Scientific Foundation SPIROSKI, Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences. 2024 Mar 15; 12(1):128-135.
https://doi.org/10.3889/oamjms.2024.11840
eISSN: 1857-9655
Category: *B - Clinical Sciences*
Section: *Dermatology*

Clinical and Dermatoscopic Characteristics of Melanoma *in situ* - Institutional Experience

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Edited by: Mirko Spiroski
Citation: Petrov A, Jashar D, Petrova D. Clinical and Dermatoscopic Characteristics of Melanoma *in situ* - Institutional Experience. Open Access Maced J Med Sci. 2024 Mar 15; 12(1):128-135. https://doi.org/10.3889/oamjms.2024.11840
Keywords: Melanoma *in situ*; Dermoscopy; Hysto-patology
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Received: 02-Dec-2023
Revised: 26-Dec-2023
Accepted: 31-Jan-2024

Funding: This research did not receive any financial support
Competing Interests: The authors have declared that no competing interests exist

Abstract

BACKGROUND: Melanoma *in situ* (MIS) is the very early stage of a skin tumor called melanoma. In recent decades, the incidence rate for melanoma has increased by 2.6%/year and MIS is the main diagnosis responsible for this increase. It is important to recognize MIS since in this phase (called the intraepidermal phase), cancer cells do not have the opportunity to spread anywhere in the body. The use of dermoscopy has contributed to the early diagnosis of melanoma. The most common dermoscopic features of melanoma are multiple structures and colors (multicomponent pattern), an atypical reticular pattern (with wide, irregular meshes), and an absence of distinguishing features (nonspecific pattern) associated with the presence of vascular structures. The clinical decision about the excision of the lesion should always be in correlation with the dermoscopic picture of the pigmented lesion. If dermoscopy is unclear and there is suspicion for MIS, surgical excision with a wide margin of more than 5 mm should be performed.

AIM: In this work, we are presenting four cases of diagnosis of MIS and their clinical, dermoscopic, and histopathological findings.

METHODS: In this work, we present four cases of diagnosis of MIS, their clinical, dermoscopic and histopathological findings.

RESULTS: The invasive melanoma cohort, compared with the MIS cohort, had an elevated risk for subsequent invasive melanoma in the first 10 years. However, the MIS cohort was more likely to develop subsequent MIS during the entire follow-up period than the invasive melanoma cohort. In our work, none of the four patients that we presented had relapsed during the first 2 years of follow-up, which is consistent with these results.

CONCLUSION: With the presentation of these cases, we want to stress and help clinicians that the main focus in dermoscopy assessment of MIS is on the asymmetry of the pigmented network and a two-color sign because many other marks of melanoma are missing.

Introduction

The European annual incidence of malignant melanoma varies from 3–5/100,000 in Mediterranean countries to 12–35/100,000 in Nordic countries, whereas it can reach over 50/100,000 in Australia or New Zealand. According to the public health institute of the Republic of North Macedonia, the incidence of melanoma malignum is 6–7 cases/100,000, which is in agreement with the incidence data in Mediterranean countries. The incidence of melanoma has been rising steadily over the last 40 years, with a trend towards stabilization of mortality, except in elderly males [1].

Melanoma patients need instructions on the avoidance of sunburns, extended unprotected solar or artificial UV exposure, and life-long regular self-examinations of the skin and peripheral LNs [III, B]. Patients must be aware that family members have an increased melanoma risk [III, B]. There is no recommendation for genetic testing [2].

A study clearly shows that a nationwide public melanoma education campaign significantly reduces the mean Breslow invasion thickness of all melanomas in patients seen in one institution [3].

It has been suggested that ultrasound examination of regional lymph nodes provides staging and prognostic information that is as accurate as sentinel node biopsy in patients who present with cutaneous melanoma. However, in most studies, the sensitivity of ultrasound in detecting nodal metastasis has been low (23% in a recent large series). For the present, sentinel node biopsy remains the most accurate method of regional node staging in patients with newly diagnosed melanoma [5].

To improve the outcomes of patients with cutaneous melanoma, treatment based on accurate staging and patient stratification into clinically relevant

stage groups is fundamental. Not only does staging inform prognostic assessment and clinical decision-making, it also facilitates centralized cancer registry reporting and the design, conduct, and analysis of clinical trials [6].

It seems reasonable to use a slightly larger surgical margin when melanoma *in situ* (MIS) is suspected to minimize the risk of incomplete diagnostic excisions while also reducing the number of unnecessary wide local excisions afterwards. We therefore suggest that a 5 mm surgical margin be used when experienced dermoscopy users have a strong preoperative suspicion of MIS and no suspicion of invasiveness. We understand that this suggestion might be controversial for some since this could lead to a slightly larger scar than necessary in cases when the excised lesion turned out to be a nevus [7].

