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ORIGINAL PAPER

Pushing and loss of elastic fibers are highly specific for melanoma and rare in melanocytic nevi

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Abstract

The histopathological differentiation of melanocytic nevi from malignant melanoma (MM) is based on well-known criteria, and is straightforward in the vast majority of cases. However, there are few cases of melanocytic lesions (ML), the diagnosis of which is very challenging or even impossible. Here we have studied several morphological characteristics with particular focus on elastic fibers (EF) to identify features, helpful for the distinction between nevi and MM. In a monocentric retrospective study we have analyzed 14 morphological histological characteristics in 30 MMs and 90 nevi, encompassing 30 compound/dermal nevi, 30 junctional nevi, 30 dysplastic nevi. All consecutive cases were retrieved from the archives of our tertiary referral centre during the 6-month study period. Nine characteristics including loss of EF in the ML, loss of EF in lesional fibrosis, pushing of the EF, UV-elastosis, loss of rete ridges of the epidermis, regression of the ML, atrophy of the epidermis, pigment incontinence, and concentric eosinophilic fibroplasia (CEF) showed a statistical significant difference ($p < 0.05$ and at least an OR > 2) distinguishing nevi from MM. Loss of EF was found in 73.1% of MM cases, but in less than 2.5% of nevi. We identified nine morphological characteristics that are helpful to differentiate melanocytic nevi from MM. A loss of the EF in a ML appeared to be highly associated with MM.

Keywords Melanocytic lesion · Regression · Pushing · Dysplastic · Atypical · Consumption

Introduction

The histopathological differentiation between a melanocytic nevus and a malignant melanoma (MM) is straightforward in the vast majority of cases. The microscopical assessment and diagnosis of melanocytic lesions (ML) is almost invariably made using slides simply stained with the hematoxylin–eosin (H&E). However, sometimes further analyses as deep tissue cuts, or immunohistochemical (IHC) stains as Melan-A, HMB-45, S-100, SOX-10, and Ki-67 are essential [12, 34]. Rarely, in particular cases, more sophisticated analyses including FISH, or chromosome genomic hybridization (CGH) is necessary [12, 44].

Despite the fact that there are several criteria to distinguish melanocytic nevi ("nevi") from MM [30], there are some ML in which this distinction is honestly very difficult or even impossible [1]. Here we sum up some issues. One should be aware, that there is a continuum between a clearly benign, and an unequivocally malignant ML [32]. This fact is underlined by a recent study shoving the genetic evolution of MM from precursor lesions through a succession of genetic alterations [36]. Moreover, some criteria are shared by both nevi and MM [25, 41]. In addition, there is not a single discriminatory criterion, which alone can be used to distinguish benign and malignant ML. Finally, the exact definition, interpretation, and assessment of important diagnostic criteria such as architectural disorders, and cellular atypia, among others, is not standardized, is mostly subjective, and remains a matter of debate among experts [5, 9]. Inter-observer and intra-observer differences in the evaluation of a difficult ML is a well-known problem [2, 13].

The diagnostic importance of some morphological criteria has been only partially studied. Specifically, there are

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few analyses of the usefulness of stromal criteria as distinctive markers between nevi and MM [11, 16, 24, 31, 37–39], and only few studies have systematically evaluated the histopathological appearance of elastic fibers (EF) in ML [14, 20–22, 42, 45], but none of them made the comparison of these observations among patients with MM and nevi. Considering that the histochemical stains are less expensive, easy to perform, and may be of great help to resolve some particular cases in dermatopathology, we focused our research on pure morphological characteristics, especially using the elastica stain.

In this histopathological study, we compared the presence/absence of several morphological features in unequivocal nevi and MM.

Materials and methods

In this monocentric retrospective study, we have analyzed 14 morphological histopathologic characteristics of 120 ML, including 30 MMs, and 90 nevi. The latter consisted of 30 compound/dermal nevi, 30 junctional nevi, 30 dysplastic nevi. The diagnosis of these various types of ML was made using criteria as previously described [30].

