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Acquired melanocytic nevi in Egyptian patients: A clinicopathological study

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Abstract

Introduction: Melanocytic nevi (MN) are the most important simulants of melanoma. Although acquired nevi are usually clinically stable, they may show abnormal clinical behavior. This study assessed the histological changes and prognosis of acquired MN with changing clinical behavior in Egyptian patients.
Methods: The study included 236 patients that were classified into two groups; Group A included nevi with abnormal clinical presentation and Group B included clinically typical nevi.
Results: Each group included 118 patients with a predominance of female patients. Abnormal clinical presentation in Group A included altered pigmentation (35.6%), rapid enlargement (30.5%), keratotic changes (16.9%), inflammation (7.6%), ulceration (5.1%), and hemorrhage (4.2%). Typical histological features were significantly higher (p = 0.008) in Group B (99.2%) compared with Group A (87.3%). Atypical histological features were significantly higher (p = 0.002) in Group A, with higher numbers of ulcerative and altered pigmented nevi. Malignant changes showed no significant difference (p = 0.47) between the two groups. No relapse was recorded after excision of any lesion.
Discussion: Among Egyptians, changing clinical behavior of MN may show histological atypia but low risk of malignant transformation. Early excision and follow-up of ulcerative and altered pigmented nevi are recommended.

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Introduction

Melanocytic nevi (MN) are considered the most important simulants of melanoma (MM) and it may be difficult to distinguish between the two lesions either clinically or histologically. Although most MN are stable and do not progress to malignancy, some nevi could be considered important risk markers and potential precursors of MM. Such nevi include dysplastic nevi (DN), congenital MN, and, to a lesser extent, acquired (common) MN (1).

Dysplastic (atypical) nevi remain an issue of controversy despite extensive investigation. On clinical grounds, the term "atypical MN" is more appropriate, whereas "dysplastic MN" describes histological characteristics. The association with MM is complex and it is often difficult to distinguish histologically between DN and MM. It is accepted that DN are characterized clinically by large size (> 5 mm in diameter) and show a mixture of marked discoloration, whereas histologically they are characterized by intradermal lentiginous hyperplasia, cytological atypia, and stromal response in addition to architectural atypia (2).

Although malignant transformation is uncommon in acquired MN, there are risk factors that increase the incidence of malignant transformation of MN. An increased number of MN has been suggested as a strong risk factor for MM (3), and sun exposure was considered the main environmental risk factor for the development of both MN and MM (4). Moreover, the similar causal pathway of some MN and MM has also led to considering these MN as precursor lesions of MM (5).

Melanocytic nevi in specific anatomical sites such as acral, genital, and flexural areas may also show unusual architecture and cytological atypia that can mimic DN and sometimes MM (6). This study recorded the clinical changes and analyzed the histological features and prognosis of acquired MN among Egyptian patients.

Material and methods

A retrospective randomized controlled study included cases diagnosed as acquired MN during the period from 2007 to 2011 at Al-Azhar University Hospitals, Cairo, Egypt. Clinical data were retrieved for each patient, including age, sex, skin type, and duration of the lesion in addition to the clinical characteristics of the lesion such as site, size, and morphology. Results of general skin examination and regional lymph nodes were also recorded to identify any associated skin tumors or abnormal changes of regional lymph nodes.

Data were collected from the computerized file system of the patient in addition to medical photography of the lesion. Because dermoscopy was only recently made available at the author's department and only a few cases in this study were evaluated by dermoscopy, it was not considered as a main tool in evaluating the lesions. All of the lesions were surgically excised as a first-line management. Cases that had been previously treated with non-surgical methods (such as laser) were excluded from the study.

Lesions were classified according to their clinical presentation into two groups: MN that showed abnormal clinical presentation were categorized as Group A, and MN with clinically typical presentation were categorized as Group B (used as a control group). Abnormal clinical presentations included any changes in size, shape, consistency, color, or surface of the nevus. Clinically typical nevi were symptom-free and they were only excised for cosmetic purposes.

Histologically, the lesions were classified as typical, atypical, or malignant. The histological criteria of typical MN were the presence of nests of melanocytes / nevus cells that are distributed at the dermoepidermal junction (junctional nevus), confined to the dermis (intradermal nevus), or with both components

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Atypical histological features included poor circumscription, asymmetry, irregular confluent nests, predominance of single melanocytes, cytological atypia, frequent mitosis, and presence of necrosis (7).