Materials and Methods

In this work, we present four cases of diagnosis of MIS, their clinical, dermoscopic and histopathological findings (Table 1).

Table 1: Dermoscopic clues for melanoma

1. Atypical network
2. Focal streaks
3. Atypical dots and globules
4. Negative pigment network
5. White shiny structures
6. Off center blotch
7. Gray dots/granules
8. Blue-white veil
9. Vascular structures
10. Peripheral tan/brown structure less areas

Skudalski *et al.* Melanoma: How and when to consider clinical diagnostic . J Am Acad Dermatol, Volume 86, Number 3 J Am Acad Dermatol, March 2022 [4].

Case 1

A 33-year-old female patient presents with a pigmentary change in the back region.

On clinical examination, there is asymmetry of the lesion in both axes, with irregularity of pigmentation (Figure 1). When examined with a dermoscope, there is a different intensity of the pigment in the pigment network, with a thickening of the pigment network in part of the lesion. The rest of the dermoscopic criteria for malignant melanoma are absent (Figures 2 and 3). Because the lesion was suspicious and showed some degree of atypia, the patient was referred for an excisional biopsy with a minimum margin of 5 mm for MIS.

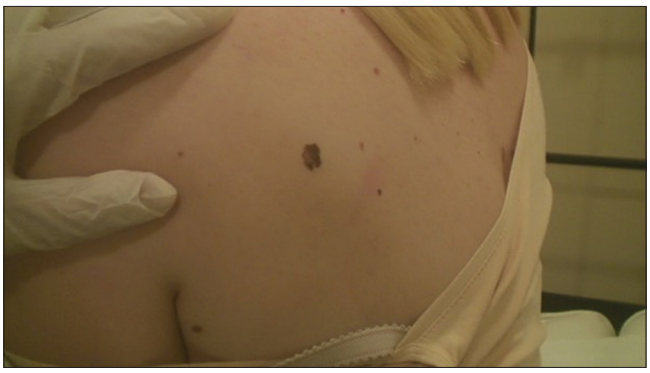

Figure 1: Suspicious melanocytic lesion on back

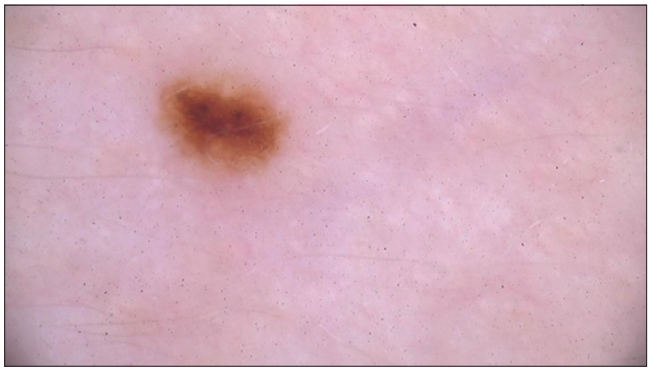

Figure 2: Dermoscopy of the lesion ×30

MIS of the lentigo maligna type was confirmed histopathologically after the excisional biopsy (Figure 4).

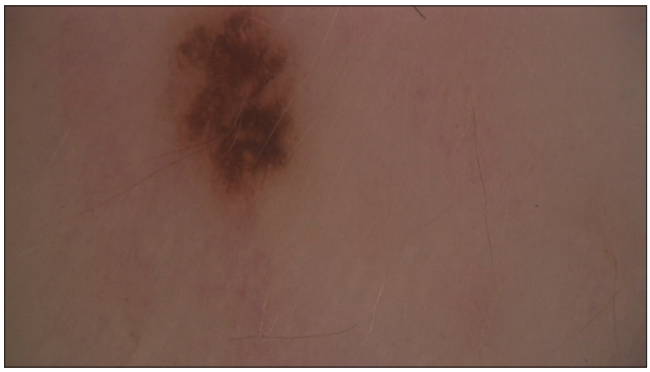

Figure 3: Dermoscopyhigher magnification ×40- asymetri and "two color" sighn

On the histopathological finding, the skin had a broad intraepidermal proliferation of melanocytes and an irregular distribution of nests and individualized melanoma cells (Figure 5). Ki67 immunohistochemical staining of atypical melanocytes revealed marked proliferation of the neoplastic cells (Figure 6). Crowding of melanocytes with hyperchromatic nuclei along the basal epidermis and focal nesting, intraepidermal ascent of melanocytes (pagetoid scatter), and involvement of the adnexal epithelium were described by pathologists (Figure 7).

