Dermatology Practical & Conceptual

PRAME Immunohistochemical Expression in Recurrent/Traumatized Melanocytic Nevi and the Pitfall of Expression by Reactive Fibroblasts

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ABSTRACT

Introduction: The recurrent/traumatized melanocytic nevus (RTMN) refers to melanocytic lesions that reappear following incomplete removal or trauma to a previous nevus, often presenting clinically and dermoscopically similar to melanoma, which complicates differential diagnosis. Histologically, RTMN exhibit melanocytic proliferation and scar tissue from prior trauma or excision. PRAME (preferentially expressed antigen in melanoma) immunohistochemistry (IHC) is emerging as a diagnostic tool for distinguishing between nevi, melanoma, and nevus-associated melanomas. However, its role in RTMN has not yet been established.

Objectives: This study aimed to evaluate the expression of PRAME in RTMN, specifically in the melanocytic and fibroblastic components, to explore its potential diagnostic utility.

Methods: A series of 22 RTMN cases from the Pathology Unit of the University of Campania Luigi Vanvitelli Hospital were reviewed. PRAME IHC was performed on formalin-fixed, paraffin-embedded tissue, and staining was evaluated in three compartments: junctional melanocytic, intradermal melanocytic, and fibroblastic scar tissue.

Results: PRAME IHC showed no positivity in the junctional or intradermal melanocytic components of any case. However, five out of 22 cases (22.7%) demonstrated PRAME positivity in the fibroblastic component, which was statistically significant (P=0.0169).

Conclusions: This study suggests that PRAME IHC is negative in the melanocytic components of RTMN, distinguishing it from melanoma. However, PRAME positivity in the fibroblastic scar component warrants careful interpretation to avoid diagnostic pitfalls. These findings emphasize the importance of considering the histological context when using PRAME as a diagnostic marker in RTMN.

Introduction

The recurrent nevus phenomenon describes the reappearance of a melanocytic proliferation at the site of a previously biopsied melanocytic nevus [1]. A closely related entity, the traumatized nevus, refers to a melanocytic lesion that has undergone physical trauma and typically exhibits reparative junctional melanocytic proliferation [2]. Owing to their overlapping histopathological features, these entities are collectively referred to as recurrent/traumatized melanocytic nevi (RTMN).

RTMN represent a significant diagnostic challenge in both clinical and dermoscopic practice due to their potential to mimic melanoma, including melanoma arising in association with a preexisting nevus [3]. Clinically, these lesions often manifest as hyperpigmented or hypopigmented areas with scar-like characteristics and asymmetrical borders [4].

The underlying biological mechanisms driving RTMN development remain poorly elucidated. However, it is postulated that recurrence may result from incomplete excision of the initial nevus, followed by subsequent skin trauma. In particular, shave excisions, frequently performed for aesthetic purposes, have been strongly associated with the emergence of recurrent nevi [5].

Histologically, RTMN may present as a junctional or compound melanocytic proliferation with mild to moderate cytologic atypia. This proliferation is frequently accompanied by dermal fibroblastic proliferation, indicative of scar formation from the prior biopsy, along with a perivascular chronic inflammatory infiltrate composed predominantly of lymphocytes and melanophages, often with melanin pigment deposition [1,6]. These histopathological features can raise concern about malignancy, particularly in the absence of clinical documentation of a previous excision [7]. Notably, intermediate- and late-stage melanomas commonly exhibit features of regression such as fibrosis and neovascularization within the papillary dermis, which may further obscure the distinction between benign reactive changes and malignant transformation.

RTMN are most commonly observed in females between the ages of 20 and 30, with the back being the most frequently affected anatomical site. Recurrence typically occurs within approximately six months following excision of the original nevus. However, there is currently no consensus regarding which specific histological subtype of nevus is most susceptible to recurrence [1,8].

