

Research Article

Clinicopathological Features of Melanocytic Nevi and Their Correlation to Cutaneous Melanoma among Patients Attending King Abdulaziz University Hospital, Jeddah, Saudi Arabia

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Abstract

Melanocytic nevi (MN) pose diagnostic difficulty due to their heterogeneous clinical, biological and molecular characteristics. Their recognition is also important because cutaneous melanomas are known to arise in pre-existing MN. **Aim:** This retrospective study aims to examine the clinical features and histopathological types of MN among patients attending King Abdulaziz University Hospital between January 2000 and December 2017. It also aims to examine the correlation of their number to cutaneous melanoma. **Materials and Methods:** All biopsy specimen data of pigmented skin lesions were collected through an electronic search of the Anatomic Pathology archives. Age, gender and site distribution and histological features were studied for different MN and their relation to cutaneous melanoma if associated. **Results:** MN were most common in the third decade of life affecting females more than males. The most frequent anatomic location was the head region, 176 (45.3%), with face being most frequent site, 45 (25.5%). Histologically the most common MN was intradermal type accounting for 217 (56%). Two dysplastic nevi and one congenital nevus was associated with cutaneous melanoma. **Conclusion:** MN most commonly affected patients in their third decade of life. Females were more affected than males. Histologically most MN were of intradermal type and were rarely associated with cutaneous melanoma.

Keywords: cutaneous, melanocytic, intradermal, congenital melanoma

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1. Introduction

The accurate and precise diagnosis of cutaneous melanocytic lesions is often very challenging to a pathologist, especially with the increasing incidence of melanoma overtaking the rates of increase of all other major cancers [1].

Melanocytic nevi (MN) usually referred to as 'moles' are benign neoplasms arising from nevus cells of neural crest origin. Beyond establishing their embryonic origin from neural crest, the histogenesis of these tumors remains the ongoing subject of speculative and divergent viewpoints. They also pose diagnostic difficulty due to their heterogeneous clinical, biological and molecular characteristics. The clinical diagnosis of most MN is suboptimal and, accordingly, histopathology is the 'gold standard' in the diagnosis and classification of MN. In literature, there is a lack of consensus among clinicians and pathologists, owing to the mixture of clinical and histopathologic features used to define the various MN [2].

Since approximately 25–33% of cutaneous melanoma (CM) is known to arise in pre-existing MN, their recognition is important for the pathologist [3]. Recognizing variants of MN and familiarity with their spectrum of histological appearances assists in distinction from CM. A cross-sectional nevus study offers evidence that nevi may be accumulated in response to both chronic and intermittent sun exposure, as inferred from body site and sunburn. Nevus densities were found to be highest on maximally or intermittently sun-exposed skin areas [4]. The presence of numerous MN is a major risk factor for CM. Nevi accumulate predominantly during childhood and adolescence, and case control studies indicate that sun exposure during early life is most critical for determining CM risk [3].

Apart from rare case reports [5] to the best of our knowledge, we found no studies from Saudi Arabia reporting the clinical or histopathological distribution of MN. The dearth in literature regarding this heterogeneous group of benign tumors among our population formed the basis for the present study.

2. Aim

The aim of this retrospective study conducted in a tertiary care hospital was to examine the distribution of clinicopathological types of cutaneous melanocytic nevi among patients attending KAAUH (King Abdulaziz University Hospital). We also studied the correlation of their number to CM.

3. Materials and Methods

3.1. Study setting and population

All biopsy specimen data of pigmented skin lesions were collected through an electronic search of the Anatomic Pathology archives between January 2000 and December 2017 among the patients attending KAAUH.