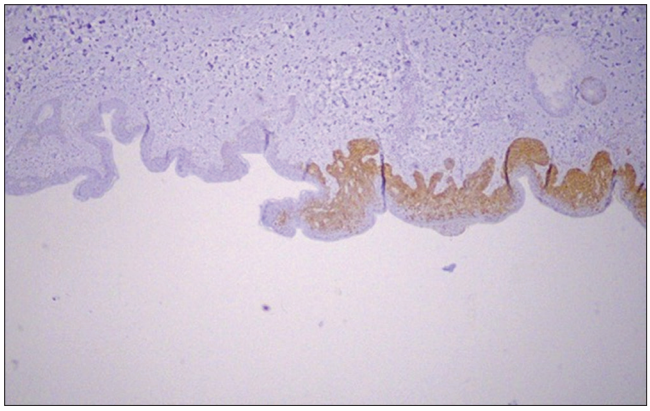

Figure 4: Pathology report-melanoma malignum in situ

After the operative treatment, the patient underwent an examination of the regional lymph basin, which was also with normal findings. Regular check-ups were recommended every 3 months during the 1st year from the initial diagnosis, and then every 6 months up to 3 years from the initial diagnosis. The patient has no signs of relapse after 3 years of operative treatment.

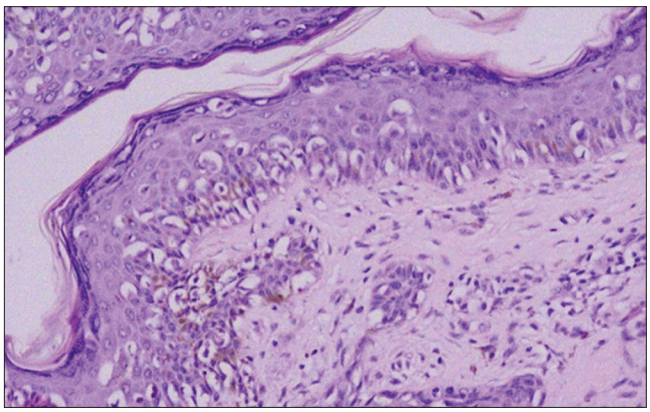

Figure 5: Skin with a broad intraepidermal proliferation of melanocytes and irregular distribution of nests and individualized melanoma cells (200×, H&E)

Case 2

A 45-year-old patient, during an examination by a gynecologist, observed a pigmentary change on the left foot, for which she was referred to a dermatologist.

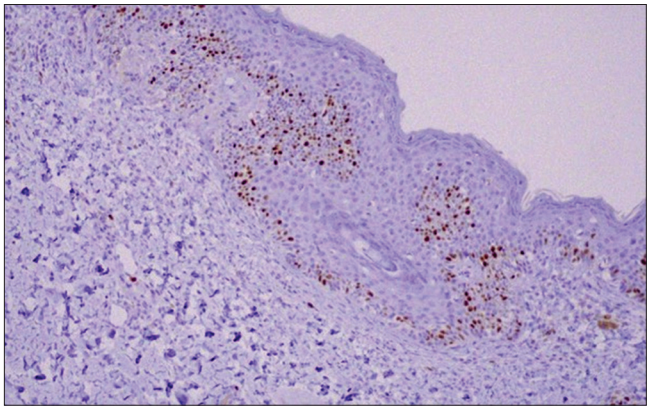

Figure 6: Ki67 immunohistochemical staining of atypical melanocytes revealed marked proliferation of the neoplastic cells (100×, Ki-67)

The dermatological clinical examination, in addition to an atypical nevus, was darkly pigmented (Figures 8 and 9).

The dermoscopic finding, in addition to the lesion that has asymmetric borders with varying intensities of pigment from light yellow to dark brown, has a tendency to create pseudopodia of the pigment network on the periphery (Figures 10 and 11).

Under suspicion of dysplastic nevus, or MIS, excision of the lesion with a surgical margin of 5 mm was recommended.

Histopathological diagnosis was made for acral lentigo MIS.

Skin with broad intraepidermal proliferation of melanocytes, irregular distribution of nests, and focal flattening of rete ridges was described by the pathologist (Figure 12). Immunohistochemical staining with p16 highlights the strong and diffuse positivity of melanocytes at the epidermal-dermal junction was seen (Figure 13).

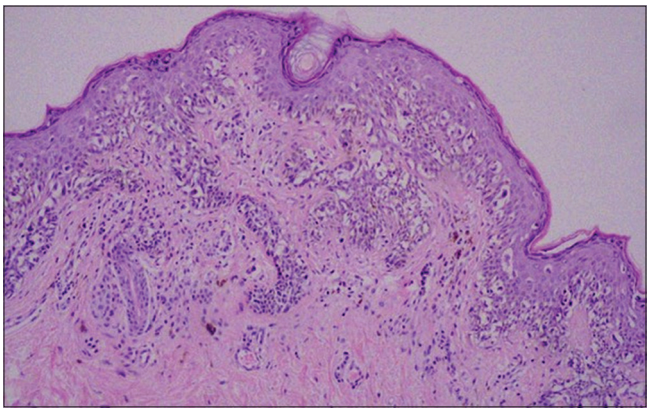

Figure 7: Crowding of melanocytes with hyperchromatic nuclei along the basal epidermis and focal nesting, intraepidermal ascent of melanocytes (pagetoid scatter) and involvement of adnexal epithelium (100×, H&E)

HMB-45 immunohistochemical staining of melanocytes in nests along the epidermal border was done (Figure 14). Intraepidermal proliferation of melanocytes with irregular and focal flattening of rete ridges and a small site of underlying superficial dermal fibrosis with nests of melanocytes was also present (Figure 15).