Any lesion showing one or more of these criteria was reviewed by three pathology experts for further evaluation and categorization of the lesion: either atypical or malignant. The diagnosis was confirmed by the opinion of two reviewers. Immunohistochemical staining using monoclonal antibodies for S100, HMB-45, and Ki-67 was carried out for specimens that showed atypical features.

The study was approved by the local ethics committee and patients' written consent was obtained for medical photography and skin biopsy. Data were collected and statistically analyzed using SPSS version 16. For quantitative data, the mean and standard deviation were calculated. The difference between two means was statistically analyzed using Student's t test. Chi-square x2 was used to analyze between numbers in two (or more) independent groups. A p value ≤ 0.05 was considered statistically significant.

Results

The study included 236 patients that were classified into two groups, each group formed of 118 patients. The majority of patients were females (64%) and the mean age at the time of diagnosis 39.6 ± 5.34 years. The duration of the lesions before excision ranged from 3 to 22 years with a majority of more than 10 years' duration (46.2%). Patients with skin type III were predominant (58.9%) and the majority of lesions (85.6%) were less than 1 cm in diameter. Skin examination showed the presence of other MN in 103 patients (43.6%) and other benign skin tumors in 31 patients (13.1%). The head and neck represented the most common anatomical site (55.5%), with a predominance of facial lesions in Group A and scalp lesions in Group B. A comparison between the two groups is summarized in Table 1.

Table 1 | Demographic data of Egyptian patients with acquired melanocytic nevi.

	Group A (N = 118) n (%)	Group B (N = 118) n (%)	Total (N = 236) n (%)
Sex			
Female	70 (59.3)	81 (68.6)	151 (64)
Male	48 (40.7)	37 (31.4)	85 (36)
Age			
Range	19–68	24–61	19–68
Mean ± SD	41.3 ± 6.52	37.9 ± 4.16	39.6 ± 5.34
Lesion duration			
‹ 5 years	13 (11)	35 (29.7)	48 (20.3)
5–10 years	38 (32.2)	41 (34.7)	79 (33.5)
› 10 years	67 (56.8)	42 (35.6)	109 (46.2)
Skin type			
Type III	66 (56)	73 (61.9)	139 (58.9)
Type IV	41 (34.7)	44 (37.3)	85 (36)
Type V	11 (9.3)	1(0.8)	12 (5.1)
Lesion site			
Head & neck	86 (72.9)	45 (38.1)	131 (55.5)
– Scalp	*24*	*32*	*56*
– Face	*48*	*5*	*53*
– Neck	*14*	*8*	*22*
Trunk	18 (15.2)	32 (27.1)	50 (21.2)
Upper limbs	8 (6.8)	19 (16.1)	27 (11.4)
Lower limbs	6 (5.1)	22 (18.6)	28 (11.9)
Lesion size			
‹ 1 cm	84 (71.2)	118 (100)	202 (85.6)
› 1 cm	34 (28.8)	0 (0)	34 (14.4)
Other melanocytic nevi	56 (47.5)	47 (39.8)	103 (43.6)
Other benign skin tumors	13 (11)	18 (15.3)	31 (13.1)

It was observed that most of scalp lesions were excised due to increased liability to trauma (especially during combing), whereas a few cases were excised due to clinical suspicion of adnexal tumor. On the other hand, most of the facial lesions were excised for cosmetic purposes, location near the eyes, and location on the beard or mustache areas interfering with shaving.

The abnormal clinical behavior of MN in Group A was in the form of altered pigmentation (35.6%), rapid increase in size (30.5%), verrucal or seborrheic keratosis-like changes (16.9%), inflammatory changes (7.6%), ulceration (5.1%), and angiomatous or vascular changes (with a pyogenic granuloma-like appearance or a variable degree of hemorrhage) (4.2%). Demographic data and histological spectrum in relation to atypical clinical forms of MN in Group A are shown in Table 2.

Histological analysis of rapidly enlarged nevi (Fig. 1) showed the presence of large fat lobules (fatty nevus) in 13 cases and pseudovascular or pseudolymphatic spaces in seven cases. Concomitant presence of sebaceous hyperplasia was observed in 10 cases, and in seven cases there was an epidermal or trichilemmal cyst. In five cases there was no significant histological finding.