3.2. Data collection

The data were collected using appropriate SNOMED (Systematized Nomenclature of Medicine) morphology codes indicating the parameters such as the date of receiving biopsy, personal identity (medical record number, age, sex, nationality, etc.), clinical and histopathological diagnosis and topography. It was rechecked manually to delete duplications, processed and analyzed in Microsoft Excel format. Target group with a histological diagnosis of MN was identified followed by a manual review of biopsy reports and histopathology slides independently and collectively to resolve any discrepancy. The MN were classified using Barnhill RL et al. [2] classification as follows: (a) Common acquired; CAMN, (b) Congenital; CMN, (c) Atypical/Dysplastic; AMN/DMN, (d) Spitz; SMN, (e) Blue; BMN. Common acquired melanocytic nevi were subclassified as: (a) Junctional; JMN, (b) Compound; CPMN, (c) Intradermal; IMN. Pigmented lesions due to vascular malformations or primary pigment disorders were excluded from this study.

Number and percentage MN distribution is calculated according to nationality, gender and sites including the most common sites.

All cases of MN were studied thoroughly from both clinical and histological aspects to examine their association with CM. The following parameters available in the CM histopathologic records were considered for clinicopathological correlation: gender, primary location, histological subtype, Breslow thickness, presence of ulceration, and histological subtype of the associated lesion. Only data available in the pathologic records were included in the study. Detailed history on the nature of sun exposure was also solicited in every instance possible.

Histological Diagnosis of Pigmented Skin Lesion	Number N = 415	Percentage (%)
Melanocytic Nevi	388	93.4%
Cutaneous Melanoma	22	5.3%
Simple Lentigo	3	0.7%
Solar Lentigo	2	0.5%

TABLE 1: Number and percentage of pigmented skin lesions among patients attending KAAUH between January 2000 and December 2017.

3.3. Statistical analysis

Data were analyzed using the computer program—Statistical Package for Social Sciences version 15 (SPP Inc., Chicago, IL, USA). Descriptive and frequency statistics were obtained for the variables studied.

4. Results

A total of 415 pigmented skin lesions were histologically identified between January 2000 and December 2017 among the patients attending KAAUH (Table 1). MN were the most common lesion accounting for 388 (93.4%) and were more common among Saudi patients, 240 (58.4%), than Non-Saudis, 169 (41.3%). MN were most common in the third decade of life (Table 2). Females, 218 (56.1%), were affected more than males, 170 (43.8%). The most frequent anatomic location was the head region (Table 3), 176 (45.3%), with face being most frequent site, 45(25.5%), followed by cheek, 33 (18.3%), nose 27 (15.3%), eyelids and scalp each 15 (3.8%), ear and lip each 10 (5.6%), chin and forehead each 8 (4.5%) and conjunctiva 5 (2.8%). Histologically, the most common MN was IMN 217 (56%) (Table 4; Figures 1-3).

Among Saudi patients, two cases (0.83%) of AMN/DMN were associated with CM and one case of multiple MN (more than 100 small nevi; 0.41%) was associated with CM. All patients were males and were aged 64, 65 and 76 years. One Non-Saudi male patient aged 78 years with multiple MN (more than 50 nevi; 0.59%) was also associated with CM (Table 5). The Non-Saudi patient who was an Asian developed CM in one of his pre-existing giant nevus on the left temple that was previously diagnosed as a giant CMN as per his previous biopsy report and histopathology slides. Patient had close follow-up for two years post excision of CMN and came back with local recurrence of an ulcerated growth at the same site. Unfortunately, the five-year

