Preferentially Expressed Antigen in Melanoma in Skin Cancer

Subjects: Dermatology

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Preferentially Expressed Antigen in Melanoma (PRAME), a member of the cancer/testis antigen family, is central to the field of skin cancer diagnostics and therapeutics. As a nuclear receptor and transcriptional regulator, PRAME plays a critical role in inhibiting retinoic acid signalling, which is essential for cell differentiation and proliferation. Its aberrant overexpression in various malignancies, particularly cutaneous melanoma, is associated with more aggressive tumour phenotypes, positioning PRAME as both a diagnostic and prognostic marker. In melanoma, PRAME is typically highly expressed, in contrast to its weak or absent expression in benign nevi, thereby improving the accuracy of differential diagnoses. The diagnostic value of PRAME extends to various lesions. It is significantly expressed in uveal melanoma, correlating to an increased risk of metastasis. In acral melanomas, especially those with histopathological ambiguity, PRAME helps to improve diagnostic accuracy.

Keywords: PRAME ; melanoma ; NMSC ; Spitz tumour ; uveal melanoma ; mucosal melanoma ; acral melanoma ; soft tissue tumour

1. Preferentially Expressed Antigen in Melanoma Expression in Melanocytic Lesions

Preferentially expressed Antigen in Melanoma (PRAME) has proven to be a valuable tool for the accurate diagnosis of melanocytic tumours, due to its unique expression pattern, and a useful marker in the differential diagnosis between malignant melanoma and other melanocytic lesions [1]. It is known that PRAME expression in benign nevi is absent or weakly stained, whereas melanomas often have a strong PRAME expression [1]. In this regard, several studies have identified PRAME as a marker of primary and metastatic melanomas with high sensitivity (>90%) and specificity in the context of melanocytic lesions [2]. In cases of metastatic melanomas, PRAME expression may also help to distinguish lymph node melanoma metastases from benign melanocytic deposits in the lymph nodes, termed nodal nevi [3]. Hence, when dealing with a metastatic disease, relying solely on PRAME expression for diagnosing melanoma is insufficient, and confirmation through supplementary immunohistochemical or molecular analyses is essential. Nevertheless, the assessment of PRAME in metastatic melanoma goes beyond diagnostic significance, potentially holding prognostic value and serving as a prospective target for immunotherapy [4]. Regarding mucosal melanocytic lesions, which are less common than cutaneous ones, several studies have focused on detecting the presence of PRAME within these lesions to assess their applicability [1]. A study by Ricci et al. found that most benign melanocytic lesions of the mucosa of the head and neck do not show positive immunostaining for PRAME. However, a minority of cases show rare positive cells scattered in the lesion without significant changes in the expression intensity or location [5]. On the other hand, a study by Toyama et al. reported that most mucosal melanomas express PRAME and a high PRAME expression correlates with a poor prognosis. Furthermore, despite the association between increased PRAME expression, the presence of pathogenic NRAS mutations, and a worse prognosis in mucosal melanomas, PRAME expression does not appear to correlate with the presence of NRAS mutations, suggesting that although both factors taken individually may be associated with worse outcomes, they may act independently in the context of mucosal melanomas [6]. Raghavan and colleagues identified that the optimal threshold for differentiating benign from malignant tumours is 60% PRAME-positive cells. This threshold, included in the scoring system devised by the author, has been shown to be effective in distinguishing between mucosal melanomas and benign melanocytic lesions in the head and neck region. In conclusion, PRAME is more commonly expressed in malignant mucosal melanocytic lesions and its increased expression is associated with a poor prognosis. This factor appears to be a prognostic indicator independent of other factors, such as NRAS mutations, and its expression does not appear to correlate with the specific location of a malignant mucosal lesion [1][5][6]. PRAME expression is highly sensitive and specific in the context of acral melanomas and is a more predictive diagnostic tool than p16 immunohistochemistry. Acral dysplastic nevi and acral Spitz nevi may show significant architectural and cellular atypia (a