Immunohistochemistry (IHC) for PRAME (preferentially expressed antigen in melanoma) is increasingly recognized as a useful adjunct in the differential diagnosis of melanocytic lesions, particularly in distinguishing between benign nevi, melanoma, and nevus-associated cutaneous melanoma [9-12]. PRAME plays a role in multiple cellular processes, including apoptosis, differentiation, growth regulation, transcriptional control, and ubiquitination. It is expressed in a range of both epithelial and non-epithelial neoplasms and has emerged as a promising target for immunotherapeutic approaches, with ongoing clinical trials investigating its potential applications.

In the context of melanocytic pathology, PRAME immunohistochemistry serves as a valuable diagnostic aid. The identification of a PRAME-positive melanocytic population within a nevus may support a diagnosis of melanoma arising in association with that nevus. However, a negative PRAME result does not definitively exclude melanoma, and interpretation should be integrated with clinical, histological, and additional immunohistochemical findings [13].

Although PRAME IHC holds potential in differentiating RTMN from melanoma, recent evidence indicates that PRAME expression may also be observed in reactive and cicatricial fibroblastic proliferations. This finding underscores a potential limitation in the specificity of PRAME IHC within the context of melanocytic lesions, particularly when evaluating recurrent or traumatized nevi [14,15].

The aim of this study was to evaluate a series of RTMN cases to assess PRAME expression in both melanocytic and fibroblastic cell populations, with the goal of elucidating PRAME's potential diagnostic utility in this specific histopathological context.

Methods and Materials

Case Selection

All cases included in this study were retrospectively selected from the archives of the Pathology Unit at the University Hospital of Campania Luigi Vanvitelli in Naples, Italy, covering the period from January 2019 to November 2024.

The inclusion criteria were: i) diagnosis of recurrent melanocytic nevus or traumatized melanocytic nevus; ii) formalin-fixed and paraffin-embedded (FFPE) tissue blocks and histological slides available; iii) histological evidence of fibroblastic proliferation.

Twenty-two cases satisfied the criteria. All the cases were reviewed by two experienced dermatopathologists and evaluated in their appropriate clinical setting. The diagnosis was confirmed in all cases.

PRAME Immunohistochemistry

Immunohistochemical staining was performed on 5 µm-thick sections obtained from formalin-fixed, paraffin-embedded (FFPE) tissue blocks using the automated Ventana BenchMark ULTRA system (Ventana-Roche Diagnostics, Meylan, France), according to the manufacturer's protocol. The antibody employed was anti-PRAME (rabbit monoclonal antibody, clone EPR20330, Ventana-Roche), provided in a prediluted, ready-to-use format with a standardized concentration. Sebaceous glands served as internal positive controls.

PRAME immunoreactivity was independently evaluated by two experienced pathologists. Assessment focused on three distinct compartments: the junctional (recurrent/proliferative) melanocytic component, the intradermal (mature) melanocytic component, and the scar-associated fibroblastic component. Nuclear staining was considered positive when more than 50% of the cells in a given compartment exhibited immunoreactivity, irrespective of staining intensity, in accordance with previously established criteria [16].

Statistical Analysis

To calculate the statistical significance of fibroblast positivity for the marker, a two-tailed binomial test was applied, assuming that the proportion of positive fibroblasts deviates significantly from a random distribution with a probability of 50% (P=0.5). The test considered both the exact probability of observing five positive cases out of 22 samples and the cumulative probability. Specifically, the probability of observing exactly five successes was calculated using the binomial distribution formula:

$$P = (X = k) = (n\ k) \cdot p^k \cdot (1 - p)^{n-k}$$

where $(n\ k)$ is the binomial coefficient.

Then, cumulative probability for values P(X≤5) and P(X≥5) was included to account for all outcomes as extreme as five observed successes. We applied the following formulas:

$$P(X \leq k) = \sum_{i=k}^{k} P(x = i)$$

$$P(X \geq k) = \sum_{i=0}^{k} P(x = i)$$

The p-value for the two-tailed test was calculated as:

$$p = 2 \cdot (P(X \leq k), P\ (x \geq k))$$

The significance threshold was set at α=0.05.