We selected all consecutive cases analyzed between 1 July, and 31 December 2011 by including the first 30 tissue specimen for each diagnosis group.

All specimens were retrieved from the archives of the Dermatopathology Unit of the Dermatology Department at the Inselspital, Bern University Hospital, Bern, Switzerland.

All lesions were previously removed by a biopsy or surgical excision, fixed in 4% buffered formalin, dehydrated, paraffin-embedded, cut and stained with H&E, and elastica stains. The slides were examined with light microscopy by the board-certified dermatopathologist (HB), and a second investigator (AS).

Collected data

The following patient demographics and characteristics were recorded: age of the patients (all > 18 years old), gender, and anatomical localization of the lesion.

The presence of following histopathological morphological characteristics in the ML as detected by light microscopy was evaluated: fibrosis, concentric eosinophilic fibroplasia (CEF), regression, desmoplasia, scar, ulceration, parakeratosis, loss of rete ridges, atrophy of the epidermis, pigment incontinence, inflammation, and UV-elastosis. We further specifically studied the following characteristics: presence/loss of EF in fibrosis, presence/loss of EF in the ML, and pushing of the EF. In MM, we also analyzed the proliferation-rate with the immunohistochemical (IHC) stain Ki-67.

The definition of some stroma-characteristics is not universally accepted and different authors may use the same word differently. Here we have used the following definitions:

- *Fibrosis* Zone in the dermis/subcutis characterized by thickened collagen fibers, and with diminution of the space between the collagen fibers, presence of some fibrocytes.
- *Concentric eosinophilic fibroplasia (CEF)* Peculiar pattern of fibrosis in the papillary dermis, which follows the undulation of the epidermal rete ridges, and of the nests of the ML along the junction zone.
- *Regression* As obligatory criteria: lesional loss/absence of melanocytes, presence of lymphocytes, melanophages, and fibrosis; while facultative criteria include loss of rete ridges, and the atrophy of the epidermis.
- *Desmoplasia* Presence of a diffuse car-wheel-pattern of fibrosis within the ML.
- *Scar* Zone in the dermis with a fibrosis characterized by a horizontal alignment of the collagen fibers with verticalized blood vessels.
- Loss of EF in ML:
  - *Complete loss of EF* Loss of > 90% of the EF in > 90% of the ML.
  - *Partial loss of the EF* Loss of > 90% of the EF in 20–90% of the ML.
- *Loss of EF in fibrosis* Loss of > 90% of EF within the zone(s) of fibrosis in the ML.
- *Pushing of the EF* Compression of the EF into the surrounding dermis by the ML resulting in the formation of a layer of thick compacted EF at the periphery (mostly at the base). The latter is most commonly observed in MM as "pushing-down" of the EF from the papillary dermis into the reticular dermis.

Whenever possible, the collagen, the elastic tissue network, and the presence of mucin in skin adjacent to the ML was used as a normal reference.

Statistical analysis

For descriptive purpose, continuous data were presented as means with standard deviations (SD), while categorical variables as numbers with percentages. Continuous variables were also categorized using clinically relevant cut-off points. The association between selected histopathological characteristics and MM, overall and for each sub-type of nevi, was investigated by means of multiple logistic regression models including age and gender as adjustment factors. In case of zero-frequency cells a continuity correction was applied

in the models. The strength of association was expressed in terms of odds ratio (OR) along with its 95% confidence interval (CI) and p value.

In addition, Chi-squared automatic interaction detection (CHAID) was used to build a classification tree which predicts overall MM based on automatically selected features [26]. For the purpose of this method, all variables with p value < 0.15 in the previous analysis were included for evaluation, along with age, gender and localization of lesions. Measures of accuracy, sensitivity and specificity were produced as well. All tests were considered statistically significant at p value < 0.05. Analyses were performed using SPSS v.20.0 (IBM corp., Armonk, NY, US).

Results

The patient demographics and general characteristics are presented in Table 1. We analyzed lesions from 120 patients, 54 men and 66 women; their age was 65.2 ± 15.1 years (mean ± SD) for patients with MM and 41.9 ± 14.8 years for patients with nevi.