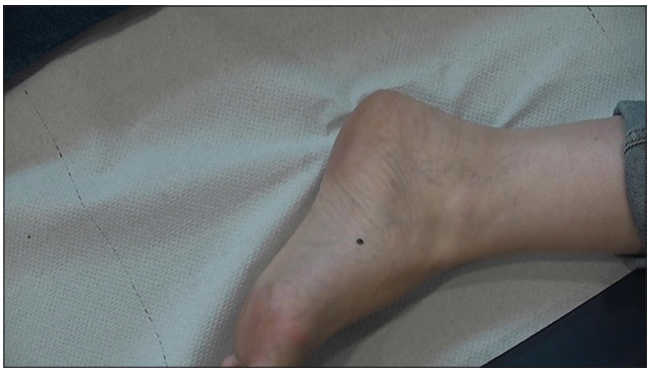

Figure 8: Macro picture

Postoperatively, the patient underwent a PET-CT due to a history of breast cancer. The PET-CT findings were normal.

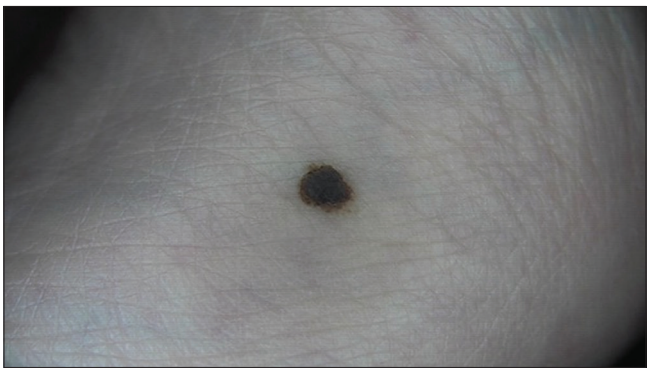

Figure 9: Close macro picture

Regular dermatological controls were advised every 3 months during the 1st year and then every 6 months during the first 3 years.

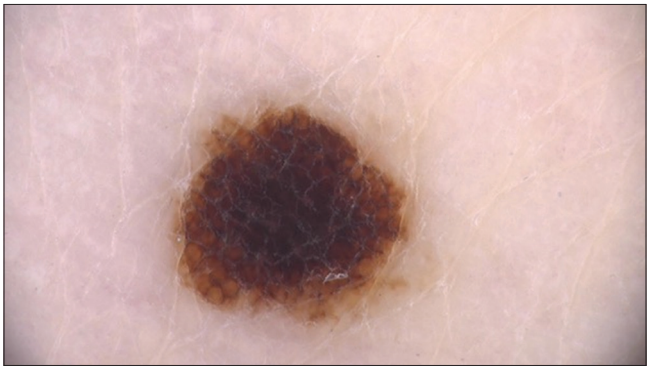

Figure 10: Dermoscopy ×30 with peripheral tendency to grow

The patient has no signs of relapse after regular control for a year.

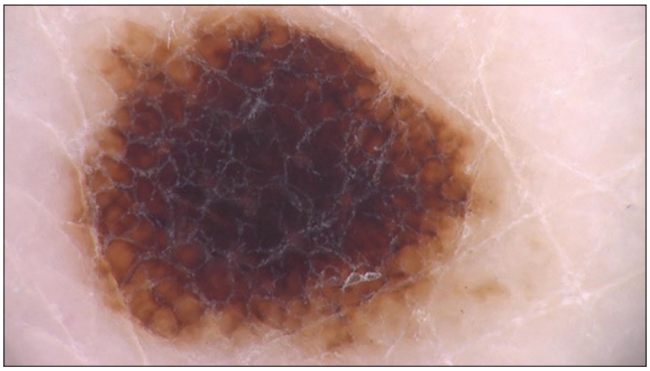

Figure 11: Dermoscopy ×40 two color intensity and peripheral asymmetry of the network

Case 3

A 50-year-old female patient comes to the examination due to a pigmentary change on her left forearm. During the clinical examination, the finding was in addition to an atypical nevus (Figure 16). The patient's medical history cannot remember how long she has had the change. The patient has a history of colon cancer treated surgically and oncological 2 years ago.