Furthermore, we analyzed potential correlations between age, sex, and anatomical site. Age was analyzed as a continuous variable using Spearman's rank correlation. The association between sex and fibroblast positivity was evaluated using Fisher's exact test, and the association with anatomical site was tested using the Chi-squared test.

Ethical Statement

This study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Ethics Committee of University "Luigi Vanvitelli" (Naples, Italy) (protocol code 282/202, approval date 6 October 2020). Informed consent was obtained from all subjects involved in the study.

Results

The study cohort comprised 22 patients, including eight females (36%) and 14 males (64%), with ages ranging from 14 to 71 years (median age: 36 years). Of the 22 cases, 16 (72.7%) were diagnosed with traumatized melanocytic nevi, while six (27.3%) were classified as recurrent melanocytic nevi. Among the recurrent cases, five had a documented history of prior shave excision, whereas one had undergone a punch biopsy. Anatomical distribution of the lesions was as follows: the dorsal region in eight cases (36.4%), the lower limbs in five cases (22.7%), the lumbar region in three cases (13.6%), the shoulder in two cases (9.1%), the gluteal region in two cases (9.1%), the chest in one case (4.5%), and the abdominal region in one case (4.).

The clinical findings of the series are detailed in Table 1.

The histological findings of an exemplary case of RTMN are shown in Figure 1.

PRAME immunohistochemistry was negative in both the junctional and intradermal melanocytic components across all 22 cases (0%). However, PRAME positivity was observed in the fibroblastic component in five cases (22.7%). The results are summarized in Table 2.

Fibroblast positivity was observed in five out of 22 cases. The probability of observing exactly five successes under the null hypothesis P(X=5) was 0.00628. The cumulative probability for P(X≤5) was 0.008450, while P(X≥5) was 0.997. Applying the two-tailed binomial test, the overall p-value was computed as:

$$p = 2 \cdot (P(X \leq 5), P\ (x \geq 5)) = 0.0169$$

Table 1. Clinical Findings.

N.	Age	Location	Recurrent or traumatized melanocytic nevus	Phototype
1	27	Dorsal	Traumatized	II
2	36	Right leg	Traumatized	IV
3	17	Abdominal	Traumatized	III
4	28	Lumbar	Traumatized	II
5	34	Dorsal	Traumatized	III
6	22	Dorsal	Traumatized	III
7	49	Gluteal	Traumatized	III
8	34	Dorsal	Traumatized	III
9	40	Dorsal	Traumatized	III
10	14	Dorsal	Recurrent (previous shaving biopsy)	IV
11	41	Dorsal	Traumatized	III
12	22	Dorsal	Traumatized	II
13	28	Chest	Recurrent (previous shaving biopsy)	II
14	42	Gluteal	Recurrent (previous shaving biopsy)	III
15	41	Left shoulder	Traumatized	II
16	43	Lumbar	Traumatized	II
17	32	Right shoulder	Traumatized	III
18	35	Right leg	Recurrent (previous punch biopsy)	III
19	58	Right thigh	Traumatized	III
20	71	Right leg	Traumatized	II
21	46	Left thigh	Recurrent (previous shaving biopsy)	III
22	48	Lumbar	Recurrent (previous shaving biopsy)	II

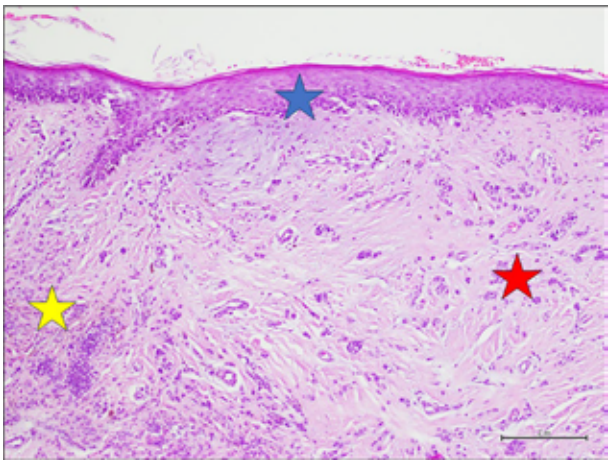

Figure 1. A traumatized nevus localized on the back of a 41-year-old female. Histological analysis revealed a compound melanocytic proliferation. The junctional component was characterized by large melanocytes arranged in small nests, exhibiting a lentiginous pattern (blue star). The dermal component consisted of mature, small melanocytes organized in extensive sheets (yellow star). A fibrous scar was present between the two components (red star) (hematoxylin and eosin stain, original magnification 100x).