The results of 14 histological morphological characteristics analyzed in all nevi ($n = 90$), and MMs ($n = 30$) are summarized in Table 2.

Table 3 shows the same characteristics comparing specifically MMs ($n = 30$), and the dysplastic nevi ($n = 30$).

A similar analysis as in Table 3 was performed also for junctional nevi ($n = 30$), compound/dermal nevi ($n = 30$). Here we summarize only the most significant findings ($p < 0.05$) of these sub-analyses, showing the characteristics favoring the diagnosis of MM versus a nevus (see supplementary material, additional Tables 3a, 3b, 3c):

Junctional nevi Loss of rete ridges ($p = 0.02$), UV-elastosis ($p = 0.003$), loss of EF in fibrosis ($p = 0.03$), loss of EF in ML ($p < 0.001$), mucin in ML ($p = 0.008$).

Compound/dermal nevi Inflammation ($p = 0.01$), pigment incontinence ($p = 0.008$), loss of rete ridges ($p = 0.02$), UV-elastosis ($p = 0.01$), loss of EF in fibrosis ($p = 0.001$), loss of EF in ML ($p = 0.001$), pushing of EF ($p = 0.003$).

In MMs we observed a Breslow-Index: < 0.5 mm in 10 cases (33%), 0.51–1 mm in 13 cases (43.3%), 1.01–2 mm in 3 cases (10%), 2.01–4 mm in 2 cases (6.7%), > 4 mm in 2 cases (6.7%).

In 4 of 17 (23.5%) MM with pushing we found a Breslow-Index of > 1 mm; the majority of MM (76.5%) showing a pushing of the EF were thin MM (Breslow-Index < 1 mm).

In MM we analyzed IHC the proliferation-index (Ki-67), in 7 of 30 (23.3%) MM the proliferation was middle/high, in 16 of 30 (53.3%) MM it was absent/little.

In all cases with a Breslow-Index > 1 mm we found a middle/high proliferation-rate.

We found a middle/high proliferation-index (Ki-67) in 4 of 17 (23.5%) MM with pushing; the majority of MM (76.5%) showing a pushing of the EF had an absent/low proliferation-index. In conclusion, we did not find a correlation between a high proliferation-index and the pushing of the EF.

Figure 1 depicts a classification tree analysis, where the statistically stronger factor of this study (loss of EF in ML) was highly specific (100%) for the detection of MM, with a sensitivity of 76.7% and an overall accuracy of 94.2%.

Table 1 General characteristics of the patients

	Nevi ($N = 90$)		Melanoma ($N = 30$)	
	N^a	%	N^a	%
Age (years)				
Mean, SD	41.9	14.8	65.2	15.1
< 40	45	50.0	2	6.7
40–59	35	38.9	7	23.3
60+	10	11.1	21	70.0
Sex				
Male	38	42.2	16	53.3
Female	52	57.8	14	46.7
Localization				
Head and neck	1	1.1	4	13.3
Arms	4	4.4	6	20.0
Legs	19	21.1	4	13.3
Trunk	61	67.8	16	53.3
Acral	5	5.6	0	0.0

SD standard deviation

[a]Numbers may not add up to the total due to missing data

Discussion

The histopathological differentiation between a melanocytic nevus and a MM is straightforward in the vast majority of cases. However, there are some ML in which this distinction is honestly very difficult or even impossible [1].

There are only few studies which have systematically assessed the diagnostic usefulness of distinct morphological features of the stroma to differentiate a benign ML from MM. Alterations of the EF in ML may provide as yet unrecognized diagnostic clues.