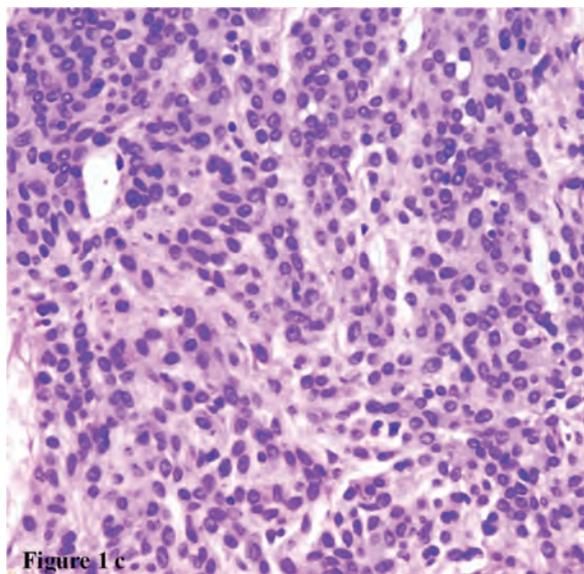
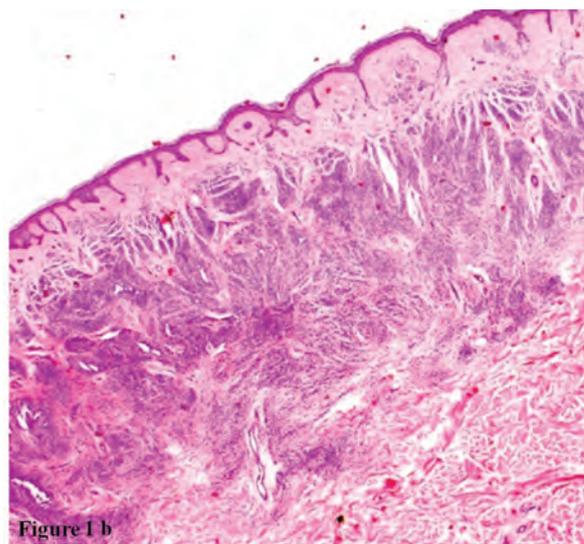


Figure 1: A common acquired melanocytic nevus on the back (Intradermal histologically). **Figure 1 b at 20 x:** Nevus cells arranged in the dermis. **Figure 1 c at 40 x:** Benign nevus cells in groups and nests.

survival assessment was not possible in these cases due to the lack of follow-up data.

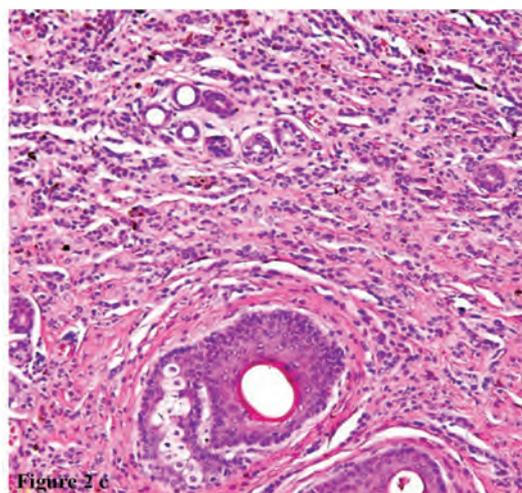
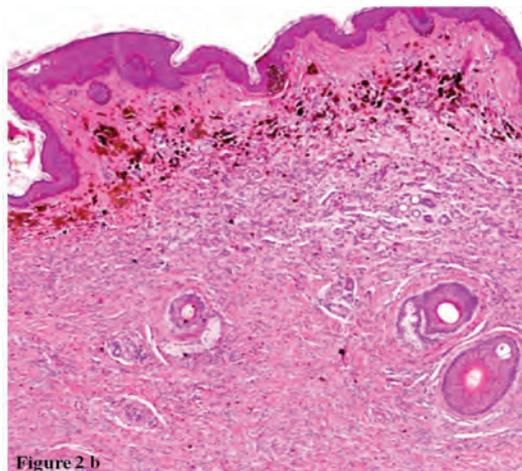


Figure 2: Black well-circumscribed congenital melanocytic nevus on the right temple. **Figure 2 b at 20 x:** Symmetrical pigment laden nevus cells arranged horizontally in the papillary and reticular dermis with maturation and progressive descent; splaying between collagen bundles. **Figure 2 c at 40 x:** Nevus cells permeating the muscles of hair shafts and blood vessels.

Applying the Mann-Whitney test, the median Breslow thickness for *de novo* CM was greater than that for nevus-associated CM ($P < 0.001$).

