UTILITY OF IMMUNOSTAING IN MELANOMA DIAGNOSIS

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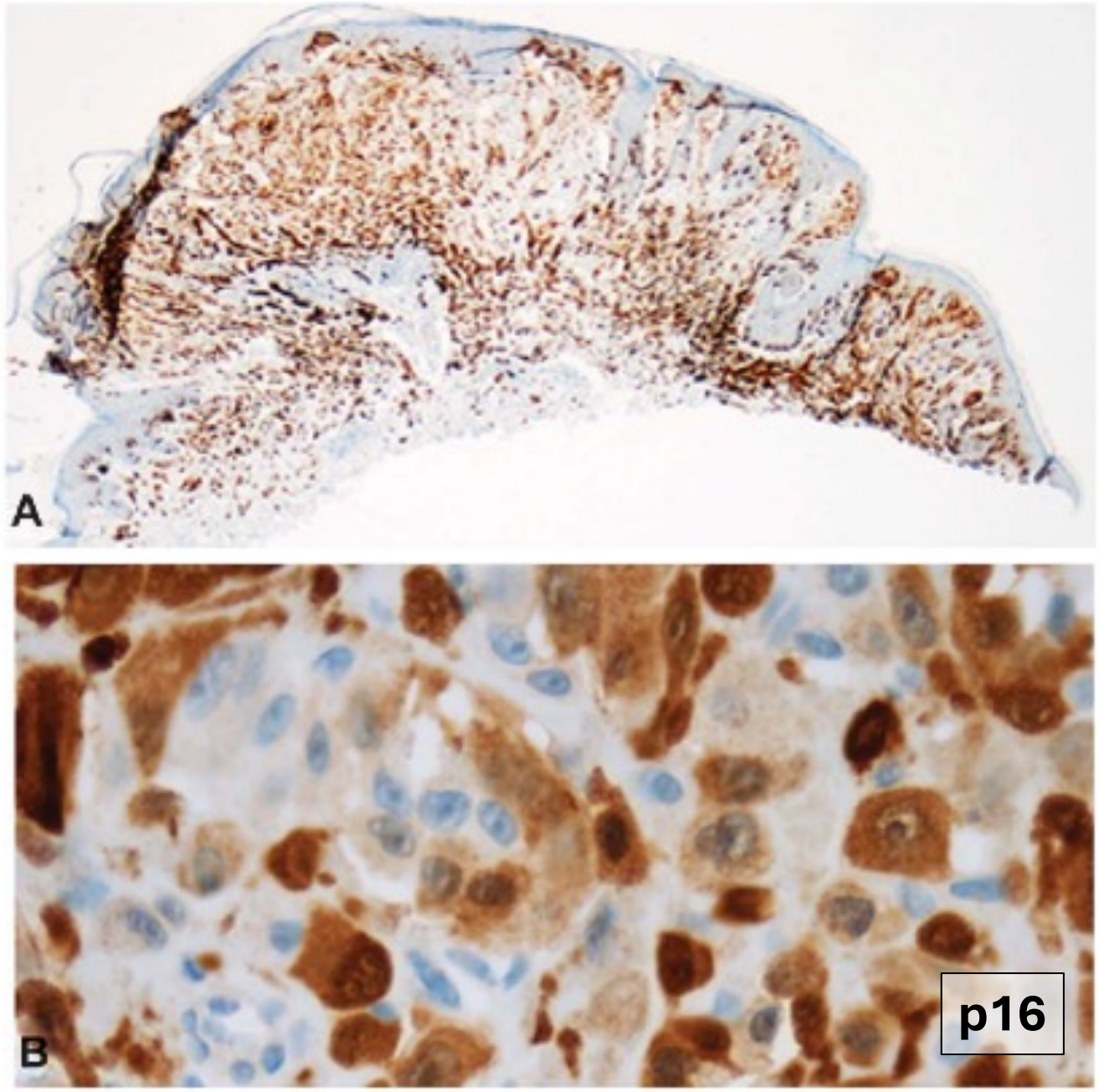
Immunostaining for Melanocytic Proliferations