Since the p-value (0.0169) is below the pre-defined significance threshold (α=0.05), we conclude that the probability of obtaining exactly five successes is very low under the null hypothesis, and it is not random but is instead statistically significant.

Table 2. PRAME Immunohistochemical Results in the Three Different Components.

Component	PRAME IHC positivity
Junctional	0/22 (0%)
Intradermal	0/22 (0%)
Fibroblastic	5/22 (22.7%)

Finally, we conducted exploratory correlative analyses to assess potential associations between PRAME fibroblast positivity and patient-related variables, including age (Spearman's rank correlation = 0.385, *P*=0.077), sex (Fisher's exact test, yielding an odds ratio of 1.05 with *P*=1.000), and anatomical site (Chi-squared test $\chi^2 = 6.39$, *P*=0.381). No statistically significant correlations was found in our dataset, although the observed trend with age may merit further exploration in larger cohorts.

Focal PRAME positivity, defined as staining in fewer than 50% of cells and thus considered negative, was observed in the junctional melanocytic component in six/ 22 cases (27.3%), in the intradermal melanocytic component in two/ 22 cases (9.1%), and in the fibroblastic population in 1/ 22 cases (4.5%).

Some examples are shown in Figures 2 and 3. Clinical and dermoscopical features of fibroblast-positive cases are shown in Figure 4.

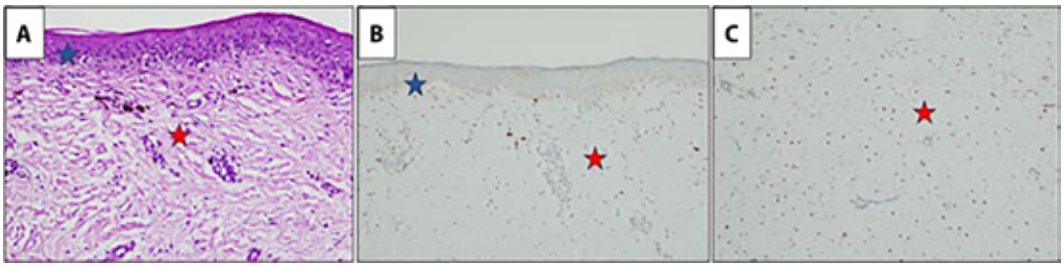

Figure 2. Epigastric region, 48-year-old male. A) Junctional melanocytic proliferation was observed, organized into small nests and exhibiting a lentiginous pattern (blue star). The dermis displayed features of fibrosis, the presence of small vessels, fibroblastic proliferation, and an accumulation of melanophages (red star) (hematoxylin and eosin stain, original magnification 200x). B) PRAME immunohistochemistry resulted negative in the junctional melanocytes (blue star) and positive in the dermal fibroblasts (red star) (PRAME immunohistochemical stain, original magnification 200x). C) PRAME-positive dermal fibroblasts (red star) (PRAME immunohistochemical stain, original magnification 200x).

Discussion

Recurrent/traumatized melanocytic nevi (RTMN) are lesions characterized by the regrowth of residual melanocytes following incomplete excision or trauma to a preexisting nevus. RTMN are relatively common, with reported recurrence rates ranging from 5% to 10% in dermatology settings where nevi are frequently removed [13,17]. These lesions predominantly affect females in their second and third decades of life, with the back being the most commonly involved anatomical site. Recurrences typically manifest approximately six months post-excision, although consensus is lacking regarding which specific nevus subtype is most susceptible to recurrence [1,18].