Our retrospective study analyzing 14 distinct histopathologic morphological characteristics in 120 ML identified 9 features which significantly differ between nevi and MM. Specifically, in multivariate analyses the presence of following findings in the ML favored the diagnosis of MM versus nevus: loss of EF in the ML, loss of EF in lesional fibrosis, pushing of the EF, UV-elastosis, loss of rete ridges of the epidermis, regression of the ML, atrophy

Table 2 Histological characteristics of patients with melanoma and nevi

	Nevi (All)		Melanoma		OR (95% CI)[b]	*p*
	N[a]	%	*N*[a]	%		
Fibrosis						
No	26	28.9	3	10.0	1	1
Yes	64	71.1	27	90.0	1.00 (0.23–4.36)	
CEF						
No	43	47.8	22	73.3	1	0.01
Yes	47	52.2	8	26.7	0.23 (0.07–0.75)	
Regression						
No	59	98.3	19	63.3	1	0.008
Yes	1	1.7	11	36.7	24.04 (2.31–249.9)	
Desmoplasia						
No	59	98.3	28	93.3	1	0.42
Yes	1	1.7	2	6.7	3.55 (0.16–76.64)	
Ulceration/erosion						
No	89	98.9	28	93.3	1	0.18
Yes	1	1.1	2	6.7	10.34 (0.34–310.8)	
Parakeratosis						
No	55	61.1	21	70.0	1	0.15
Yes	35	38.9	9	30.0	0.43 (0.14–1.36)	
Lesional inflammation						
No	24	26.7	0	0.0	1	0.30
Yes	66	73.3	30	100.0	2.28 (0.48–10.85)	
Pigment incontinence						
Absent	2	2.2	3	10.0		
Focal	74	82.2	14	46.7	1	
Heavy	14	15.6	13	43.3	5.45 (1.65–17.98)[c]	0.005
Loss of rete ridges						
Intact	87	96.7	13	43.3	1	< 0.001
Loss	3	3.3	17	56.7	28.43 (5.38–150.1)	
Lesional atrophy epidermis						
Intact	90	100.0	21	70.0	1	0.04
Atrophy	0	0.0	9	30.0	7.82 (1.08–56.42)	
UV-elastosis						
No	87	96.7	7	24.1	1	< 0.001
Yes	3	3.3	22	75.9	48.31 (7.75–300.9)	
Loss of EF in fibrosis						
No EF	10	16.7	24	88.9	1	< 0.001
Normal	50	83.3	3	11.1	0.05 (0.01–0.21)	
Loss of EF in ML						
No EF	0	0.0	19	73.1	1	0.003
Partial loss	19	21.1	7	26.9	0.11 (0.02–0.48)	
Normal	64	71.1	0	0.0	0.01 (0.002–0.07)[d]	< 0.001
More EF	7	7.8	0	0.0		
Pushing down phenomenon						
No	60	100.0	8	32.0	1	< 0.001
Yes	0	0.0	17	68.0	48.98 (5.92–405.3)	
MIB-1						
Absent	–	–	2	8.0	–	–
Little	–	–	16	64.0		
Middle	–	–	2	8.0		
High	–	–	5	20.0		

CI confidence interval, *OR* odds ratio, *n.c.* not computable

[a]Numbers may not add up to the total due to missing data or not assessable parameters

[b]Multiple logistic regression models including terms for age and gender. In case of zero-frequency cells a

Table 2 (continued)

continuity correction was applied in the models

[c]Absent and focal pigment incontinence were joined together

[d]Normal and more EF were joined together

of the epidermis, pigment incontinence, and concentric eosinophilic fibroplasia (CEF). In contrast, following features were not helpful distinguishing MM from nevi: fibrosis, desmoplasia, ulceration/erosion, parakeratosis, and inflammation.

When patients were classified based on a regression tree analysis, the presence of "loss of EF in the ML" favored the diagnosis of MM versus nevus in 94.2% of cases, with a sensitivity of 76.7% and a specificity of 100% (Fig. 1).