large nuclear size, irregularly shaped nuclei, hyperchromatic nuclei, or prominent nucleoli), which makes them difficult to distinguish from acral melanoma. The study by Jeffrey D. McBride et al. shows that all compounds, dysplastic and Spitz nevi, were negative for PRAME expression. All melanomas showed PRAME 4+ expression. In acral melanomas, PRAME was 4+ positive in a wide range of Breslow thicknesses, from thin melanomas (Breslow 0.4 mm) to thick melanomas (Breslow at least 13 mm) [7]. In thicker melanomas, however, there was regional variation in the intensity of the nuclear expression of PRAME, equalling 4+ PRAME. According to this research, in cases with 1+ to 3+ staining, additional ancillary tests may be important, depending on the associated clinicopathological features. The results give further confidence in the use of PRAME immunohistochemical staining in the evaluation of melanocytic malignancies. According to the literature, especially in acral melanomas characterised by doubtful or misleading histopathological features, PRAME assumes an important role as an immunohistochemical marker that, although not capable of confirming the diagnosis, is able to support the histological diagnosis [8]. PRAME is an intriguing biomarker and a potential therapeutic target in the field of ocular melanomas, particularly uveal and conjunctival melanomas.[4,5] Understanding its role and implications in these diseases requires a deeper understanding of the molecular biology of melanomas, the specific features of uveal and conjunctival melanomas, and emerging therapeutic strategies targeting PRAME [9][10]. Uveal melanoma originates from melanocytes of the uvea, which includes the iris, ciliary body, and choroid. It differs from cutaneous melanoma in genetics, behaviour, and response to treatment. Unlike cutaneous melanoma, which often involves mutations in the BRAF gene, uveal melanoma commonly has mutations in the GNAQ and GNA11 genes [10]. The overexpression of PRAME in uveal melanoma has been linked to a worse prognosis and an increased risk of metastasis, particularly in the liver [11]. Conjunctival melanoma, although rarer than uveal melanoma, is equally serious and arises from the conjunctiva covering the white part of the eye and inner eyelids. It shares some histopathological features with uveal and cutaneous melanomas [12]. The role of PRAME in conjunctival melanoma is less well known, but is being explored as a potential biomarker for early diagnosis and prognosis [13]. The overexpression of PRAME in melanomas represents a significant opportunity for cancer immunotherapy. Strategies to exploit this target include cancer vaccines, which stimulate the immune system to recognise and attack PRAME-expressing tumour cells, using PRAME peptides to elicit a more targeted and robust anti-tumour response [14]. Furthermore, it is believed that the integration of checkpoint inhibitors with PRAME-targeted therapies could potentially enhance the immune system's response to the tumour [15]. This synergy could be due to PRAME's influence on the tumour's immune environment, suggesting a holistic approach to enhance the body's natural defence against cancer [16]. The role of PRAME in ocular melanomas and its potential as a therapeutic target represent interesting opportunities. However, challenges remain. The variability of PRAME expression among different tumours, the understanding of its precise role in tumour biology, and the optimisation of immunotherapeutic strategies to target PRAME are areas of active research [17]. Future studies focusing on molecular pathways involving PRAME and clinical trials exploring PRAME-targeted therapies will shed more light on its potential in the management of uveal and conjunctival melanoma. Subungual melanoma can also be difficult to diagnose and PRAME could help in the diagnostic process. Several studies have evaluated the potential of PRAME immunoreactivity to differentiate benign subungual melanocytic proliferation (SMP) from malignant subungual melanocytic lesions, with relative sensitivity and high specificity in differentiating benign from malignant subungual melanocytic lesions [18][19][20]. This antibody has also proved to be diagnostically valuable in detecting melanoma cells in small specimens with minimal disease [21]. However, in some cases, such as acral Spitz nevi, melanomas in situ, and small, thin, invasive melanomas, PRAME did not correlate with morphological features [18][22]. Furthermore, in some subungual melanomas (SUM) and non-subungual acral melanomas (AM), PRAME expression was negative, whereas in some benign nevi, it was positive [23]. There is little conclusive evidence for the use of PRAME in amelanotic melanoma and further studies are needed to understand its potential use.