Marker	Histologic Situation
Melan-A/MART-1 (Cytoplasmic)	Microinvasion Sentinel lymph node (SLN) screening
SOX-10 (also neural) (Nuclear)	Desmoplastic dermis Residual melanoma in excision scar Melanoma in situ in sun-damaged epidermis
Ki67/Melan-A	Dermal melanoma (>5% mitotic index)
S100 (also neural) (Nuclear and cytoplasmic)	Metastasis Desmoplastic dermis
p16 (*CDKN2A gene*) (Nuclear)	Melanoma (silenced, absent expression or homozygous deletion). sporadic: 26%; familial: 44%
BAP-1 (Nuclear)	BAP-1 inactivated nevus or melanocytoma (not melanoma); spitzoid or biphasic morphology
PRAME (Nuclear)	Melanoma (+92% melanoma; -84% nevi)
HMB-45 (Cytoplasmic)	Invasive melanoma (paradoxical expression), SLN screening
MITF (nuclear)	Metastatic melanoma, melanocytic differentiation

Mosaic cytoplasmic and nuclear expression of p16: homozygous CDKN2A deletion is unlikely

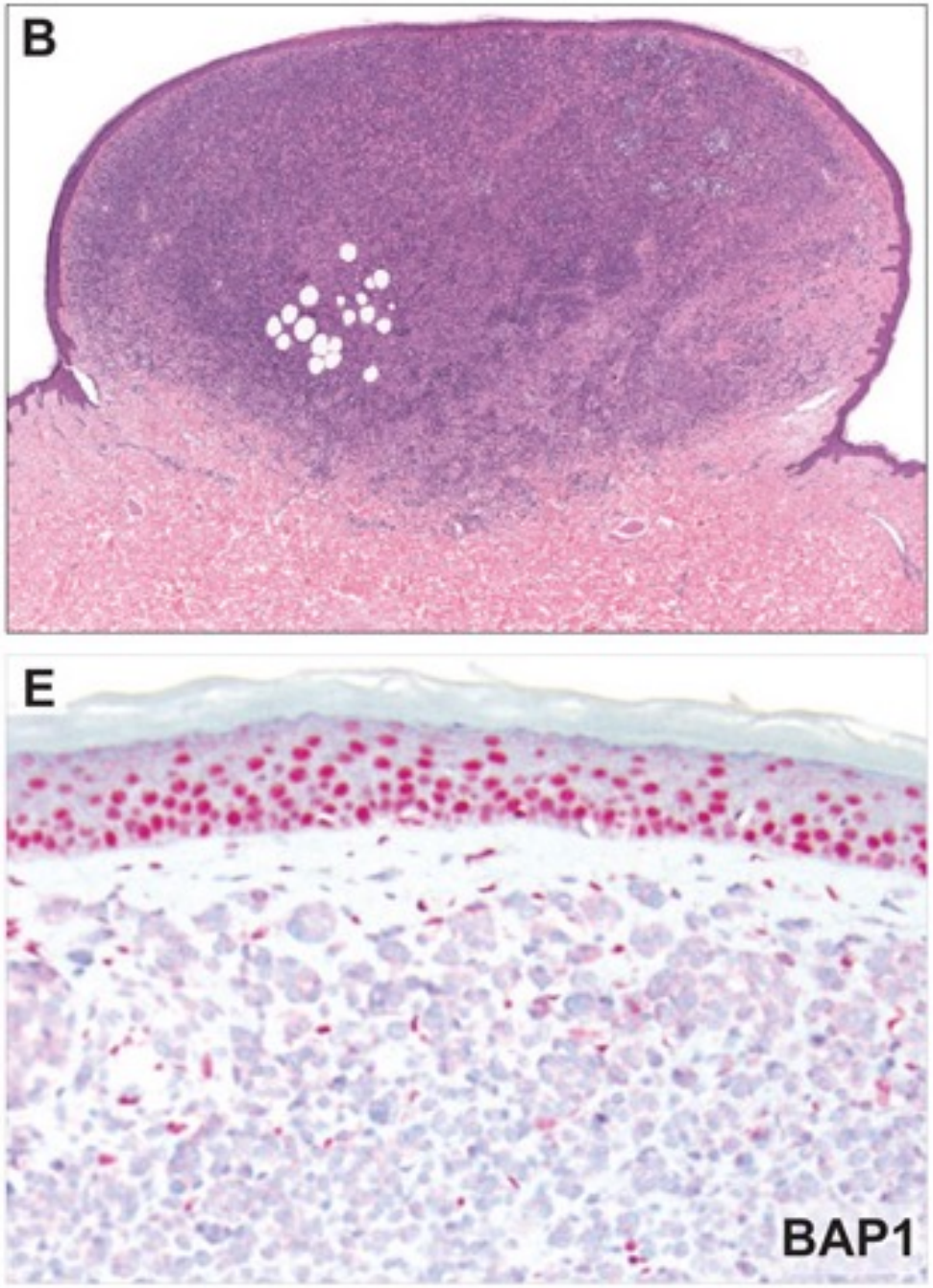
- High risk melanoma families (8-12% of all melanomas)
- Mapped to 9p21 susceptibility locus (20-44%), sporadic (20%)
- Germline mutations: *p16 (CDKN2A)* and *CDK4*
- p16 protein detected by IHC, expression completely lost “homozygous CDKN2A deletion is likely.”
- Not lost in all melanomas
- Not tested in various types of atypical nevi