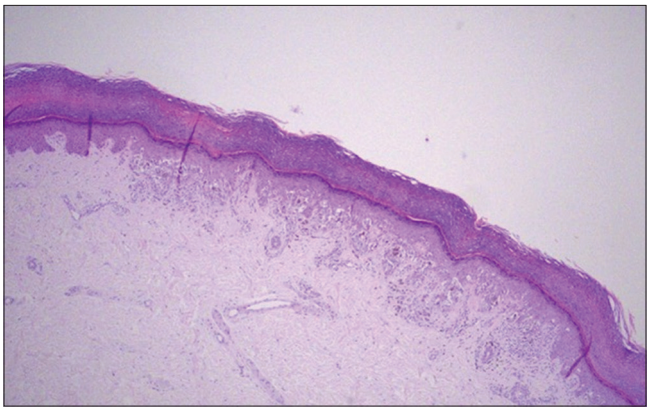

Figure 12: Skin with broad intraepidermal proliferation of melanocytes with irregular distribution of nests and focal flattening of rete ridges (50×, H&E)

Dermoscopically observed asymmetry of the pigment network with bicolor from brown to black and a tendency for pseudopodia towards the environment (Figure 17).

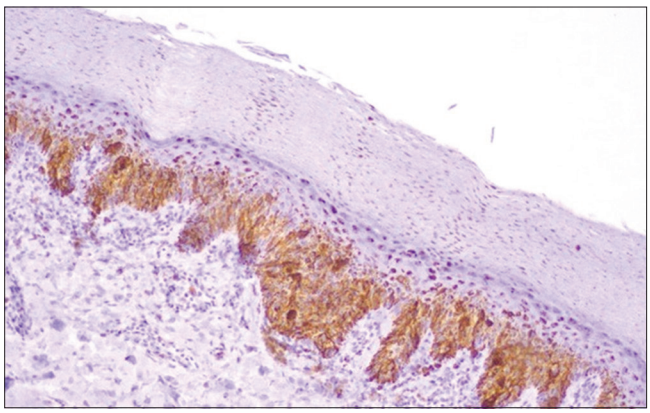

Figure 13: Immunohistochemical staining with p16 highlights the strong and diffuse positivity of melanocytes at the epidermal-dermal junction (100×, p16)

In cases of suspicion of MIS, surgical excision with a minimum margin of 5 mm was advised.

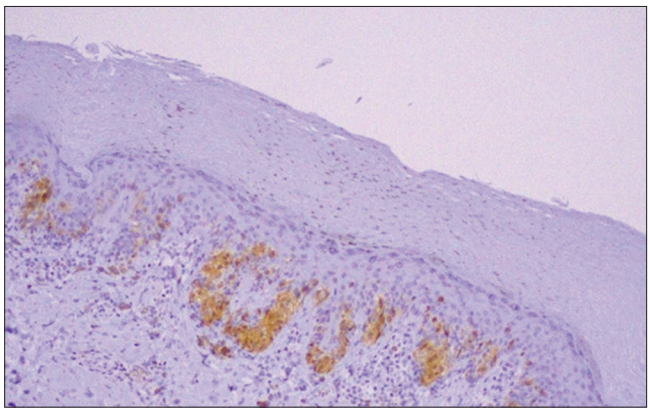

Figure 14: HMB-45 immunohistochemical staining of melanocytes in nests along the epidermal border (100×, HMB-45)

After surgical excision, MIS was confirmed with histopathology.

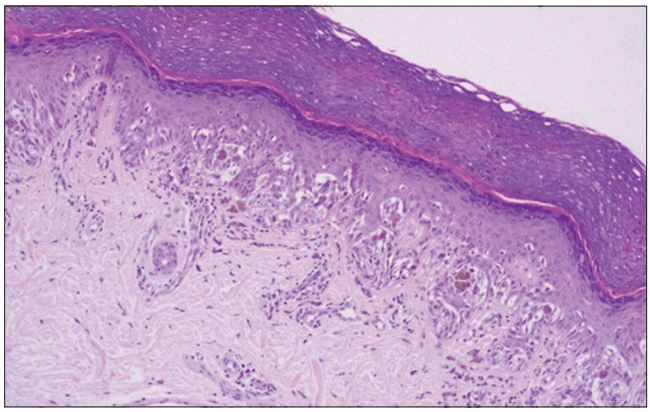

Figure 15: Intraepidermal proliferation of melanocytes with irregular and focal flattening of rete ridges and a small site of underlying superficial dermal fibrosis with nests of melanocytes (100×, H&E)

Melan-A immunostaining with marked positivity of the melanocytes in the epidermal compartment was found (Figure 18).

Atypical intraepidermal melanocytes with variable amounts of cytoplasm and enlarged nuclei with chromatin ranging from dense to pale and prominent nucleoli were present (Figure 19).