Here we discuss some findings in order of importance (with decreasing statistical significance):

A complete intralesional loss of EF was found in up to 73% of MMs, but in none of the nevi (Fig. 2). Differently, a partial intralesional loss of EF was found in up to 27% of MMs, and similarly in up to 21% of nevi. 84% of MMs with a complete loss of EF also showed a pushing of the EF. One may assume that the loss of EF is due to a rapid growth of the MM, which pushes aside the EF. However, our results cannot support this hypothesis, because we did not find a significant correlation between pushing of the EF and a high proliferation-index (Ki-67). Moreover the majority of MM (76.5%) showing a pushing of the EF were thin MM (Breslow-Index < 1 mm). There must be another explanation for the pushing-phenomenon, possibly immunologic, responsible for the disappearance of the EF [20]. Further studies are necessary to clear these questions.

Other authors [21, 22] also described "decreased to absent" EF in MM, but did not quantify their findings in comparison to nevi. A previous study showed that a complete loss of EF in MM seems to be an adverse prognostic factor [14].

We observed a slightly increase of the quantity of EF in few nevi, but in none of the MMs. Massi [29] and Kamino [22] indeed described an augmentation of EF in congenital melanocytic nevi, mostly in the periphery of the ML.

Similarly as other authors [20, 22] we observed a "pushing" of EF in MM (68%), but not at all in nevi. Moreover, we saw a "pushing" of the EF in up to 73% of the MMs with regression. Differently, Kamino et al. found a "pushing" in all MMs with regression [21]. It is important to remember that the displacement of EF is common in several other malignant skin tumors as basal cell carcinoma, and squamous cell carcinoma, and is not specific for MM [20].

UV-elastosis was seen in up to 76% of MMs, but significant more rarely in nevi. The exact role of UV damage of the skin in the pathogenesis of MM has been frequently studied and debated among experts [17, 36], nevertheless it is a matter of fact that solar elastosis in the skin is one of the criteria favoring malignancy in the diagnostic procedure of a ML [20, 30, 42].

Loss of rete ridges of the epidermis and lesional atrophy of the epidermis were found in up to 57% and 30% of MM respectively, but both only significant more rarely in all types of nevi. When loss of rete ridges was observed, both fibrosis and dermal inflammation were always present. Lorenzo Cerroni [19] previously advised the importance of these criteria. Subsequent studies demonstrated that MMs with consumption of the epidermis (COE) (combination of thinning of the epidermis and loss of rete ridges) had a 37% increased tumor cell proliferation [7], and an increased Breslow-Index [43], in comparison to MMs with normal epidermis. Moreover similarly as in our study they did not found COE in common nevi, and in only 2.5% of high-grade dysplastic nevi.

Regression is a debated characteristic and unfortunately, its definition and assessment are not standardized, and are subjectively interpreted by different experts [4, 21, 23, 25, 27, 28, 33]. Therefore, its occurrence in published studies may vary from 10 to 35% of cases [6, 8, 11, 35]. We observed a regression significantly more frequent in MM (up to 37%) than in nevi, where we saw it only in one single case. Similarly as previously described [6, 21], we found a regression in MM mostly in men (72.7%), and mainly on the trunk (81.8%).

In > 90% of our cases, regression was seen in thin MMs with a Breslow < 1 mm. The prognostic role of regression, and whereas regression is more frequent in thin or thick MMs, is unanimously debated in the literature [3, 4, 35]. However, in a recent review and meta-analysis the authors found that overall regression in MM was a protective factor for survival [18].

In all MMs, and in 73.3% of nevi we observed an inflammation. However, as previously reported [10, 15, 28, 40], it is important to understand the substantial differences among the different nevi. We observed an inflammation in 40% of compound/dermal nevi, showing a significant difference from MM; and in 83.3% of junctional nevi, and in 96.7% of dysplastic (Clark) nevi, without any significant difference from MM.