RTMN often exhibit morphological characteristics that closely resemble melanoma, creating significant challenges in differential diagnosis at clinical, dermoscopic, and histopathological levels. While a history of prior trauma or incomplete removal can aid diagnostic suspicion, this information is not always available, as patients may be unaware of or unable to recall such events.

Clinically and dermoscopically, RTMN frequently display symmetry alongside irregular pigmentation, making them among the benign lesions that often exhibit dermoscopic features suggestive of malignancy [19]. Histologically, RTMN can be conceptualized as comprising three distinct components: i) a superficial/junctional melanocytic component representing the proliferative portion of the lesion; ii) a dermal melanocytic component corresponding to the residual pre-existing nevus; and iii) an intermediate component characterized by cicatricial fibroblastic proliferation and, occasionally, a chronic inflammatory infiltrate, reflecting the scar tissue resulting from trauma or excision.

From a diagnostic perspective, the superficial/junctional melanocytic component is of paramount importance, as it may display atypical morphological features that mimic melanoma in situ. These features include thickened and irregular rete ridges, mildly disorganized basal melanocytes, and subtle nuclear enlargement or hyperchromasia. Although pagetoid spread, and peri-adnexal dermal extension are uncommon, they can occasionally be observed [5]. The primary differential diagnosis is superficial spreading melanoma arising within a pre-existing nevus (nevus-associated melanoma). Accurate differentiation can be challenging and necessitates comprehensive integration of clinical, dermoscopic, and histopathological data.

PRAME (preferentially expressed antigen in melanoma) is a cancer-testis antigen expressed by melanoma and various other malignant neoplasms; it has recently emerged as a valuable marker in the differential diagnosis of melanocytic lesions. Immunohistochemical detection of PRAME has demonstrated significant differential expression patterns between melanoma and benign nevi [10,12,20]. Notably, prior studies have indicated that PRAME IHC is particularly useful in diagnosing nevus-associated melanoma, showing positivity in melanoma cells while remaining negative in benign nevus cells [13,21]. Consequently, PRAME may serve as a helpful diagnostic tool in evaluating RTMN, given that the primary differential diagnosis often involves nevus-associated melanoma. However, the presence of fibroblastic proliferation within RTMN can pose a diagnostic challenge, as emerging evidence has documented PRAME expression in reactive fibroblasts and scar tissue [14,15].

In this study, we evaluated PRAME immunohistochemical expression in a series of 22 RTMN cases, examining three distinct lesion components: superficial/junctional melanocytic proliferation, the intradermal nevus component, and fibroblastic proliferation associated with scar tissue. Notably, none of the cases demonstrated PRAME positivity in the junctional component. While the limited sample size represents a study limitation and constrains the generalizability of these findings, this observation remains clinically significant, given that the principal differential diagnosis for RTMN is melanoma arising from a pre-existing nevus.