Nevi with keratotic changes revealed two histological variants; a papillomatous type and a seborrheic keratosis–like type that also showed papillomatosis in addition to marked hyperkeratosis and numerous horn cysts. Both types were darkly pigmented with increased melanin pigmentation in the epidermis and upper dermal nests (Fig. 2). Atypical changes were observed in 10% of keratotic nevi and only 2.8% of enlarged nevi, and none of them showed malignant transformation.

Angiomatous nevi were characterized histologically by a mixture of nevocellular nests and various-sized vascular spaces in addition to variable degrees of intradermal hemorrhage (Fig. 3). Inflammatory nevi showed a ruptured hair follicle in seven cases (Fig. 4), and spongiotic dermatitis with crust formation (Meyerson's phenomenon) was observed in two cases. Neither inflammatory nor angiomatous nevi showed any atypical features or malignant transformation. In the majority of cases, dermal nests of nevus cells were easily recognized by routine histological examination. However, in some cases immunostaining with S100 was required to identify the nevus cells.

Histological analysis showed the predominance of intradermal nevi (67%) compared with compound nevi (27.1%) and junctional nevi (5.9%). Atypical histological features were significantly higher (p = 0.002) in Group A (11%) compared to Group B (0.8%). Out of 13 cases that showed atypical histological features in Group A, nevi with altered pigmentation (five cases) and nevi with surface ulceration (five cases) represented the majority of cases. The most striking histological findings included the presence of numerous atypical cells, dermal nevomelanocytes with large pleomorphic nuclei, and atypical features of dermal nests in addition to focal or sporadic staining for HMB-45 and Ki-67 (Fig. 5).

Malignant transformation was proved in only 1.7% of clinically abnormal MN without a significant difference between the two groups (Table 3). The first lesion of malignant transformation was proved in a compound nevus that was located on the thigh and showed increased pigmentation, enlarged size, and ulceration. The second lesion was a junctional nevus on the sole that showed altered pigmentation with increased size.

Follow-up was recorded for all nevi with atypical and malignant features for 1 year. Recurrence was recorded in three cases of atypical nevi and total excision was performed for all cases without relapse. Although nevi with malignant transformation showed no recurrence of the lesion, lymph node metastasis was recorded in both cases after 2 and 9 months, respectively.

Table 2 | Clinical characteristics and histological spectrum of acquired melanocytic nevi in Group A.

	Pigmented nevi (n = 42)	Enlarged nevi (n = 36)	Keratotic nevi (n = 20)	Inflamed nevi (n = 9)	Ulcerative nevi (n = 6)	Angiomatous nevi (n = 5)	Total N (%)
Sex							
Female	23	26	11	5	4	1	70 (59.3)
Male	19	10	9	4	2	4	48 (40.7)
Age							
Range	19–62	22–54	22–68	37–55	27–44	41–57	19–68
Mean ± SD	40.7 ± 5.26	39.2 ± 3.81	43.5 ± 8.45	49.4 ± 2.55	35.1 ± 4.87	47.6 ± 4.87	41.3 ± 6.52
Lesion duration							
‹ 5 years	7	3	0	3	0	0	13 (11)
5–10 years	18	9	4	5	1	1	38 (32.2)
› 10 years	17	24	16	1	5	4	67 (56.8)
Skin type							
Type III	20	27	6	7	3	3	66 (56%)
Type IV	17	6	12	2	2	2	41 (34.7%)
Type V	5	3	2	0	1	0	11 (9.3%)
Lesion site							
Head & neck	32	29	10	6	5	4	86 (72.9)
– Scalp	*5*	*14*	*2*	*2*	*1*	*0*	*24*
– Face	*20*	*14*	*2*	*4*	*4*	*4*	*48*
– Neck	*7*	*1*	*6*	*0*	*0*	*0*	*14*
Trunk	5	5	8	0	0	0	18 (15.2)
Upper limbs	3	1	1	2	0	1	8 (6.8)
Lower limbs	2	1	1	1	1	0	6 (5.1)
Lesion size							
‹ 1 cm	28	29	17	6	2	3	85 (72)
› 1 cm	14	7	3	3	4	2	33 (28)
Histological spectrum							
Typical	36	35	18	9	0	5	103 (87.3%)
Atypical	5	1	2	0	5	0	13 (11%)
Malignant	1	0	0	0	1	0	2 (1.7%)