Conclusion

We describe nine morphological characteristics with significant differences distinguishing nevi from MM. Especially the loss of EF in the ML, and the "pushing" of the EF, are

Table 3 Histological characteristics of patients with melanoma and dysplastic nevi

	Dysplastic nevi		Melanoma		OR (95% CI)[b]	*p*
	N[a]	%	*N*[a]	%		
Fibrosis						
No	0	0.0	3	10.0	1	0.04
Yes	30	100.0	27	90.0	0.07 (0.005–0.88)	
CEF						
No	5	16.7	22	73.3	1	0.001
Yes	25	83.3	8	26.7	0.08 (0.02–0.34)	
Regression						
No	30	100.0	19	63.3	1	0.07
Yes	0	0.0	11	36.7	7.86 (0.82–75.3)	
Desmoplasia						
No	29	96.7	28	93.3	1	0.71
Yes	1	3.3	2	6.7	1.76 (0.09–34.13)	
Ulceration/erosion						
No	30	100.0	28	93.3	1	0.56
Yes	0	0.0	2	6.7	2.46 (0.11–52.56)	
Parakeratosis						
No	14	46.7	21	70.0	1	0.11
Yes	16	53.3	9	30.0	0.36 (0.10–1.26)	
Inflammation						
No	1	3.3	0	0.0	1	0.98
Yes	29	96.7	30	100.0	0.95 (0.03–32.44)	
Pigment incontinence						
Absent	0	0.0	3	10.0		0.002
Focal	28	93.3	14	46.7	1	
Heavy	2	6.7	13	43.3	31.20 (3.64–267.2)[c]	
Loss of rete ridges						
Intact	28	93.3	13	43.3	1	0.004
Loss	2	6.7	17	56.7	13.10 (2.32–73.86)	
Atrophy epidermis						
Intact	30	100.0	21	70.0	1	0.23
Atrophy	0	0.0	9	30.0	3.60 (0.44–29.31)	
UV-elastosis						
No	28	93.3	7	24.1	1	0.001
Yes	2	6.7	22	75.9	43.02 (4.57–404.6)	
Loss of EF in fibrosis						
No EF	7	23.3	24	88.9	1	< 0.001
Normal	23	76.7	3	11.1	0.06 (0.01–0.29)	
Loss of EF in ML						
No EF	0	0.0	19	73.1	1	0.02
Partial loss	8	26.7	7	26.9	0.12 (0.02–0.71)	
Normal	19	63.3	0	0.0	0.02 (0.003–0.18)[d]	< 0.001
More EF	3	10.0	0	0.0		
Pushing of EF						
No	30	100.0	8	32.0	1	0.004
Yes	0	0.0	17	68.0	23.72 (2.71–207.5)	

CI confidence interval, *OR* odds ratio, *n.c.* not computable

[a]Numbers may not add up to the total due to missing data or not assessable parameters

[b]Multiple logistic regression models including terms for age and gender. In case of zero-frequency cells a continuity correction was applied in the models

[c]Absent and focal pigment incontinence were joined together

[d]Normal and more EF were joined together

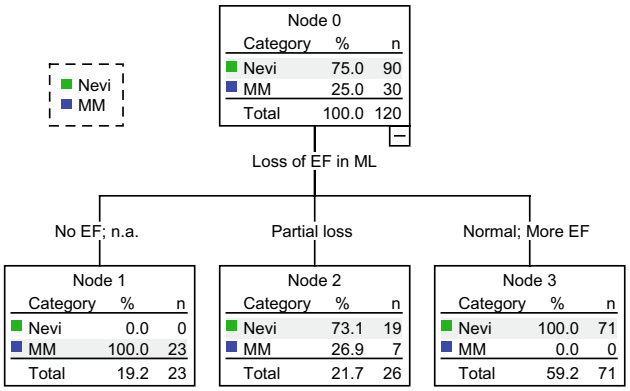

Fig. 1 Classification of patients with melanoma or nevi based on classification tree analysis

associated with MM. Moreover, the assessment of the EF is a rapid, cheap, and easily performed method available in most histopathology laboratories.

Limitations

This was a small, pure retrospective study without any prognostic factor analysis. The interpretation of (some) morphological criteria is subjective.

