Challenges and considerations in melanoma diagnosis: Insights from 2 cases with negative pigmented lesion assay results

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INTRODUCTION

Melanoma, with its aggressive nature and metastatic potential, demands early detection and intervention for optimal outcomes. While histopathologic examination remains the gold standard, adjunctive techniques such as dermoscopy and confocal microscopy improve diagnostic accuracy.[1] The pigmented lesion assay (PLA), a gene expression test targeting long intergenic nonprotein coding RNA 518 (*LINC00518*) and preferentially expressed antigen in melanoma (*PRAME*), aims to rule out melanoma and ideally reduce the number of surgical biopsies, especially in cosmetically sensitive areas.[2] Here, we discuss 2 cases where PLA yielded negative results (PLA(−)), but subsequent biopsy and excision revealed malignant melanoma.

Abbreviations used:

LINC00518:	long intergenic nonprotein coding RNA 518
MIS:	melanoma in situ
MM:	malignant melanoma
NNB:	number needed to biopsy
NPV:	negative predictive value
PLA:	pigmented lesion assay
PRAME:	preferentially expressed antigen in melanoma

CASES

Case 1: A 40-year-old female sought cosmetic consultation for a long-standing brown spot on her left nasal ala, previously assessed by nonphysician dermatology extender as benign and treated with liquid nitrogen and laser therapies. Despite multiple treatments, the lesion persisted, prompting PLA testing for diagnostic assistance. Although the lesion was PLA (−), a dermoscopic examination at cosmetic consultation by a board-certified dermatologist revealed pigment heterogeneity, prompting a shave biopsy for definitive assessment (Fig 1). Tissue histopathology revealed melanoma in situ (MIS), further verified with a subsequent punch biopsy (Fig 2). PRAME immunostain was strongly 4+ nuclear positive in a subset of atypical melanocytic lineage cells. Six weeks later, Mohs surgery was performed and uncovered invasive malignant melanoma with a Breslow depth of 0.5 mm. At the 3-week postoperative visit, there was a well-healing scar without evidence of recurrence (Fig 3).

Case 2: A 44-year-old female with no prior history of skin cancer presented for a general skin examination. She presented with multiple regular, symmetrical, evenly-colored nevi throughout her body, along with a clinically and dermatoscopically irregular brown patch on her right medial malar cheek. Over 2 years ago, the lesion was PLA (−), but given the persistent irregularity, a shave biopsy was performed and confirmed a diagnosis of MIS. Subsequent wide local excision with 1 cm margins revealed residual tumor, necessitating re-excision for clear margins, and then acellular dermal regeneration graft placement. The patient developed mild

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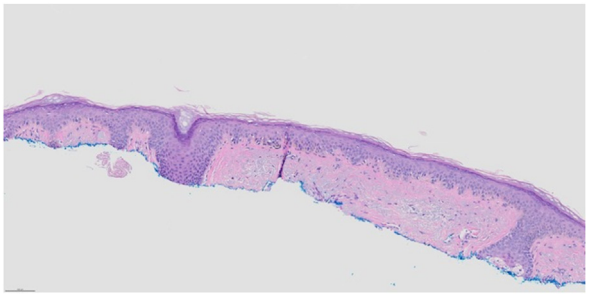

Fig 1. Left nasal ala shave biopsy. Hematoxylin and eosin showed atypical intraepidermal melanocytic proliferation extending to peripheral margins. A PRAME immunostain highlighted melanocytic lineage cells and supported the diagnosis of melanoma in situ.

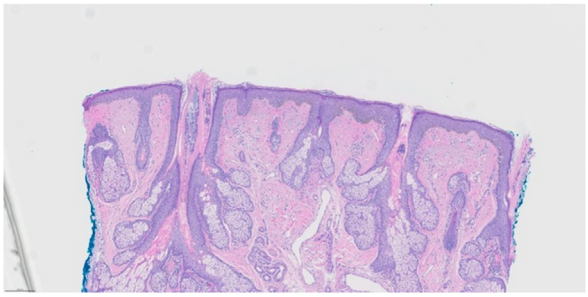

Fig 2. Left nasal ala punch biopsy. Hematoxylin and eosin showed a proliferation of atypical melanocytes at the dermoepidermal junction, with areas of confluence.

hypertrophic scarring but showed no signs of melanoma recurrence postoperatively (Fig 4).

DISCUSSION

Diagnosing melanoma presents inherent challenges due to its clinical propensity to mimic benign lesions and have subtle atypical features, cosmetic concerns and implications of biopsy scarring, and histopathologic thresholds in diagnosis. Early detection is crucial to minimize complications. Visual assessment followed by surgical biopsy and histopathology has historically been the gold standard, but its sensitivity ranges from 65% to 84%, specificity between 5% and 10%, and negative predictive value between 85% and 89%.[1] This approach often requires a relatively high number of surgical biopsies to identify a single melanoma, with the number needed to biopsy for dermatologists averaging around 20.[1]