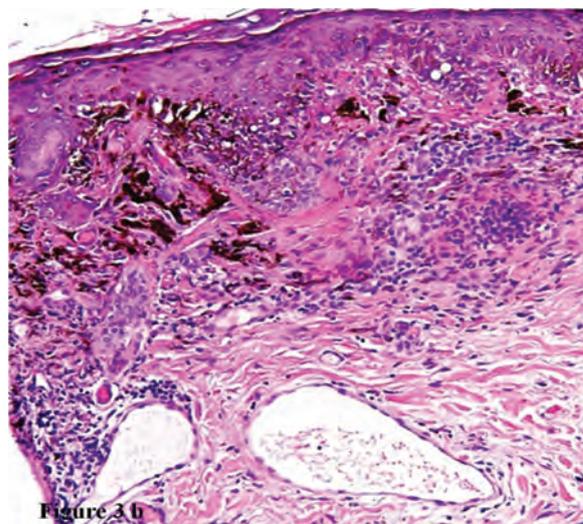


Figure 3: Atypical/dysplastic nevus on the trunk with irregular borders and variegated color distribution. **Figure 3b at 40 x:** Atypical/dysplastic melanocytic nevus exhibiting architectural asymmetry, vague borders and irregular pigmentation of dermal nevus cells. Nevus cells show nuclear hyperchromasia, and dusty melanin are spindled and parallel to the surface. Note the bridging of irregular and adjacent rete ridges and vascular dilation.

5. Discussion

MN have been notoriously known for their common association with CM [3, 6]. Individuals with many nevi and individuals with large acquired nevi (> 5 mm in diameter) are at increased risk for developing CM, especially those exhibiting increased variability of size, shape, and color [7]. In a prospective study of a high-risk patient cohort, 54.2% of CM were associated with MN [8]. Patients with many nevi and without previous melanomas or traits of familial atypical mole and multiple melanoma syndrome were reported to have a higher frequency of nevus-associated melanomas [8]. We found similar correlation in our study since both the patients with multiple nevi associated

Percentage (%)	Number N = 388	Age
14%	55	Less than 10 year
14%	55	11 to 20 year
22.6%	88	21 to 30 year
17.2%	67	31 to 40 year
18.2%	71	41 to 50 year
4.3%	17	51 to 60 year
3.6%	14	61 to 70 year
2.23%	9	71 to 80 year
3%	12	Unknown

TABLE 2: Frequency distribution of MN by age among patients attending KAAUH between January 2000 and December 2017.

Percentage (%)	Number N = 388	Anatomic Location
45.3%	176	Head
3%	12	Neck
4.3%	17	Chest and axilla
10%	39	Upper extremity
10%	39	Lower extremity
6.7%	26	Abdomen
7.7%	30	Back
4.6%	18	Perineum
7.9%	31	Unspecified

TABLE 3: Anatomic location of MN among patients attending KAAUH between January 2000 and December 2017

with CM had no familial atypical mole or multiple melanoma syndrome. Despite all of the preceding facts, there remain arguments in literature against the notion of MN being precursor lesions of CM indicating that it requires histopathological evidence of total occupancy of the MN by neoplastic melanoma cells to validate any such progression. There is also a lack of substantial clinical or molecular evidence strongly validating the progression of MN to melanoma in order to legitimize the claims of 'precursor' label given to MN. Most MN either disappear or remain stable during life with fewer than 5% undergoing detectable change when closely monitored [9]. Oncogene-induced

Percentage (%)	Number N = 388	Histological Diagnosis
56%	217	Intradermal melanocytic nevus
14.4%	56	Compound melanocytic nevus
22.4%	87	Congenital melanocytic nevus
2.8%	11	Junctional melanocytic nevus
1.8%	7	Atypical/Dysplastic melanocytic nevus
1.8%	7	Blue melanocytic nevus
0.7%	3	Spitz melanocytic nevus

TABLE 4: Frequency of histopathological categories of MN among patients attending KAAUH between January 2000 and December 2017.

