ridge distortion, fibrosis and the presence of central focal intra-epidermal migration and involvement of the suprapapillary plates) and cytological criteria (nuclear size, nucleoli size and chromatin type). NADs with mild atypia (Fig. 1) are circumscribed and symmetrical, displaying light rete ridge distortion and cosinophilic fibrosis of the papillary dermis. The nevus cells are arranged, principally forming nests on the inferior tip and part of the lateral faces of the rete ridges without affecting the suprapapillary plates in the dermoeipidermal union and without intra-epidermal migration. The nuclei of the melanocytes in the dermoeipidermal junction are ovoid and ellipsoid with condensed chromatin and are no larger than the surrounding keratinocytes, also with a small nucleolus.

NADs with moderate atypia (Fig. 2) are lesions that are more symmetrical than well circumscribed, displaying elongation and more pronounced distortion of the rete ridges, above all in the center of the lesion with fusion of adjacent rete ridges. The nevus cells are arranged principally in nests at the base and lateral face of the rete ridges, possibly affecting the suprapapillary plates focally. Likewise, it is possible to observe focally, in the center of the lesion, minimal intra-epidermal migration. At the cytological level, the majority of the melanocytes usually display a size equal to the keratinocytes with some of larger size.

Finally, NADs with severe atypia (Fig. 3) are not usually totally symmetrical, but they are well circumscribed at the epidermal level. Distortion of the rete ridges is very pronounced with fusion of adjacent rete ridges, along with prominent cosinophilic fibrosis. The nevus cells, which are arranged predominantly in well-formed nests, are also found at the tip and lateral faces of the rete ridges, but there is also marked fusion of nests situated on the adjacent rete ridges. In addition, there exists more involvement of the suprapapillary plates and also, at the center of the lesion and focally, there is minimal intra-epidermal migration. At the cytological level, melanocytes usually present elongated cytoplasm and larger nuclei than the keratinocytes with prominent nucleoli.

The criteria used are not free from a certain amount of subjectivity for which reason some groups have proposed more objective methods for grading, also based on histological criteria. Shea et al. proposed a method based on some architectural criteria, such as circumscription, symmetry, nest cohesiveness, suprabasal melanocytes, confluence and single cell proliferation, as well as cytological criteria, such as round/euchromatic nuclei, nuclear enlargement, cell enlargement and prominent nucleoli to which they assigned a value of 0–1, obtaining a score that allowed them to classify lesions into three grades of atypia (mild, moderate and severe).
The evolution of dermatopathology, along with the development and introduction of new molecular biology techniques with the identification of new biomarkers, has opened a new field that may allow the classification of lesions in function of their prognoses in a completely objective and reproducible manner, putting an end to the eternal debates regarding the subjectivity of the currently utilized grading criteria. However, the jury is still out.

References