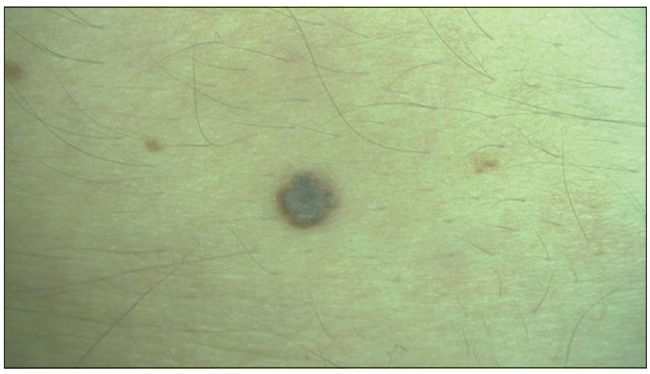

Figure 16: Atypical mole on forearm

Immunohistochemical staining with p16 highlights the distribution of melanocytes along the dermal-epidermal border (Figure 20).

After 1 year of regular check-ups, the patient has no signs of relapse.

Case 4

A 42-year-old patient presented to the examination due to a pigmentary change in the skin in the lumbar area (Figure 21).

Dermoscopically, unevenness of the pigment network, asymmetry, multicolor, and the appearance of a blue veil were noticed.

The dermoscopic finding was suspicious for early melanoma (Figures 22-26).

A surgical excision with a margin of 5 mm is advised for suspected melanoma malignum. Postoperative histopathology findings confirmed MIS.

After regular follow-up, the 10-year-old patient is free of disease.

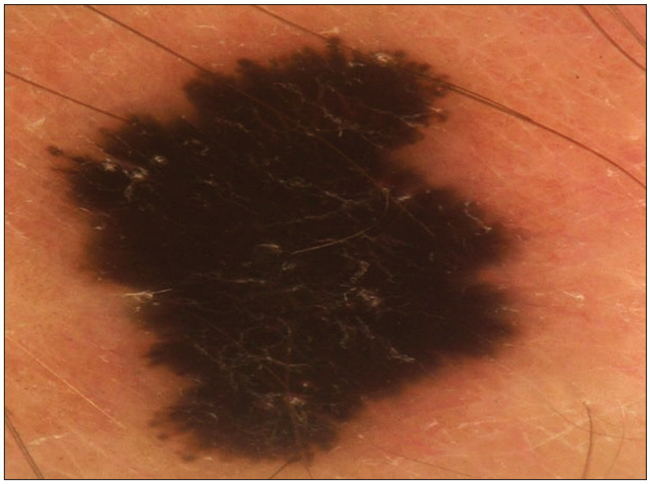

Figure 17: Dermoscopy of the lesion, asymmetry, and pseudopodia of pigmented network

Discussion

MIS is the very early stage of a skin tumor called melanoma. In recent decades, the incidence rate for melanoma has increased by 2.6%/year and MIS is the main diagnosis responsible for this increase. It is important to recognize MIS, since in this phase (called the intraepidermal phase), cancer cells don't have the opportunity to spread anywhere in the body.

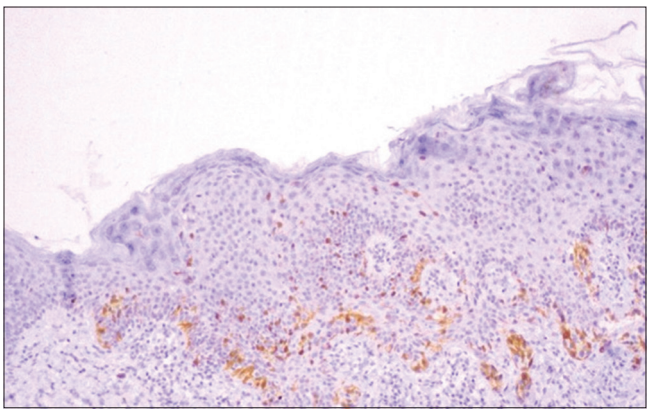

Figure 18: Melan-A immunostaining with marked positivity of the melanocytes in the epidermal compartment (200×, Melan-A)

Recognizing MIS is important because of the possibility of developing invasive melanoma in other locations. The risk of subsequent melanoma of any stage was higher in the MIS cohort than the invasive melanoma cohort after 2 years following the first melanoma, although the risk was not different between the 2 cohorts for the first 2 years.