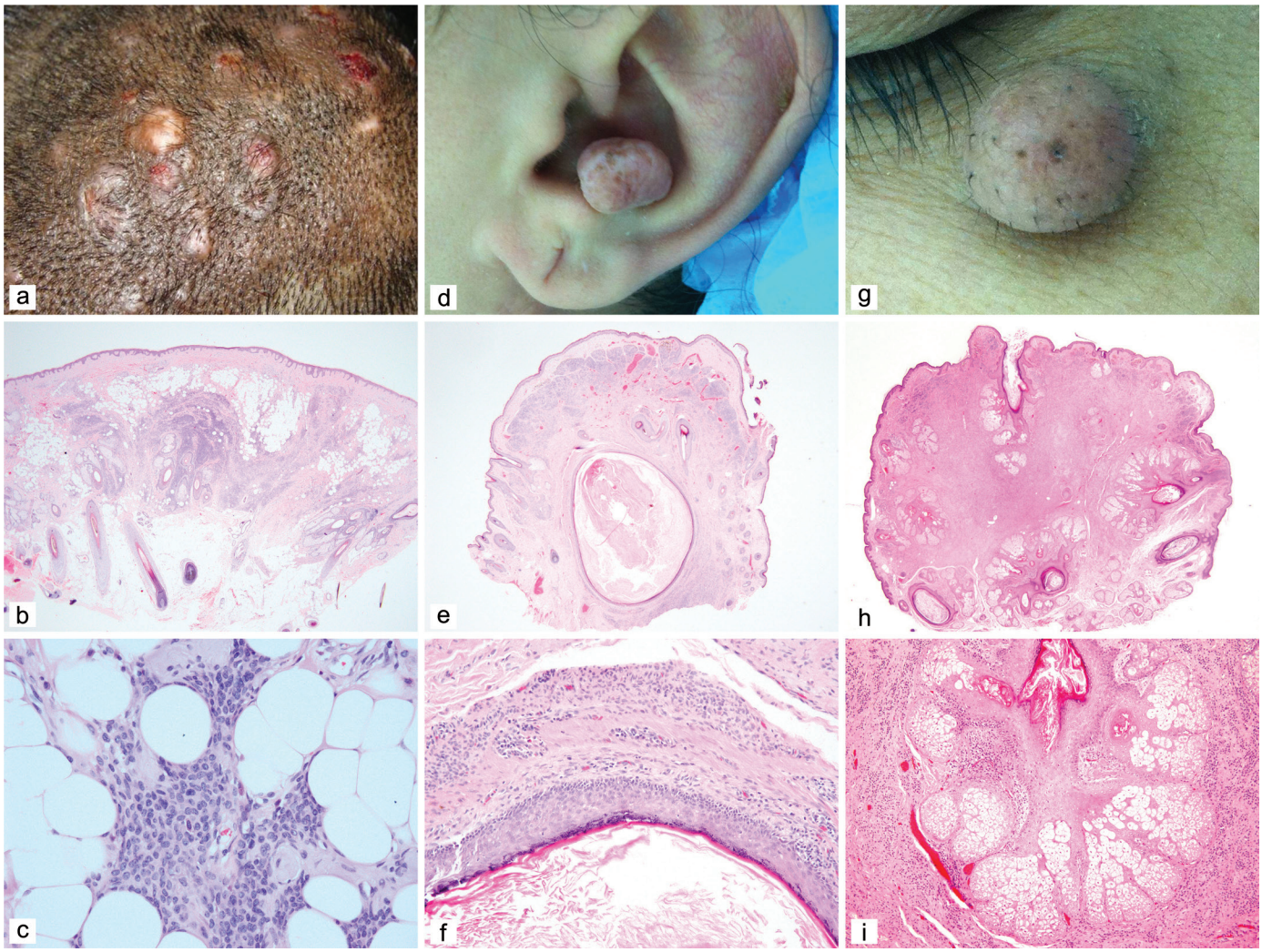

Figure 1 | Rapidly enlarged nevi on the scalp (a), ear (d), and face (g). Histological examination showed marked accumulation of fat cells (fatty nevus) (b and c, HE × 20 and × 400), large epidermal cysts (e and f, HE × 20 and × 400), and sebaceous hyperplasia (h and i, HE × 20 and × 400).