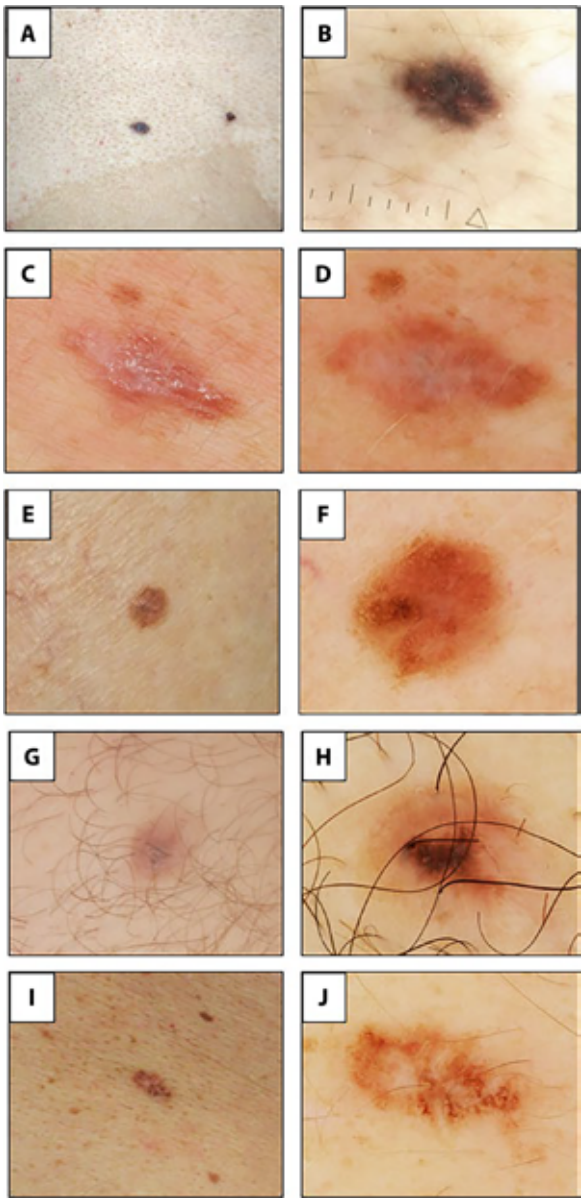

Figure 4: Clinical and dermoscopical features of fibroblast-positive cases. Case 1: 22-year-old male with a traumatized melanocytic nevus on the back. A) Clinical image: pigmented, asymmetric nevus with a slightly raised central area. B) Dermoscopy: asymmetric lesion with irregularly distributed hyperpigmented blotches and structureless brown areas. Case 2: 43-year-old female with a traumatized melanocytic nevus on the back. C) Clinical image: pinkish-brown lesion with dome shaped distributed areas and irregular borders. D) Dermoscopy: asymmetric structureless brown pigmentation with whitish-grey central area and crystalline structures. Case 3: 71-year-old female with a traumatized melanocytic nevus on the right leg. E) clinical image: brown macule with focally hyperpigmented central area. F) Dermoscopy: patchy reticular network with focal area of irregular hyperpigmented network. Case 4: 46-year-old male with a recurrent melanocytic nevus on the left thigh. G) Clinical image: pigmented lesion arising within a hypopigmented scar, with blurred and asymmetric borders. H) Dermoscopy: reticular and structureless pigmentation with radial streaming and central scar-like depigmentation. Case 5: 48-year-old male with a recurrent melanocytic nevus on the back. I) Clinical image: brown macule with irregular pigmentation located within a surgical scar, with blurred borders. J) Dermoscopy: brown structureless areas, atypical pigment network and crystalline structures.

PRAME IHC has proven valuable in this diagnostic setting, as prior studies have established its positivity in melanomas developing from nevi [13,21]. Our results, however, indicate that PRAME is consistently negative in the junctional component of RTMN.

The presence of cicatricial fibroblastic proliferation within RTMN introduces a potential diagnostic pitfall when interpreting PRAME staining. Indeed, several reports have documented PRAME expression in benign fibroblasts and scar tissue [14]. Specifically, Plotzke et al. found that 24% of scars exhibited diffuse and strong PRAME expression comparable to that seen in desmoplastic melanoma [15]. In their cohort, PRAME positivity exceeding 50% of fibroblasts was observed in 11 of 21 (52.4%) scar cases. In contrast, our study identified PRAME positivity above this threshold in the fibroblastic population in five of the 22 cases (22.7%). It is important to highlight that our analysis focused on fibroblastic proliferations within RTMN lesions rather than on simple scar tissue.