DiSano et al. AJDP 2013

BRCA1 Associated Protein-1 (BAP-1)

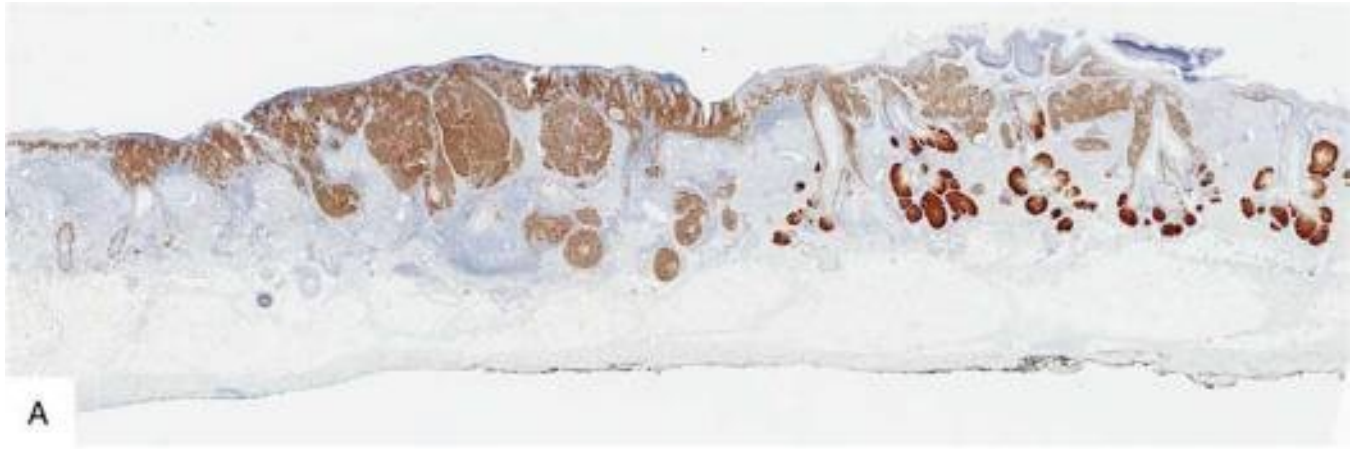
- Multiple (from 5 to >50) cutaneous lesions in members of two families with germline mutations in BAP1
- Elevated incidence of uveal melanoma, cutaneous melanoma and mesothelioma
  - Wiesner et al. *Nat Genet*. 2011
- Marker for a hereditary BAP1-associated cancer syndrome
- BAP-1 deficiency in sporadic melanocytic neoplasms with biphasic and epithelioid spitzoid features
- WHO: BAP-1 inactivated nevus or melanocytoma
- Overall indolent clinical course