Parameters of Lesion	De novo CM	CM arising in Pre-existing MN
Gender/mean age	10 Males/8 Females 55 Years	4 Males 71.5 Years
Location	13 Lower extremity 4 Head & neck 1 Perianal	1 Sole of foot 2 Left leg 1 Trunk
Histological type	9 Superficial spreading 4 Nodular 3 Lentigo maligna 2 Acral lentiginous	4 Superficial spreading
Presence of ulceration	13 Present 5 Absent	Present
Histological subtype of associated lesion	None	2 AMN/DMN 1 CMN 1 MMN
Nature of sun exposure	Prolonged in all	Intermittent in all

Note: MN: Melanocytic Nevi; CM: Cutaneous Melanoma; AMN/DMN: Atypical/Dysplastic melanocytic nevus; CMN: Congenital melanocytic nevus; MMN: Multiple melanocytic nevus.

TABLE 5: Correlation of *de novo* CM and that arising from pre-existing MN among patients attending KAAUH between January 2000 and December 2017.

senescence explains in part why most MN are stable and do not undergo progression to CM [9].

The low incidence of CM has remained stable over past few decades in this high sun area of Saudi Arabia that is located between 15° and 32° North latitude despite the presence of significant amounts of potentially carcinogenic and biologically active short UV wavelengths [10–12]. This low incidence could be explained by several factors such as the skin type of Saudi population being Fitzpatrick types III–V, which protects against photo-induced DNA damage due to greater melanin density and the conservative cultural norm of full body cover among men and women that also prevents direct skin exposure [11]. This mandates against the Western trend of persistent increase in overall incidence of CM and its correlation to sun exposure carcinogenesis, suggesting that UVR may not be an important factor in the pathogenesis of CM among this and other darkly pigmented populations [13]. Given the Saudi model of melanocytic disease progression, it seems reasonable to infer that the potential carcinogenic role of UVR is blocked by greater melanin density in the skin of Saudi patients, as most CM here arise *de novo* [14]. In a previous study from KAAUH, 3 out of 16 (11.5%) CM were associated with MN with two being AMN/DMN [10]. In the current study, we found similar association with an additional case of multiple MN among both Saudi and Non-Saudi associated with CM. There were some interesting historical and histological aspects in most of our cases. First, that as per medical records available, none of the patients had history of familial atypical mole or multiple melanoma syndrome. Second, all had history of intermittent as opposed to prolonged or chronic sun exposure. Third, histologically all had superficial spreading melanoma with Breslow thickness of 1 mm. The fact that MN were reasonably more common among females than males even though they remained culturally more confined and skin covered than males also adds to refute the claims of UVR-related pathogenic progression of MN to CM in the context of this population. Thus, prophylactic excision of MN in this population is an unsuitable strategy to prevent CM [7]. MN that undergo malignant change may result in CMs that are thicker and thus potentially have a worse prognosis than *de novo* CMs [14]. By confocal microscopy, abrupt transition, localized distribution of junctional atypical cells and the presence of dense dermal nests have been reported as the most helpful criteria for categorizing a CM as arising from an MN [15]. A recent study by S. Y. Tan and others, USA [16], reported that patients with low MN count were more likely than patients with high MN counts to develop CM with more aggressive features, older age, greater Breslow thickness, higher mitotic activity and lower likelihood of superficial

spreading CM. This discrepancy in conflicting data from different studies could partly be explained by the different population groups studied.

The most exciting finding in the molecular genetics of MN and CM is the discovery of oncogenic BRAF mutations in both. This finding indicates that activation of the mitogen-activated protein kinase pathway may be a critical initiating step of melanocytic proliferation and that the fundamental difference between MN and CM may lie in the inhibitory machinery for this oncogenic signaling. Studies from families with multiple CMs and AMN/DMN (familial atypical multiple mole-melanoma [FAMMM] syndrome, also known as B-K mole syndrome) have identified germline mutations of the p16 gene (CDKN2A) on chromosome 9p21, which encodes a negative regulator of cell growth. Constitutive kinase activation of the BRAF (V600E) mutation points to a possible role of this intracellular signaling kinase in nevogenesis [17]. Germline mutations have not been found in subjects with CAMN. Rather, somatic mutations of BRAF (V600E) on chromosome 7q34 have been detected in the majority of them [18]. In patients harboring germline mutations in CDKN2A, however, reduction or loss of wild-type p16 expression occurs in nevus cells [19]. Increased BRAF mutation with age along with the lack of a UVR magnitude-BRAF mutation association suggests that duration of exposure rather than UVR exposure dose is the more likely link to acquiring the mutation among CAMN [20]. Recent studies on different CMN sizes have clarified further the genetic landscape, revealing a consistent relationship between the size of lesion and mutation status [21]. While CAMN and small CMN show a high frequency of BRAF mutations regardless of their anatomic localization, the mutations are rare in medium-sized CMN and giant CMN or Spitz nevi [21]. A recent study from Riyadh reported CMN as being present in 1.9% of newborn infants with skin type 5 with no environmental or genetic factors seemingly involved [22].

