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PRAME expression is similar in scar and desmoplastic melanoma

PReferentially expressed Antigen in MElanoma (PRAME) is a cancer-testis antigen upregulated in a multitude of human neoplasms, while minimally expressed in normal adult tissues except germ cells.[1] The PRAME immunostain has gained interest in recent years, particularly in the realm of diagnostically challenging melanocytic lesions. Large cohorts have shown diffuse PRAME expression in 80%–83% of all melanomas; on the other hand, benign melanocytic nevi showed little to absent expression.[2–6] Unlike most other types of melanoma, however, only a minority of desmoplastic melanomas (35%) were reported to show diffuse PRAME staining.[2] More recently, PRAME expression has been reported in reactive fibroblasts of mature scars in five of 11 skin excisions for melanocytic lesions.[7] We have observed the same phenomenon in our practice, which prompted us to further characterize the frequency, extent, and intensity of PRAME immunoreactivity in scar fibroblasts, and to compare these findings with desmoplastic melanoma.

This study was conducted according to a protocol previously approved by the Institutional Review Board at our institution. Twenty-one scars from skin excisions of non-melanocytic lesions (18 conventional scars, one hypertrophic scar, and two keloids) and 10 desmoplastic melanomas were included. All diagnoses were confirmed by a dermatopathologist (M.P.C.). One representative block containing the largest volume of the scar was selected from each scar specimen. For desmoplastic melanomas, one representative block containing the most "pure" tumor away from any areas of scarring was selected from each case. Sections of 4-μm thickness were deparaffinized, and heat-induced epitope retrieval was performed on the Ventana Benchmark Ultra immunostainer using cell conditioning 1 buffer (Ventana). The slides were then incubated with a rabbit monoclonal PRAME antibody (EP461, Cell Marque, prediluted) for 60 min at room temperature. Immunoreactivity was detected using the OptiView Universal DAB Detection Kit (Ventana). Two dermatopathologists (M.P.C. and S.C.B.) evaluated the fibroblasts in the scars and the lesional melanocytes in the desmoplastic melanomas, and assigned an "extent score" (0 = negative; 1+ = 1%–25% of cells staining; 2+ = 26%–50%; 3+ = 51%–75%; 4+ = 76%–100%)[2] and an "intensity score" (0 = negative; 1 = mild; 2 = moderate; 3 = strong) to each case. A "combined score" was also calculated in each case by adding the extent score and the intensity score.

The results are summarized in Table 1. Most scars contain a variable number of PRAME-positive fibroblasts (Figure 1A–F), with diffuse (extent score of 4+) and strong (intensity score of 3) staining observed in 24% and 19% of these cases, respectively. Only 10% of scars were completely devoid of staining. Overall, scars had an average extent score of 2.5 (of 4) and an average intensity score of 1.7 (of 3). All 10 desmoplastic melanomas showed some degree of PRAME staining (Figure 1G–L), but only two (20%) showed diffuse and strong expression. As a group, desmoplastic melanoma had an average extent score of 2.7 and an average intensity score of 1.8. Two-tailed *t* tests comparing the average extent, intensity, and combined scores between the two groups did not reveal any statistically significant differences. Furthermore, no significant difference was identified when comparing specimens with and without solar elastosis, suggesting that PRAME expression was not related to chronic sun damage. Focal nuclear blush in keratinocytes and staining in rare background melanocytes were seen in nine (43%) and 12 (57%) scars, respectively. All clear-cut melanoma in situ in the desmoplastic melanoma cases showed diffuse and strong PRAME staining.