2. Preferentially Expressed Antigen in Melanoma Expression in Spitzoid Lesions

Interestingly, PRAME immunoreactivity has also been observed in Spitz nevi [24], as well as in solar lentigines and benign uninjured skin [1]. Indeed, an intriguing aspect of PRAME expression is its variability within Spitz nevi [1]. In their 2022 study, Koh et al. observed the strong diffuse staining of PRAME in 20% of Spitz nevi, 0% of atypical Spitz tumours, and 82% of spitzoid melanomas. This research shows a significant discrepancy in the expression of PRAME in spitzoid melanomas compared to Spitz nevi/tumours, demonstrating that it may be a valuable additional tool in resolving the diagnostic ambiguity often associated with these lesions and may be particularly effective in identifying spitzoid melanomas [25]. Their results agree with those of Googe et al., who reported in their study that only one of eleven Spitz nevi was diffusely positive, two were partially positive, and 73% of the Spitz nevi in their sample were PRAME-negative. Based on their experience, they suggested that diffuse PRAME reactivity in neoplastic melanocytes is typically indicative of malignancy [2]. In contrast, Raghavan et al. emphasised the need for caution in interpreting PRAME immunohistochemistry results in spitzoid neoplasms [24]. In their cohort of cases, the results showed that most Spitz nevi and atypical Spitz tumours completely lacked PRAME expression. However, it is important to note that some of these

lesions (one Spitz nevus, one atypical Spitz tumour, and one spitzoid melanoma) occasionally showed diffuse PRAME expression. Consistent with the findings of Raghavan et al., Warbasse et al. conducted a study to evaluate the correlation between PRAME staining and FISH results in spitzoid and other difficult-to-diagnose melanocytic neoplasms. However, their conclusions were not as expected as they found that PRAME immunohistochemistry did not show a strong correlation with FISH results in spitzoid melanocytic neoplasms. Consequently, their study did not confirm the relevance of PRAME as an effective screening tool in this context. The researchers also highlighted the lack of consensus in the literature on the appropriate percentage of melanocytes with positive staining required to classify a lesion as 'diffusely positive'. This ambiguity, they suggested, adds a level of complexity to the interpretation of PRAME test results in different studies [26]. Furthermore, Gerami et al. discovered a statistically significant correlation between PRAME expression and the diagnosis of atypical spitzoid melanocytic neoplasms. This implies that immunohistochemistry for PRAME can serve as a valuable supportive tool for suspected diagnoses. However, given occasional occurrences of false-positive and false-negative test results, it remains essential to correlate these findings with clinical and histologic observations, as well as results from additional tests, especially when interpreting diagnostically challenging spitzoid melanocytic neoplasms [27]. In McAfee's 2023 study, an analysis of fifty-six cases of spitzoid neoplasms revealed that fifteen cases (27%) had diffuse PRAME expression. Of these, seven (47%) were FISH-positive, all of which were diagnosed as spitzoid melanoma. In contrast, the eight cases that showed positive PRAME expression but were FISH-negative included seven diagnoses of atypical Spitz tumours (AST) and one case was identified as a spitzoid melanoma, representing a discordant case. Importantly, this research did not find a statistically significant association between the PRAME expression and FISH status, as widespread PRAME expression was also found in several benign lesions [28]. The results of all these studies demonstrate the difficulties associated with relying on PRAME alone in the complex landscape of spitzoid lesions and highlight the importance of integrating multiple diagnostic approaches for a comprehensive evaluation.

