Research Article ISSN: 2836-3647

American Journal of Pathology & Research

PRAME Immunohistochemistry Differentiates Severely Dysplastic Nevus from Melanoma In Situ

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Received: 24 Jun 2023; **Accepted:** 01 Aug 2024; **Published:** 10 Aug 2024

Citation: Kelsey Mills, Jordan Farnham, Jeminat Braimoh, et al. PRAME Immunohistochemistry Differentiates Severely Dysplastic Nevus from Melanoma In Situ. American J Pathol Res. 2024; 3(1): 1-4.

ABSTRACT

In epithelial-lined organs, severe dysplasia equates with carcinoma in situ. In melanocytic lesions, some authors and pathologists distinguish severe dysplasia from melanoma in situ. Treatment strategies and prognostic implications differ for these lesions. While histologic features are useful in differentiating these neoplasms, this study evaluated PRAME immunohistochemistry in severely dysplastic nevus and melanoma in situ to determine if this new immunohistochemical marker is helpful in this context. Results showed that melanoma in situ and severely dysplastic nevus differ with regard to PRAME immunoreactivity which can help distinguish these lesions along with histologic features. While larger samples and prospective follow-up are ideal, it appears that use of PRAME immunohistochemistry will help pathologists differentiate these two lesions and ensure dermatologists treat each appropriately.

Keywords

Dysplastic nevus, Melanoma in situ, PRAME immunohistochemistry.

Introduction

In epithelial-lined organs, severe dysplasia, such as severe squamous dysplasia and high grade glandular dysplasia, equates with squamous and glandular carcinoma in situ. In melanocytic lesions, it is common for many authors and pathologists to distinguish severe dysplasia from melanoma in situ [1,2]. Treatment strategies and prognostic implications differ for these lesions [3]. While histologic features are useful in differentiating these neoplasms, we evaluated Preferentially Expressed Antigen in Melanoma(PRAME) immunohistochemistry in severely dysplastic nevus and melanoma in situ to determine if this new immunohistochemical marker is helpful in this context. Cases previously reported from 2019-2024 by consultant histopathologists with a diagnosis of severely dysplastic nevus or melanoma in situ had PRAME immunohistochemistry applied. Cases were blindly reviewed by consultant pathologists and graded for PRAME immunoreactivity as showing 1+ staining (<or= to 10%) of cells showing nuclear staining, 2+ (25 to 70% staining) and 3+ (>or= 90% staining). Cases were then separated by diagnosis of severely dysplastic nevi and melanoma in situ. Fifteen cases of severely

dysplastic nevus and 15 cases of melanoma in situ were stained with PRAME immunohistochemistry. PRAME was positive in only <=10% of lesional cells (1+ staining) in 87% of severely dysplastic nevi. In contrast, 87% of melanoma in situ cases were PRAME positive in >= 90% of lesional cells (3+ staining). One case of severely dysplastic nevus showed 3+ staining with PRAME, and one, 2+ staining (immunoreactivity in approximately 70% of lesional cells).

Methods

Forty cases were identified via CoPath laboratory information archive for report completeness audit and 30 of these were reported as either severly dysplastic nevus (n=15), defined as showing atypical melanocytes 3x the size of basal keratinocytes, or melanoma in situ (n=15), defined as showing atypical melanocytes with full thickness upward migration. Cases had been previously reported from 2019-2024 by consultant histopathologists following review of hematoxylin and eosin-stained sections and immunohistochemistry with melan A and HMB-45. PRAME was also applied.

Cases were blindly reviewed by consultant pathologists and graded for PRAME immunoreactivity as showing 1+ staining (<or= to 10%) of cells showing nuclear staining, 2+ (25 to 70% staining) and 3+ (>or= 90% staining). Cases were then separated by diagnosis of severely dysplastic nevi and melanoma in situ.

Results and Discussion

Fifteen cases of melanoma in situ and 15 cases of severely dysplastic nevus were stained with PRAME immunohistochemistry. PRAME was positive in 13/15 or 87% of melanoma in situ cases in >= 90% of lesional cells showing strong nuclear staining (3+; Figure 1). In contrast, only <=10% of lesional cells, 1+ staining, was seen in 13/15 or 87% of severely dysplastic nevi (Figure 2). One case of severely dysplastic nevus showed 3+ and one 2+ staining with PRAME.