A genetic substrate of some type clearly underlies at least a component of the AMN/DMN phenotype. For example, AMN/DMN as well as CM express DNA mismatch repair genes at a lower level and have a higher rate of microsatellite instability at markers near the CDKN2A (p16) locus than do MN [22].

CMN remain a subject of controversy with respect to the risk of malignant transformation with the greatest risk currently thought to be in childhood, although in the current study it was in a 78-year-old male. Studies indicate a lower risk (0.7 to 2.9%) than had previously been estimated with the highest risk occurring before puberty [24–26]. The controversy over the years have been partly due to the difficulties of histological diagnosis and partly due to the publishing bias toward cases of CM. The

incidence of CM actually varies enormously with the severity of the congenital phenotype. The risk for small single CMN is very low, whereas where the largest CMN is > 40 cm projected adult size, and accompanied by multiple smaller CMN, the lifetime risk has been estimated at 10–15%. Genes described as mutated in single CMN include NRAS, 11, 12 BRAF, 11, 13, 14, 15, 16, 17, 18 MC1R, 11, 19 and TP 53 11. In multiple CMN and CMN syndrome it is possible to assign causality to postzygotic mutations in NRAS in 80% of cases [24].

The presentation of Spitz MN also overlaps with the clinical and histopathologic features of CM, so a differential diagnosis can be difficult to make [27]. The spectrum of Spitzoid neoplasms includes Spitz nevi, atypical Spitz tumors, and Spitzoid melanomas. Molecular genetics has evolved to the point that Spitzoid lesions are now classified according to their distinctive molecular-genetic alterations in order to predict their biological course. At one end are the SMN with 11p amplification and/or HRAS mutations, BAP1 loss and BRAF V600E mutation that exhibit a typical morphology and predictably benign clinical behavior and at the other end are the Spitzoid melanomas with homozygous deletion of 9p21 that exhibit increased risk for metastasis and death [28].

Few investigators have studied the genetic profiles of blue nevi. Combined data from these studies indicate that GNAQ is by far the most common genetic anomaly (82.8%). BRAF V600E mutations are rare (6.7%); NRAS mutations have not yet been identified [29, 30].

NRAS, HRAS, BRAF and GNAQ have been identified among different MN, and since these mutations can also be found in CM, a further understanding of nevogenesis will have a direct impact on melanoma research efforts [31].

This study has certain limitations such as small number of cases and the loss of follow-up among those that were associated with CM. These should be kept in mind while interpreting the presented results. However, to the best of our knowledge, except a few case reports [22, 32] no large-scale study on MN has been published in this region.

In conclusion, MN are common among patients attending KAAUH in the third decade affecting Saudi more than Non-Saudi, females more than males with face being the most common location. The most common histological type is intradermal nevus. Two Saudi patients and one Non-Saudi with pre-existing dysplastic and congenital nevi, respectively, were associated with CM indicating least frequency of such association.

Further molecular studies are required to validate this association in terms of progression. Also, factors such as genetic predisposition could be involved in the nevogenesis within this population that warrants population-based studies.

Conflict of Interests

The authors declare that neither this research nor the article has any form of conflict of interest including financial interest or commercial association with any of the subject matter or products mentioned in this article.

Ethical Clearance

The procedures followed in the present study were approved by and are in accordance with the ethical standards of the King Abdulaziz University Hospital's ethical committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2000.

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