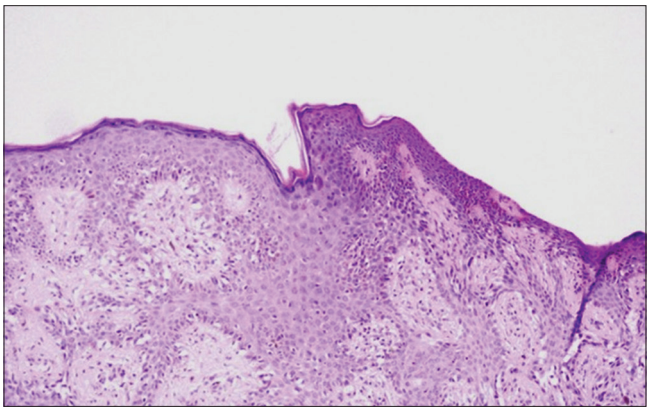

Figure 19: Atypical intraepidermal melanocytes with variable amounts of cytoplasm and enlarged nuclei with chromatin ranging from dense to pale and prominent nucleoli (200×, H&E)

The invasive melanoma cohort, compared with the MIS cohort, had an elevated risk for subsequent invasive melanoma in the first 10 years. However, the MIS cohort was more likely to develop subsequent MIS during the entire follow-up period than the invasive melanoma cohort [8]. In our work, none of the four patients that we presented had relapsed during the first 2 years of follow-up, which is consistent with these results.

The clinical decision about the excision of the lesion should always be in correlation with the dermoscopic picture of the pigmented lesion. If dermoscopy is unclear and there is suspicion for MIS, surgical excision with a wide margin of more than 5 mm should be performed.

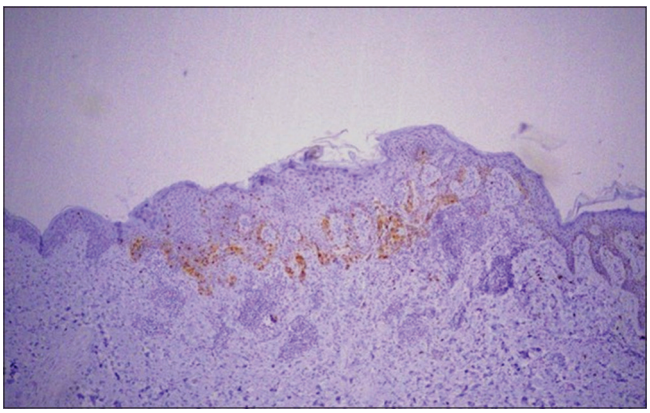

Figure 20: Immunohistochemical staining with p16 highlights the distribution of melanocytes along the dermal-epidermal border (100×, p16)

The use of dermoscopy has contributed to the early diagnosis of melanoma. The most common dermoscopic features of melanoma are multiple structures and colors (multicomponent pattern), an atypical reticular pattern (with wide, irregular meshes), and an absence of distinguishing features (nonspecific pattern) associated with the presence of vascular structures [9]. Most of the dermoscopy findings that we describe in the presentation of our patients were in accordance with the above criteria.

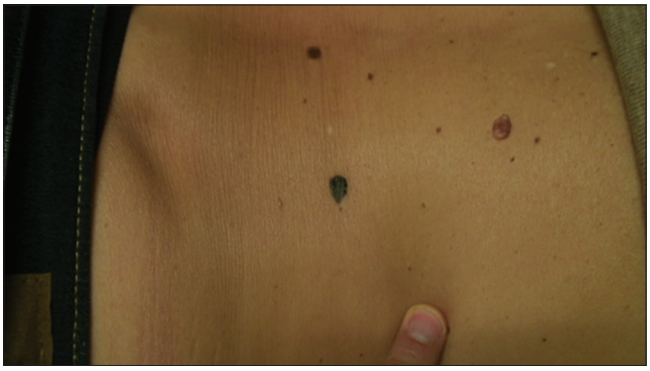

Figure 21: Clinically suspicious lesion

Dermoscopy is a cheap, 20-year-old method used worldwide in which doctors use a handheld device called a dermatoscope to look at the skin magnified by about 10 times, allowing them to see things that would not be visible to the naked eye. The authors analyzed images of 120 MIS and 213 nevi (moles) using dermoscopy and RCM, which allowed them to identify several features related to MIS diagnosis (RCM aspects of intraepidermal melanoma were not yet well known [10].

In the study of Borsari *et al*., they used a multistep algorithm combining dermoscopy with confocal microscopy with a very high percentage of diagnostic assessment of MIS. Dermoscopic features independently associated with MIS diagnosis were an atypical pigment network and regression, with a risk 3 and 4 times higher of malignancy, respectively. An atypical reticular pattern and regression are already well-known dermoscopic diagnostic features of MIS [10].

Figure 22: Close macro picture

An analysis of a group of authors in the name of the International Dermoscopy Society, provides evidence that digital dermoscopy follow-up of melanocytic skin lesions demonstrated the early detection of melanomas with a low rate of excisions. Using digital dermoscopy follow-up, the proportion of MIS and thin melanomas is higher than expected in the general population. Clear differences exist in clinical outcome according to the follow-up interval: Short-term follow-up is mainly focused on the assessment of individual lesions, so a lower NNM is required and patients have a lower mean of lesions monitored, while medium- and long-term follow-up is used for the surveillance of patients with atypical mole syndrome or high nevi count, among other risk factors, so a higher mean of lesions monitored and a higher NNM are required. Criteria for the selection of patients and lesions may influence the clinical outcome, as only high-risk individuals and/or the most atypical lesions seem to benefit from digital follow-up. We found that the chances of detecting a melanoma during surveillance increase as the length of follow-up extends, so surveillance must be maintained over time in high-risk populations [11].