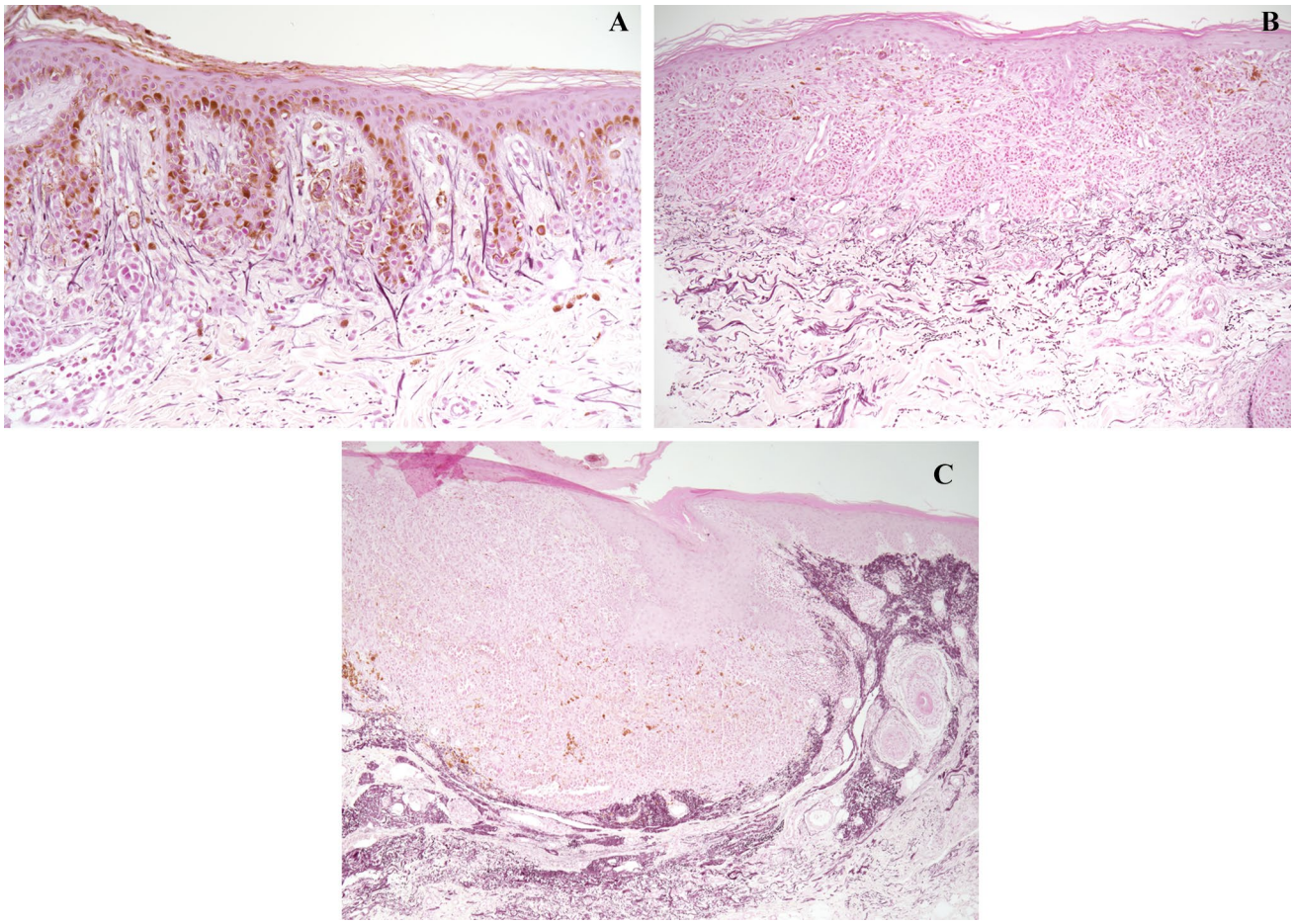

Fig. 2 **a** Melanocytic nevus with normal distribution of the EF within the ML; **b** melanoma with complete loss of the EF within the lesion; **c** melanoma with complete loss of the EF within the lesion, and "pushing" of the EF at the base of the lesion

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Compliance with ethical standards

Ethical approval Reviewed and approved by the ethics committee of the Canton of Bern, Switzerland (KEK-229/14).

Conflict of interest The authors declare that they have no conflict of interest.

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