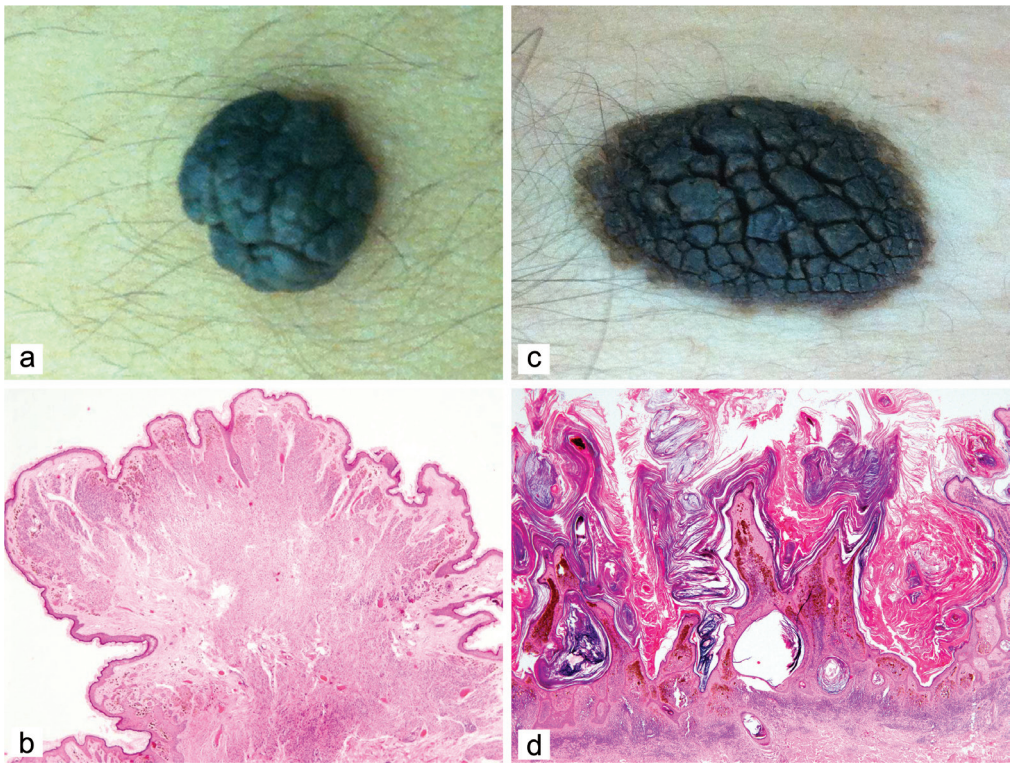

Figure 2 | Keratotic nevi presented with large pigmented lesions, either pedunculated nodule (a) or well-demarcated plaque (c). Histological examination showed either marked papillomatosis (b, HE × 40) or seborrheic keratosis–like changes with formation of many horn cysts (d, HE × 100).