We found that PRAME expression in the fibroblastic proliferation of RTMN was statistically significant (P=0.0169). Histologically, these cases exhibited a population of PRAME-positive spindle-shaped cells within the dermis, embedded in a fibrotic stromal background. Careful morphological assessment using hematoxylin and eosin-stained sections is essential to accurately distinguish these PRAME-positive fibroblasts from melanocytes, thereby preventing potential diagnostic confusion. Distinguishing fibroblasts from spindle-shaped melanocytes in desmoplastic melanoma can be challenging due to their similar morphology, especially under routine histological examination. However, several key histological and immunohistochemical features help guide the differential diagnosis. Histologically, fibroblasts typically display small, uniform, elongated or oval nuclei with fine chromatin and inconspicuous nucleoli. Their cytoplasm is scant and often not easily visible. They tend to align in an orderly fashion along collagen bundles, showing a non-infiltrative, reactive pattern. Mitotic figures are usually absent or very rare. In contrast, spindle-shaped melanocytes in melanoma often have larger, more pleomorphic and hyperchromatic nuclei, frequently with prominent nucleoli [22-23]. These cells may show a more abundant eosinophilic cytoplasm and are arranged in a disorganized, infiltrative pattern. Atypical mitoses may be observed, and there is often evidence of invasion into surrounding structures, such as adnexal elements, nerves, or blood vessels. Immunohistochemistry is crucial to making a definitive distinction. Melanocytic cells in desmoplastic melanoma are typically positive for S100 protein and SOX10, both of which are highly sensitive markers. HMB45 and Melan-A are often negative in desmoplastic variants but may be expressed in other melanoma subtypes. In contrast, fibroblasts

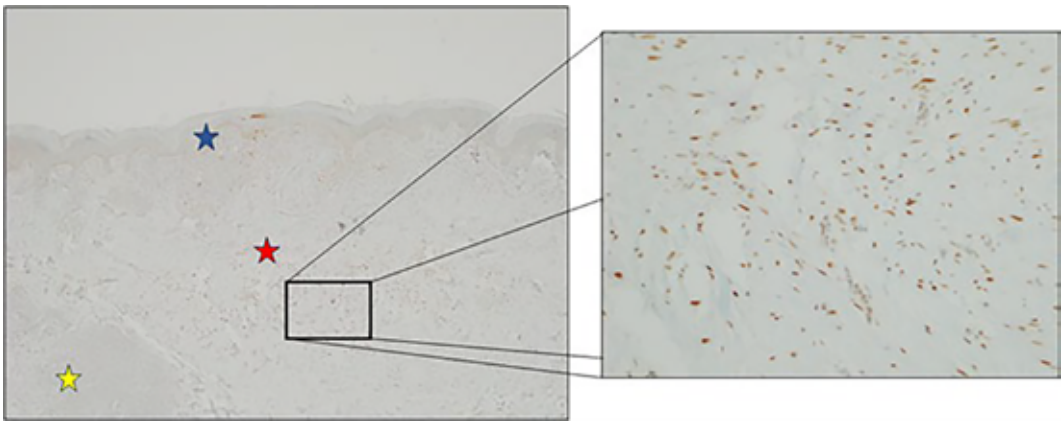

Figure 3. Left leg, 45-year-old male. PRAME immunohistochemistry was negative in both junctional (blue star) and dermal (yellow star) melanocytes, while it was positive in the dermal scar (indicated by the red star and the enlargement on the right).

are usually negative for melanocytic markers such as S100 and SOX10, but they may express CD34, which is helpful in identifying dermal fibroblastic populations. Vimentin is positive in both cell types and is therefore not diagnostically useful on its own. Clinical context also plays a significant role: the presence of a previous pigmented lesion or ulceration may point towards melanoma, especially if spindle cells are S100- and SOX10-positive in a desmoplastic stroma. On the other hand, spindle cells that are negative for melanocytic markers and positive for CD34 are more likely to represent reactive fibroblasts in a scar.

The main limitation of this study is its sample size. However, this is the first study to evaluate the role of PRAME in the diagnosis of RTMN.

Conclusions

In conclusion, our evaluation of PRAME expression in a series of RTMN highlights its potential diagnostic utility. PRAME was consistently negative in both the junctional and intradermal melanocytic components across all cases, contrasting with its established positivity in melanoma arising from a nevus and thereby reinforcing its role in differential diagnosis. Conversely, PRAME expression was significantly detected in the reactive fibroblasts within the scar component. This finding is critical for pathologists to recognize, as it may help prevent misinterpretation of PRAME positivity as melanocytic in origin.

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