In epithelial-lined organs, severe dysplasia equates with carcinoma in situ. In melanocytic lesions, authors and pathologists typically recognise severely dysplastic nevus and melanoma in situ as distinct entities [1,2]. This can be confusing for clinicians and pathologists alike and treatment strategies and prognostic implications differ for dysplastic nevi and melanoma in situ [3]. In a previous study [4], it was identified that histologic features are useful in differentiating these neoplasms. Blindly PRAME immunohistochemistry was evaluated in severely dysplastic nevus and melanoma in situ to determine if this new immunohistochemical marker might be helpful in this context.

PRAME has emerged as a significant marker for melanoma as it is significantly overexpressed in both primary and metastatic melanomas. It's utility as a diagnostic marker to help distinguish melanoma from benign melanocytic lesions has been well documented [5-7]. PRAME is also expressed in melanoma in situ, making it valuable for diagnosing early-stage melanoma.

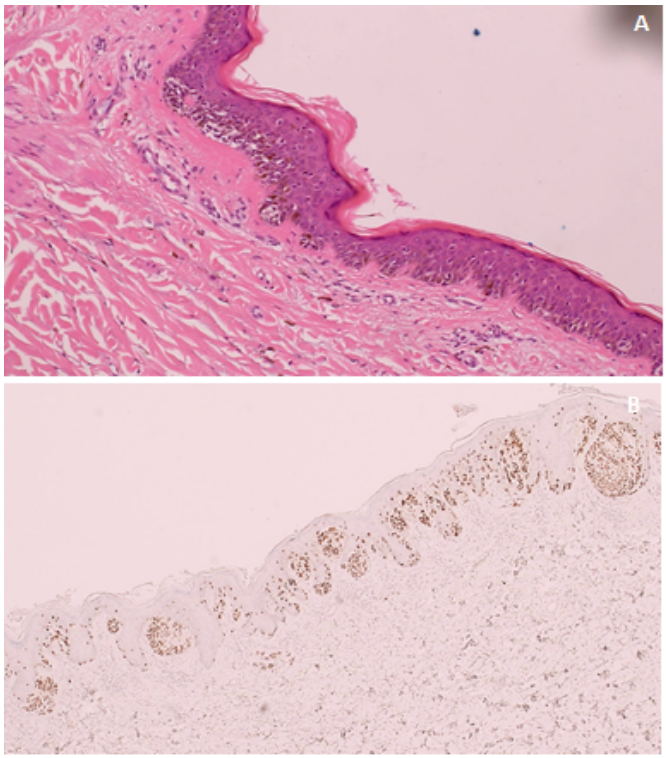
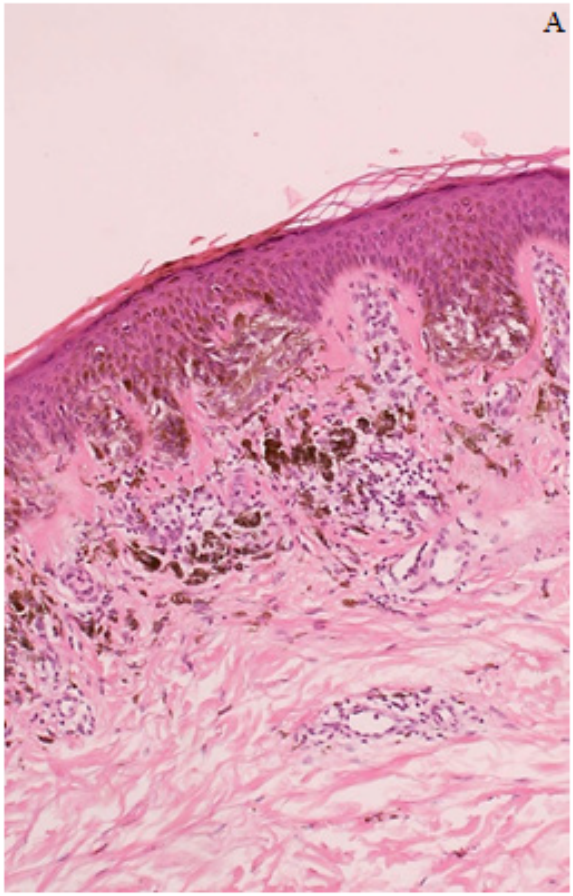


Figure 1: Melanoma in situ; a) H and E and b) PRAME (>or=90% staining, 86% of cases), medium and low power.