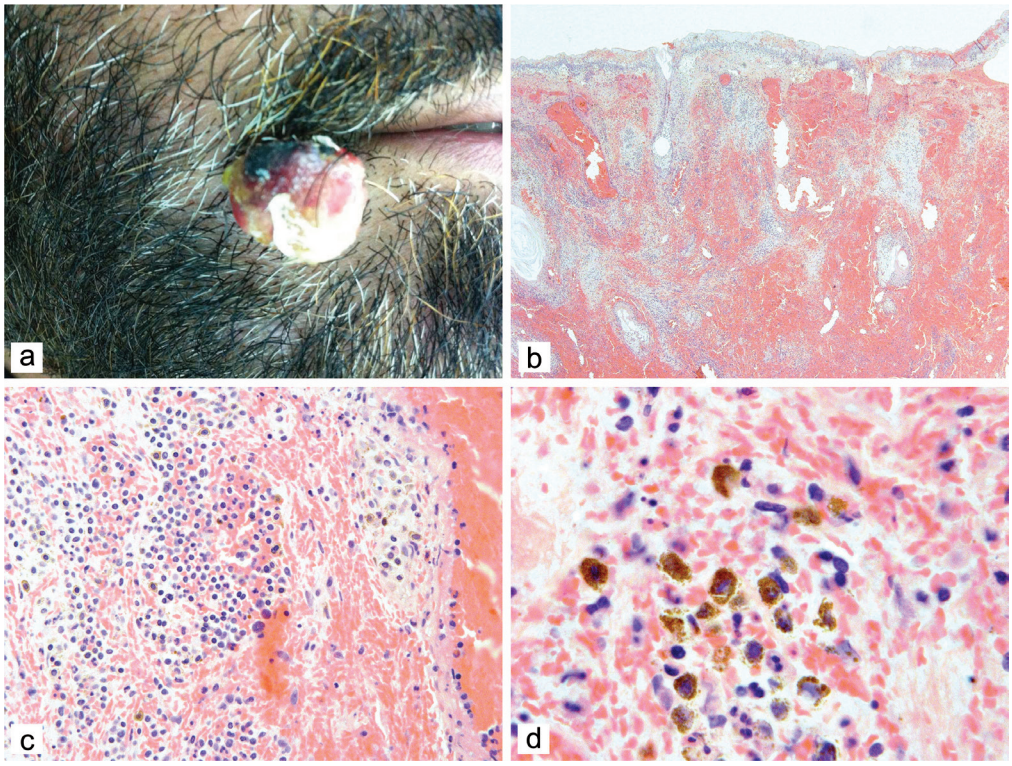

Figure 3 | Angiomatous nevus on the mouth angle (a) showed surface ulceration (b, HE × 20) with prominent hemorrhage (c, HE × 200) and mixed nevus cells with RBCs (d, HE × 1,000).

Table 3 | Association between histological features of acquired melanocytic nevi in both groups.

	Nevi with typical histological features		Nevi with atypical histological changes		Nevi with malignant transformation	
	Group A	Group B	Group A	Group B	Group A	Group B
Dermal type	78	92	1	0	0	0
Compound type	22	6	9	1	1	0
Junctional type	3	9	3	0	1	0
Total	103 (87.3%)	117 (99.2%)	13 (11%)	1 (0.8%)	2 (1.7%)	0 (0%)
p value	0.008		0.002		0.47	

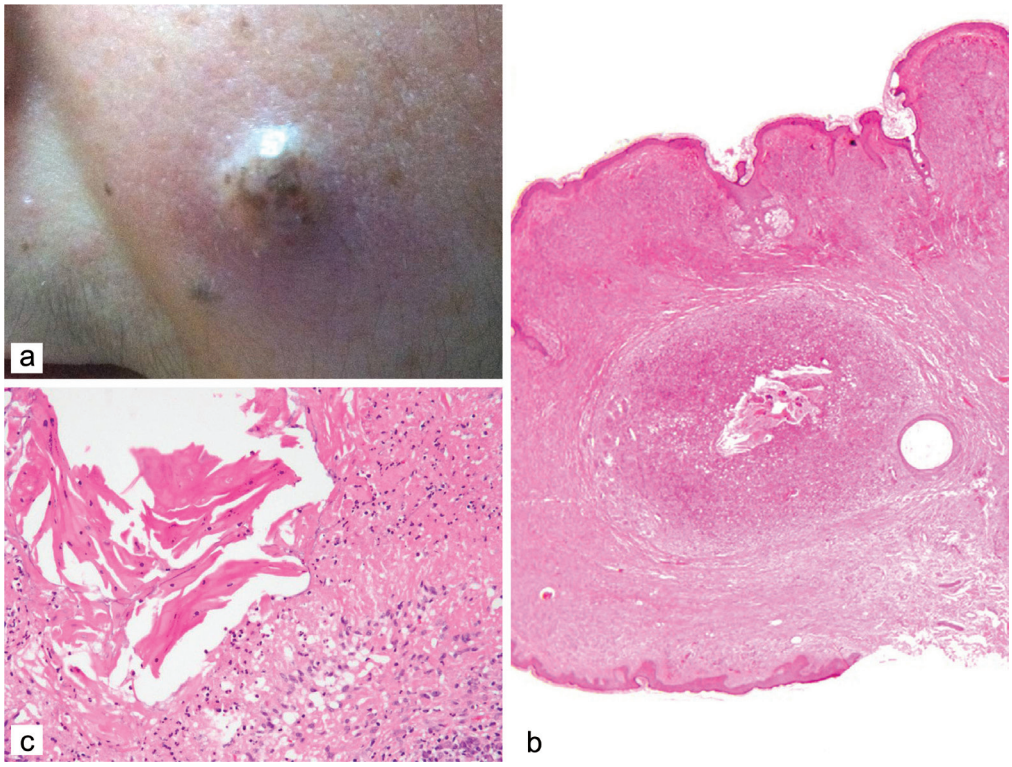

Figure 4 | Inflamed nevus on the cheek (a) showed ruptured hair follicle on the mid dermis (b, HE × 20) with mixed inflammatory reaction surrounding keratinous debris (c, HE × 400).