A recent study found PRAME-positive fibroblasts in five (4%) of 140 cases (11 of which were wide excisions), although it was not clear if a scar was present in all 140 cases.[7] All five cases in their series were reported to show strong nuclear staining. Our results provided additional information with regard to the extent of PRAME staining based on the percentage of positive cells, according to a common scoring method outlined in a widely cited study.[2] It should also be noted that our cohort of scars was limited to skin excisions for non-melanocytic lesions, in order to minimize the possibility of an unrecognized melanocytic lesion present within the scar. Our findings indicate that PRAME expression is common in scars. Although most scars displayed weak to moderate staining in ≤75% of fibroblasts, diffuse and strong PRAME expression can be observed in a small subset of cases. While the biological basis of this phenomenon remains unclear, at least one previous study has shown low level of PRAME

TABLE 1 PRAME scores in scars and desmoplastic melanomas

	Scar ($n = 21$)	Desmoplastic melanoma ($n = 10$)	p
Extent score			
0	2 (10%)	0	-
1+	2 (10%)	1 (10%)	-
2+	6 (29%)	3 (30%)	-
3+	6 (29%)	4 (40%)	-
4+	5 (24%)	2 (20%)	-
Average	2.5	2.7	0.62
Intensity score			
0	2 (10%)	0	-
1	7 (33%)	4 (40%)	-
2	8 (38%)	4 (40%)	-
3	4 (19%)	2 (20%)	-
Average	1.7	1.8	0.7
Combined score			
≤5	15 (71%)	8 (80%)	-
6	3 (14%)	0	-
7	3 (14%)	2 (20%)	-
Average	4.1	4.5	0.64

Abbreviation: PRAME, PReferentially expressed Antigen in MElanoma.