Figure 23: Dermoscopy of the lession

This study of Wei *et al*. revealed interesting epidemiologic and clinical features of MIS. First, the increase in MIS detection relative to invasive melanoma

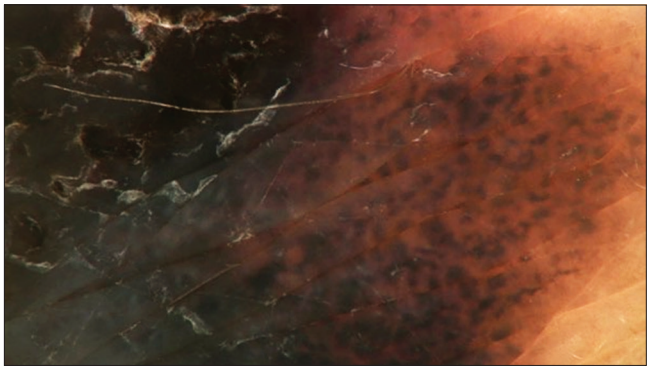

Figure 24: Dermoscopy ×40 obvious changing of pigmented network

over 30 years (women) and 20 years (men) of cohort follow-up did not correspond to a reduction in melanoma mortality. In addition, invasive and MIS showed distinct anatomic distributions, which may have greater implications for biologic behavior at distinct anatomic sites. Invasive melanomas are diagnosed at a younger age than *in situ* lesions; invasive melanomas were more likely than MIS to be found on the lower extremities in both men and women. Albeit, an overwhelming percentage of invasive melanomas were found above the waist [12].

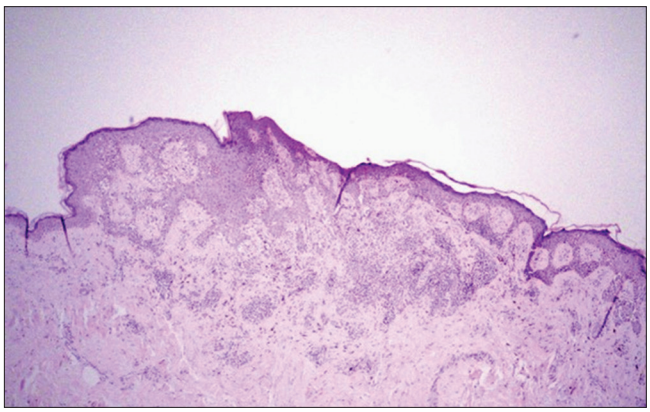

Figure 25: Atypical intraepidermal melanocytes (50×, H&E)

The medium average of our patients with MIS was 42 years; all of the patients that we presented in this study are female. Two of them have MIS located on the trunk and two on the extremities. Two of the presented patients have second malignancies (breast and colon cancer).

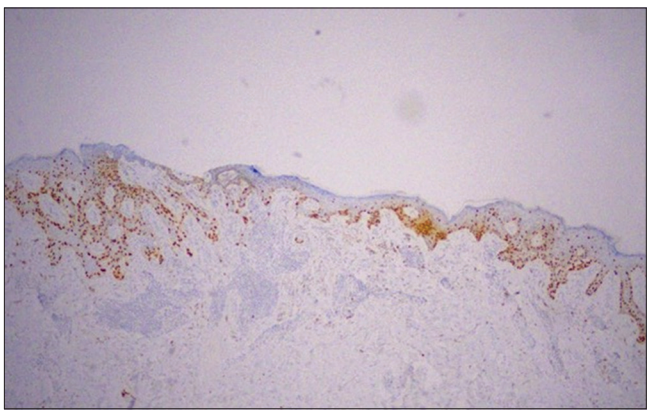

Figure 26: SOX-10 immunostaining, highlighting crowding of melanocytes and abundant pagetoid scatter (100×, SOX-10)

Conclusion

With the presentation of these cases, we want to stress and help clinicians that the main focus in dermoscopy assessment of MIS is on the asymmetry of the pigmented network and a two-color sign because many other marks of melanoma are missing.

The approach to excise when there is obvious asymmetry is justified because two colors and asymmetry could be indicative of MIS. MIS should be recognized and differentiated firstly from benign lesions but also, frequently, from advanced melanoma. The diagnosis of all tumors is confirmed by histopathology, which justifies surgical excision. Because of the recommended narrow margin of 5 mm around the possible MIS, there is an opportunity to make a diagnostic and therapeutic approach (in accordance with NCCN criteria for MIS surgical margin) in one step without significant impact on the esthetic look.

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