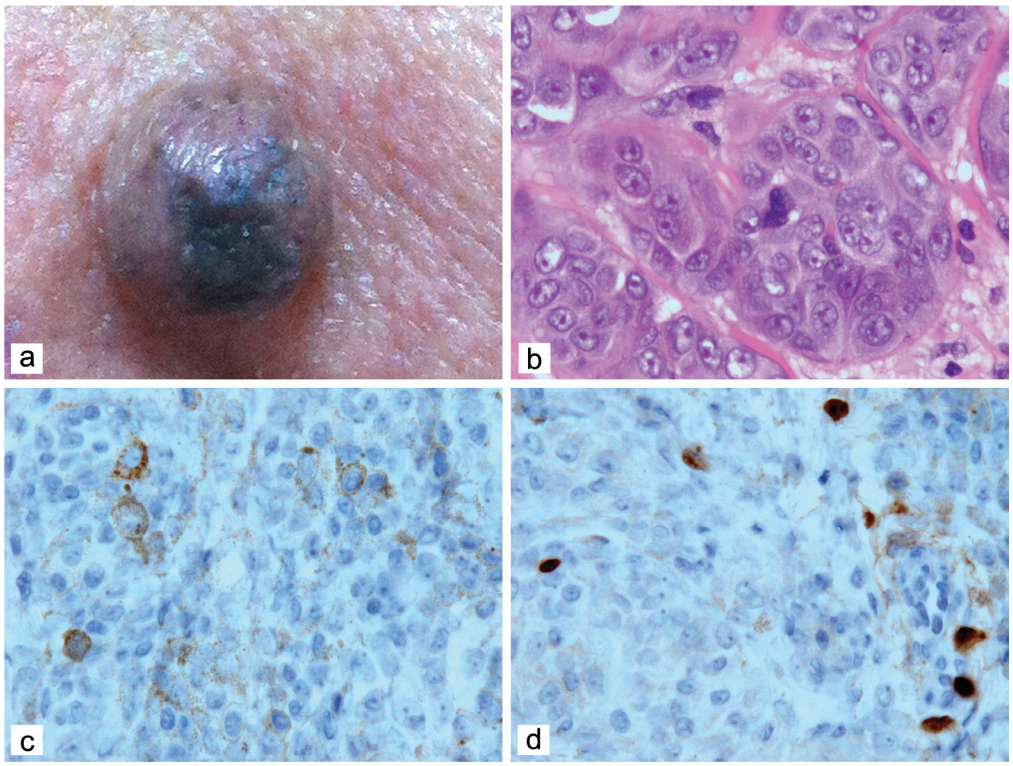

Figure 5 | Ulcerative nevus on the face (a) showed sporadic atypical cells within the dermal nests (b, HE × 1000). Some cells were positive for HMB-45 stain (c, immunostain × 400) whereas other cells were positive for Ki-67 stain (d, immunostain × 400).

Discussion

Melanocytic nevi among the Egyptian population are believed to have a benign course, and surgical excision is usually requested either for cosmetic purpose or due to changes in clinical behavior with the fear of melanoma transformation. It was found that there is increased incidence of benign MN in middle-aged individuals and in females of all ages, whereas DN and MM were more common in males, with a higher incidence of MM among the older age group (8).

It is widely accepted that there are several recognizable melanocytic precursors of cutaneous melanoma. The common melanocytic precursors include dysplastic MN, congenital nevi (of any size), acral MN, and darkly pigmented lesions of mucous membranes (9). It was suggested that early recognition of these melanocytic precursor lesions, particularly in high-risk individuals, and careful photographic follow-up or prophylactic excision of these lesions may be the most effective means of reducing the morbidity and mortality of cutaneous melanoma (10).