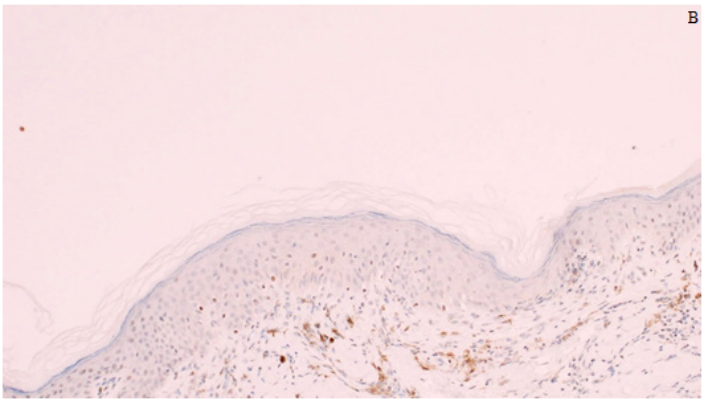


Figure 2: Severely dysplastic nevus; a) H and E and b) PRAME (<or=10% staining, 86% of cases), medium and low power.

In a 2018 study, the immunohistochemical expression of PRAME in 400 melanocytic tumors were examined, including 155 primary and 100 metastatic melanomas, and 145 melanocytic nevi. PRAME showed diffuse nuclear immunoreactivity in 87% of metastatic and 83.2% of primary melanomas. Specific subtypes showed high PRAME expression: acral melanomas (94.4%), superficial spreading melanomas (92.5%), nodular melanomas (90%), lentigo maligna melanomas (88.6%), and desmoplastic melanomas (35%). Both in situ and nondesmoplastic invasive melanoma components showed PRAME expression, while 86.4% of the 140 cutaneous melanocytic nevi were PRAME-negative [5]. A more recent study in 2023 was conducted to assess PRAME and p16 staining in melanocytic nevi and malignant melanoma. The study showed that 'most malignant melanomas showed positive/diffuse PRAME expression (89.6%); on the other hand, 96.1% of nevi did not express PRAME diffusely' [6]. The study indicated high specificity and sensitivity within the biomarker, 'PRAME had a sensitivity and specificity of 89.6% and 96.1%, respectively, for melanomas versus nevi. Also, a PRAME+/p16- melanocytic lesion is unlikely to be a nevus where most nevi were PRAME-/p16+'. This further confirmed PRAME's potential in distinguishing melanocytic nevi from malignant melanomas. In a study of 259 tumours: 141 benign, 31 dysplastic (pre-cancerous), and 87 malignant melanomas using PRAME and HMB-45, Rasic et al. found PRAME was strongly positive in most melanomas but only rarely in benign tumours. HMB-45 was less reliable. When both markers showed strong positive results, it was very unlikely to be a benign lesion [8]. Chen et al. [9], found that 98% of benign nevi didn't show PRAME, while a high percentage of melanomas did: 90% of primary and 93% of metastatic melanomas were PRAME-positive. The marker was found in all superficial spreading melanomas and melanomas from congenital nevi, most other melanoma types, but not in desmoplastic melanomas or the majority of clear cell sarcomas (melanoma of soft parts). It should be noted that PRAME can be expressed in non-melanocytic neoplasms such as breast carcinoma, non-small cell lung cancer, renal cell carcinoma, ovarian carcinoma, leukaemia, synovial sarcoma and myxoid liposarcoma [10].

While PRAME immunohistochemistry appears useful in helping to distinguish severely dysplastic nevi from melanoma in situ, challenges occur when severely dysplastic nevi show increased PRAME immunoreactivity in the 2+ or 3+ range, for example, 70% -90% staining of lesional cells. In these instances, we recommend reliance on light microscopic histologic features to help differentiate these lesions, including lesion symmetry, appearance of rete ridges, presence of lentiginous growth, pagetoid spread, pattern of fibroplasia and presence of large atypical melanocytes with 'cherry-red' nucleoli [4]. Future studies with larger sample sizes and the gamut of mildly, moderately and severely dysplastic melanocytic nevi will further assess and document the utility of PRAME immunohistochemistry in these challenging pathologic lesions.

Conclusion

Our study demonstrates that melanoma in situ and severely dysplastic nevi exhibit distinct differences in PRAME immunoreactivity, providing a valuable diagnostic tool to differentiate between these lesions alongside histologic features. Although larger sample sizes and prospective follow-up studies are necessary for further validation, our findings suggest that PRAME immunohistochemistry will aid pathologists in accurately distinguishing these lesions, thereby enabling dermatologists to administer appropriate treatments.

Acknowledgements

Linda Bredin, Laboratory Scientist, Sligo University Hospital for her assistance in performing immunohistochemistry.

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