3. Preferentially Expressed Antigen in Melanoma Expression in Non-Melanoma Skin Cancer (NMSC)

Several studies have analysed the expression of PRAME in cutaneous non-melanoma carcinoma (NMSC) with interesting results. Elsensohn A et al. [29] analysed many histopathological entities in the NMSC spectrum, including well-to-poorly differentiated squamous cell carcinoma (SCC), basal cell carcinoma (BCC), basosquamous carcinoma, and Merkel cell carcinoma (MCC). Almost half of the samples showed some level of PRAME expression. Many cases showed low intensity, with staining observed in less than 25% of cells. BCCs were more likely to show staining, often accentuating the peripheral palisade cells [29]. Focusing on melanocytes of the dermal–epidermal junction (DEJ), 18% of NMSC samples showed a focal expression of high-intensity PRAME. SCCs were strongly associated with this pattern, with almost half (11/23, 48%) showing the random positivity of junctional melanocytes. The presence of rare, scattered melanocytes at the DEJ with high-intensity PRAME staining in 18% of NMSC samples examined, particularly in SCCs, suggests an association with extensive sun exposure. This finding has implications for the assessment of sample margins in chronically sun-damaged skin. Of note, BCC, SCC, and sebaceous carcinoma all showed low levels of PRAME immunoreactivity, with varying percentages of cases showing nuclear staining (BCC 59.4%, SCC 37.1%) [18]. PRAME expression in MCC, a rare and aggressive neuroendocrine neoplasm, merits discussion. In fact, MCC was found to be the second most common non-melanoma skin cancer to show some degree of PRAME expression (57% of lesions) and the most common NMSC tested showing staining in more than 25% of lesions. In fact, two Merkel cell carcinomas showed high-intensity staining in more than 75% of the tumour cells [29]. Melanoma and Merkel cell carcinoma both fall within the histopathological differential diagnosis of blue cell tumours, so it would be prudent to note that some Merkel cell carcinomas show a diffuse high-intensity expression of PRAME. Furthermore, PRAME expression in basal cell carcinoma and Merkel cell carcinoma is a potential pitfall that could lead to a misdiagnosis of malignant melanoma, especially in small biopsies and when melanoma is clinically suspected. Therefore, pathologists should be aware of the possible immunopositivity of PRAME in non-melanoma skin tumours [30]. The research suggests that PRAME expression in MCC may have potential diagnostic implications by helping to differentiate Merkel cell carcinoma from other cutaneous malignancies.

4. Preferentially Expressed Antigen in Melanoma Expression in Sebaceous Carcinoma

PRAME appears to lack a specific informational value in the histopathological diagnostics of Sebaceous Carcinoma (SC), where other markers such as adipophylline can offer significant indications. However, in the context of subclassifying sebaceous carcinoma into grades I–II–III, following the guidelines of the latest WHO 2018, PRAME shows potential utility. It emphasises the presence of mature sebaceous differentiation foci, predominant in grades 1–2 and nearly absent in grade 3 of Sebaceous Carcinoma [31].

5. Preferentially Expressed Antigen in Melanoma Expression in Soft Tissue Tumours

Regarding soft tissue tumours, a study is reported in the literature of 350 soft tissue tumours of >50 histotypes, in which PRAME immunoreactivity was graded from 0 to 4+ based on the percentage of positive cells. PRAME was expressed in 111 lesions, including various malignancies such as melanoma, synovial sarcoma, and myxoid liposarcoma, with varying degrees of diffuse positivity. Although the specificity of PRAME in soft tissue pathology is not perfect, it can serve as a valuable diagnostic adjunct in specific cases where expression patterns contrast with other lesions. Notably, several tumour types, including spindle cell lipoma and dermatofibrosarcoma protuberans, showed consistently negative PRAME expression. Furthermore, it could be useful in the differential diagnosis between melanoma and clear cell sarcoma (CCS) [30][32].

In addition, recent studies, including one investigating PRAME immunohistochemistry in dedifferentiated and undifferentiated melanoma, have strengthened the diagnostic value of PRAME. This research found that both primary and metastatic dedifferentiated and undifferentiated melanomas exhibited strong and diffuse nuclear PRAME staining, effectively distinguishing them from atypical fibroxanthoma and pleomorphic dermal sarcoma. The results underscore the role of PRAME as a first-line screening tool in the detection and management of these challenging melanoma cases and highlight its utility even in the absence of recognisable conventional melanoma precursors [33].

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