In the current study, malignant transformation was only proved in 1.7% of MN with atypical clinical presentation, whereas in clinically typical MN there was no malignant transformation in any case. Although the proper estimation of the transformation rate needs a wide-scale study with a large number of cases, this study's results suggest a low incidence of malignant transformation of MN among the Egyptian population. In agreement with this suggestion, Tsao et al. also concluded that the risk of malignant transformation of moles is low, especially in younger individuals. However, MN that persist into old age have an increased risk of malignant transformation (11). In this study, the effect of age on the prognosis of MN was almost eliminated by the presence of a matched-age control group.

Atypical MN not only increases the chance of progression to MM but also predisposes the patient to development of MM at other sites. Salava et al. found that clinically atypical and microscopically dysplastic nevi can be associated with an increased incidence of melanoma (12). Kang et al. also found that the risk of melanoma in individuals with atypical nevi is significantly greater than expected and the elevated risk was demonstrated even though careful, regular evaluations and removal of more atypical lesions were performed (13).

Although there was no record of any cutaneous melanoma diagnosed in patients with clinically atypical MN, this could be attributed to the low incidence of skin cancer among Egyptians (only representing 5% of the malignant tumors of the entire body). Moreover, there is low incidence of MM (8%) compared with other malignant epidermal tumors such as basal cell carcinoma (77%) and squamous cell carcinoma (15%) (14). These results were in agreement with Carli et al. (15), who found that the presence of large nevi and clinically atypical nevi among Italians did not result in an increased risk for cutaneous melanoma when the number of acquired MN was considered.

In this study, malignant transformation was observed in junctional and compound nevi, but not in any intradermal nevus. This may have contributed to the higher proliferative activity of nevus cells during the first stages, whereas with an intradermal nevus the cells become fully matured. It was suggested that MM arising from a nevus is more characterized by abrupt transition, localized distribution of junctional atypical cells, and the presence of dense dermal nests. Moreover, MM arising from acquired or congenital nevi are predominantly composed of roundish, monomorphous cells, whereas melanomas arising either de novo or from dysplastic nevi were characterized by markedly pleomorphic cells (16).

In this study, atypical histological features were significantly higher in MN with abnormal clinical behavior compared with clinically typical MN, and these changes were observed more among ulcerative and pigmented nevi. The most striking histological features in dysplastic lesions included cytological atypia, irregular confluent nests, and scattered mitosis. The correlation between clinical atypia and histological dysplasia was variable in previous reports. It was suggested that DN cannot be considered a distinct clinicopathological entity because histological dysplasia is found in a range of nevi that may or may not show clinical atypia (17).

Callaghan et al. found that the clinical characteristics associated with histological dysplasia include a macular component, irregular borders, and the presence of three or more colors, whereas asymmetry, diameter greater than 5 or 6 mm, and progression were not associated with atypical histological characteristics (18). However, Barnhill and Rouch found that nevus size, irregular border, ill-defined border, macular component, and pink color were associated significantly with histological dysplasia. Among these features, nevus size and irregular borders were more correlated with histological atypia (19). These reports suggested the difficulty in correlation between clinical atypia and histological dysplasia of MN.

There was also a controversy about the presence of atypical histological features in acquired MN. It was reported that atypical histological features among acquired MN might be present in 72% or 87.8% of cases (20, 21), This led to reinforcing the concept that DN could not be fully accepted as a distinctive histological entity because the histological features can also observed in nevi that are not classifiable as DN by other clinical and histological criteria (21). It was also suggested that lesions that have taken the critical step of violating the upper size limit of acquired MN might be the most favorable candidates for consideration of the diagnosis of DN (22).

One of the limitations of this study was the absence of dermoscopy features, which is an important tool in evaluating pigmented skin lesions. Although this would be appropriate in developed countries, in most developing countries and for most general dermatologists dermoscopy is usually not available and the main evaluation of pigmented lesions is based on clinical experience. This study could be beneficial in increasing the clinical awareness of variable changes of acquired MN among dermatologists, especially in developing countries.

Conclusion

Among Egyptian patients, acquired MN with abnormal clinical behavior are associated with significant histological atypia but a low risk of malignant transformation. Ulceration and altered pigmentation are important clinical clues for histological atypia. Early excision, careful histological examination, and close monitoring of such nevi are recommended.

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