Advancements in noninvasive diagnostic technology offer an appealing approach for evaluating pigmented lesions and reducing unnecessary surgical procedures. Studies in adults with pigmented lesions are suspicious for melanoma support using the two-gene PLA (*LINC00518* and *PRAME*), independently possessing a sensitivity of 91%, specificity of 69%, negative predictive value of 99%, and mean number needed to biopsy of 3.[2] Its intended use is to aid the surgical biopsy decision and may be especially beneficial in cases involving cosmetically sensitive areas or numerous atypical lesions.[2] Additionally, it can be helpful in diagnosing early melanoma cases, such as MIS and T1 thin melanoma, particularly when histopathologic diagnosis is challenging. Despite its promising metrics, a recent systematic review questioned the reliability of sensitivity and specificity for PLA given most existing studies have a potential conflict of interest and Risk Bias and Applicability results displayed low quality of studies.[3] Other limitations of PLA include insufficient tissue yield in approximately 14% of samples, an inability to test pigmented lesions on the soles and palms, and reduced efficacy for testing certain melanoma subtypes such as desmoplastic melanomas, which display lower frequencies of PRAME.[3]

In Case 1, the challenges posed by atypical pigmented lesions and the limitations of relying solely on PLA testing are evident. Despite being PLA (−) the very same week that the biopsy ended up being taken, the persistence of the pigmented lesion along with dermoscopic atypical findings which could have been obscured by prior treatments raised concern and prompted further investigation. Subsequent histopathologic analysis confirmed MIS with positive PRAME immunohistochemistry, highlighting the importance of thorough clinical assessment and integration of multiple diagnostic modalities. Additionally, the identification of invasive melanoma during Mohs surgery underscores the potential for a deeper component within even a relatively small lesion, emphasizing the need for vigilant follow-up and intervention.

In Case 2, the patient presented with multiple pigmented skin lesions and an irregular brown spot on her cheek that was previously PLA (−) over 2 years ago. Visual assessment and clinical suspicion led to the decision to biopsy the lesion which returned a histopathologic diagnosis of MIS. It is unclear how long a PLA result is valid, but one study found that over 99% of PLA (−) lesions surveilled over a 12-month period were appropriately managed with observation alone.[3] Our case emphasizes the need for longer-term PLA (−) follow-up studies and the importance of exercising caution regarding past PLA (−) results, as lesions can evolve over time.

Overall, a comprehensive, multidisciplinary approach to melanoma diagnosis and management remains essential. PLA holds promise in reducing the benign to malignant ratio among biopsies, but its limitations underscore the necessity of clinical judgment and histopathologic analysis.

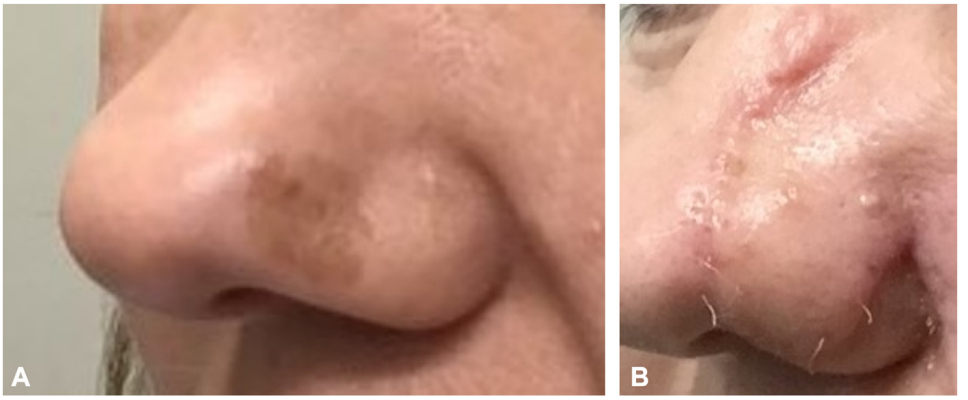

Fig 3. 40-year-old female with a persistent *brown* macule on her left nasal ala (**A**). Pigmented lesion assay returned negative 10 days before biopsy proven melanoma-in-situ. Three weeks after Mohs surgery, there was a well-healing scar with no evidence of recurrence (**B**).

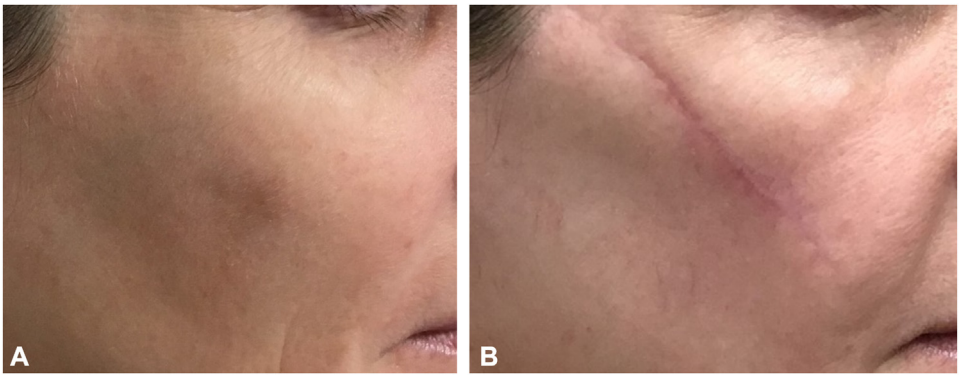

Fig 4. 45-year-old female with an atypical *brown* patch on her right cheek that was pigmented lesion assay negative 2 years prior to presentation (**A**). Biopsy and histopathology revealed melanoma-in-situ and the patient required re-excision, resulting in hypertrophic scarring (**B**).

Conflicts of interest

None disclosed.

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