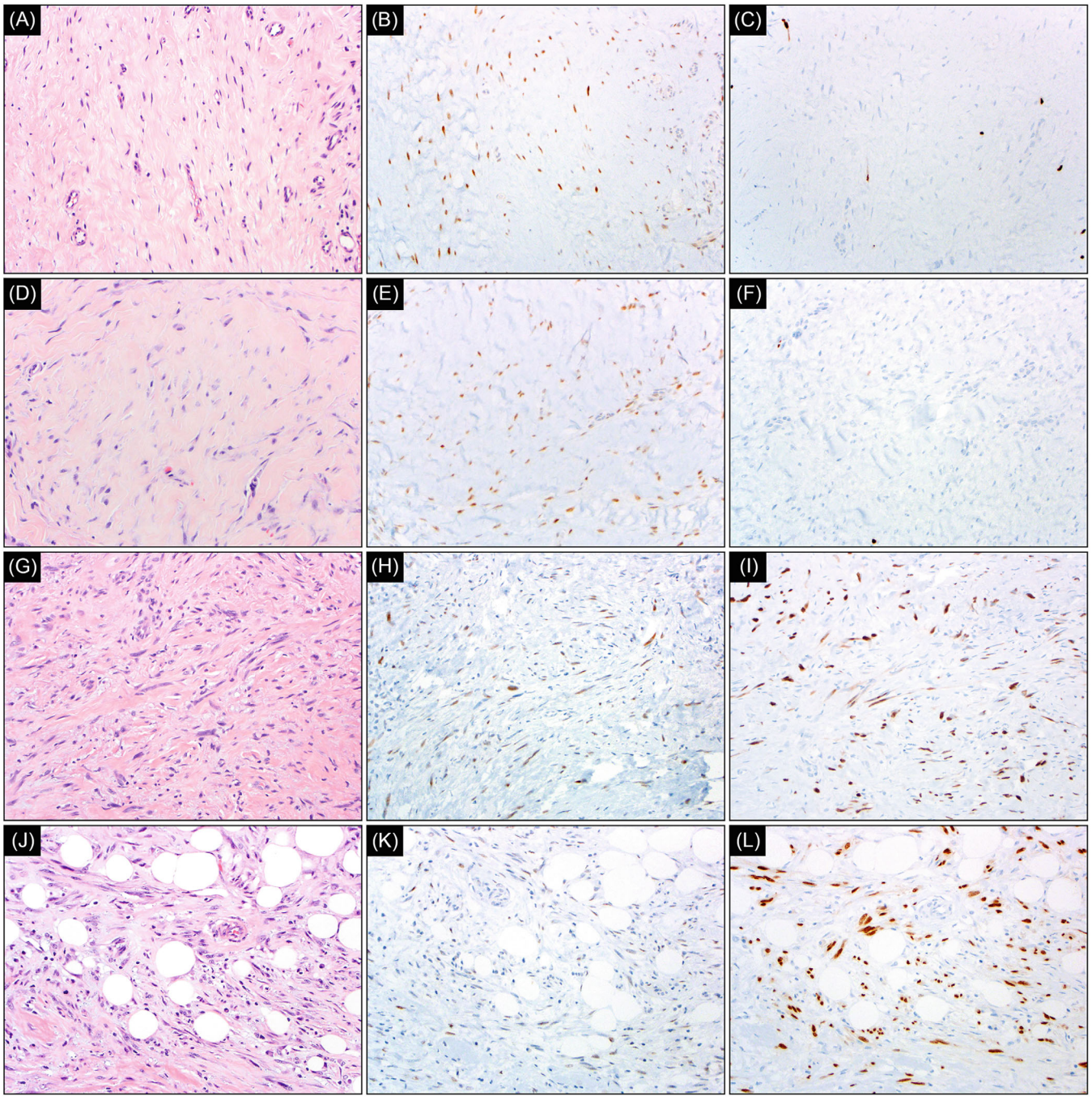

FIGURE 1 PReferentially expressed Antigen in MElanoma (PRAME) expression in scars and desmoplastic melanomas. A cellular area in a keloid (A) reveals diffuse (extent score 4+) and strong (intensity score 3) nuclear PRAME staining in the fibroblasts (B). SOX10 highlights rare cells within this area (C). Another scar (D) shows similar diffuse and strong PRAME staining (E). This scar is largely devoid of SOX10-positive cells (F). A desmoplastic melanoma (G) shows strong (intensity score 3) nuclear PRAME staining in 50%–75% of tumor cells (extent score 3+) (H). SOX10 highlights all melanoma cells (I). Another desmoplastic melanoma shows moderate staining (intensity score 2) in <25% of tumor cells (extent score 1+). SOX10 reveals the extent of melanoma cells (L). (A, D, G, J: H&E, ×200; B, E, H, K: PRAME ×200; C, F, I, L: SOX10, ×200)

expression in adult fibroblasts by quantitative PCR.[8] Objectively, non-specific immunoreactivity cannot be entirely excluded.

In our cohort of desmoplastic melanomas, we found a lower rate of diffuse PRAME expression (20% cases) compared to a previous report (35% cases).[2] Such difference may be attributed to the smaller number of cases and the different antibody clones used in our study. Most importantly, we found no significant difference in PRAME expression between scars and desmoplastic melanomas. Histopathologically, it is well known that desmoplastic melanoma may closely resemble scar, making the distinction notoriously challenging.[9] Our study highlights another important diagnostic pitfall, namely the similar degree of PRAME expression by desmoplastic melanoma and scar.

Based on our results, PRAME should not be used as the sole melanoma marker in this differential diagnosis. We also advise against its use in assessing margin status in excision specimens for desmoplastic melanoma, as PRAME-positive fibroblasts may potentially extend to the specimen margins, while desmoplastic melanoma cells may lack PRAME expression. In our experience, S100 and SOX10 are more reliable in delineating the extent of desmoplastic melanoma,[10] although the presence of S100 and SOX10-positive cells in scars is another known diagnostic pitfall.[11,12] As such, PRAME, S100, and SOX10 should always be evaluated with caution and in conjunction with careful histomorphologic examination in determining the presence, and delineating the borders, of desmoplastic melanoma.

The small number of cases in our study precluded separate analysis of new and mature scars, or keloidal/hypertrophic and hypocellular scars. Future studies may expand on each group to further explore any relationship between PRAME expression and the different types, age, and cellularity of scars.

AUTHOR CONTRIBUTIONS

May P. Chan designed the research study and analyzed the data. Jaclyn M. Plotzke, Nicholas A. Zoumberos, Scott C. Bresler, and May P. Chan collected the data. Jaclyn M. Plotzke and May P. Chan wrote the manuscript. All authors performed the research and critically reviewed the manuscript.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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