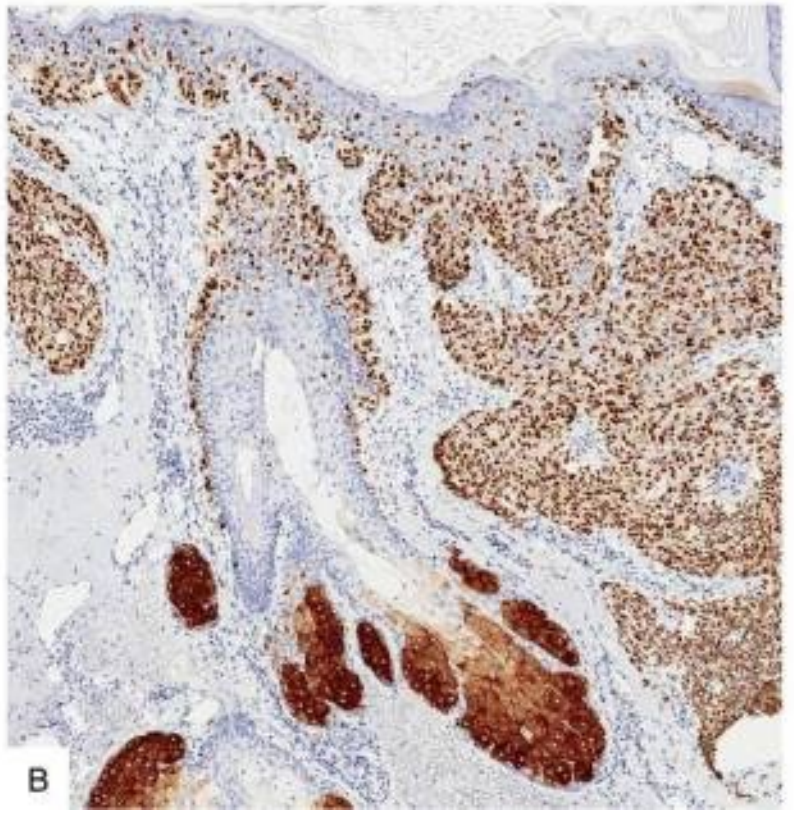


Wiesner et al. (Bastian) AJSP 2012

PRAME expression in melanocytic tumors

- PRAME (PReferentially expressed Antigen in MElanoma)
- Melanoma-associated antige isolated by autologous T cells in a melanoma patient
- Expressed in variety of cance
- Expressed in 83-94% of melanomas
- Negative in 86% of nevi





Lezcano et. (Busam) AJSP 2018

- Compared sensitivity and specificity of SOX-10
- Other markers: MITF, HMB-45, Melan-A and S100
- Specimens: melanoma excision, scar and desmoplastic melanoma

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SOX10 immunostaining distinguishes desmoplastic melanoma from excision scar

Background: Sry-related HMG-BOX gene 10 (SOX10), a nuclear transcription factor that plays an important role in schwannian and melanocytic cell differentiation, has recently been shown to be a useful marker in the diagnosis of melanocytic and schwannian tumors. Fibroblasts and histiocytes that could histopathologically mimic melanoma cells often express S100, which complicates the evaluation of melanoma excision specimens for residual tumor. Distinguishing melanoma cells from immature fibrocytes or histiocytes is made more challenging in desmoplastic melanoma excision specimens.
Methods: We compared the utility of melanoma markers [SOX10, S100, HMB-45, Melan-A and micropthalmia transcription factor (MiTF)] in 3 invasive, 9 desmoplastic and 14 intraepidermal melanomas. We also evaluated 18 excision scars. The staining intensity for all the cellular components in melanoma and scar specimens was scored.
Results: SOX10 strongly highlighted all *in situ*, invasive and desmoplastic melanomas. In contrast, MiTF expression was weak to absent in desmoplastic melanomas. In scars, S100 highlighted background spindled fibrocytes and histiocytes with greater intensity than SOX10. MiTF highlighted multi-nucleated histiocytes, while SOX10 did not.
Conclusion: Our results showed that SOX10 was strongly expressed by desmoplastic melanoma. Furthermore, SOX10 was less likely than S100 and MiTF to be expressed by background fibrocytes and histiocytes within scars.

Ramos-Herberth FI, Karamchandani J, Kim J, Dadras SS. SOX10 immunostaining distinguishes desmoplastic melanoma from excision scar.
J Cutan Pathol 2010; 37: 944–952. © 2010 John Wiley & Sons A/S.

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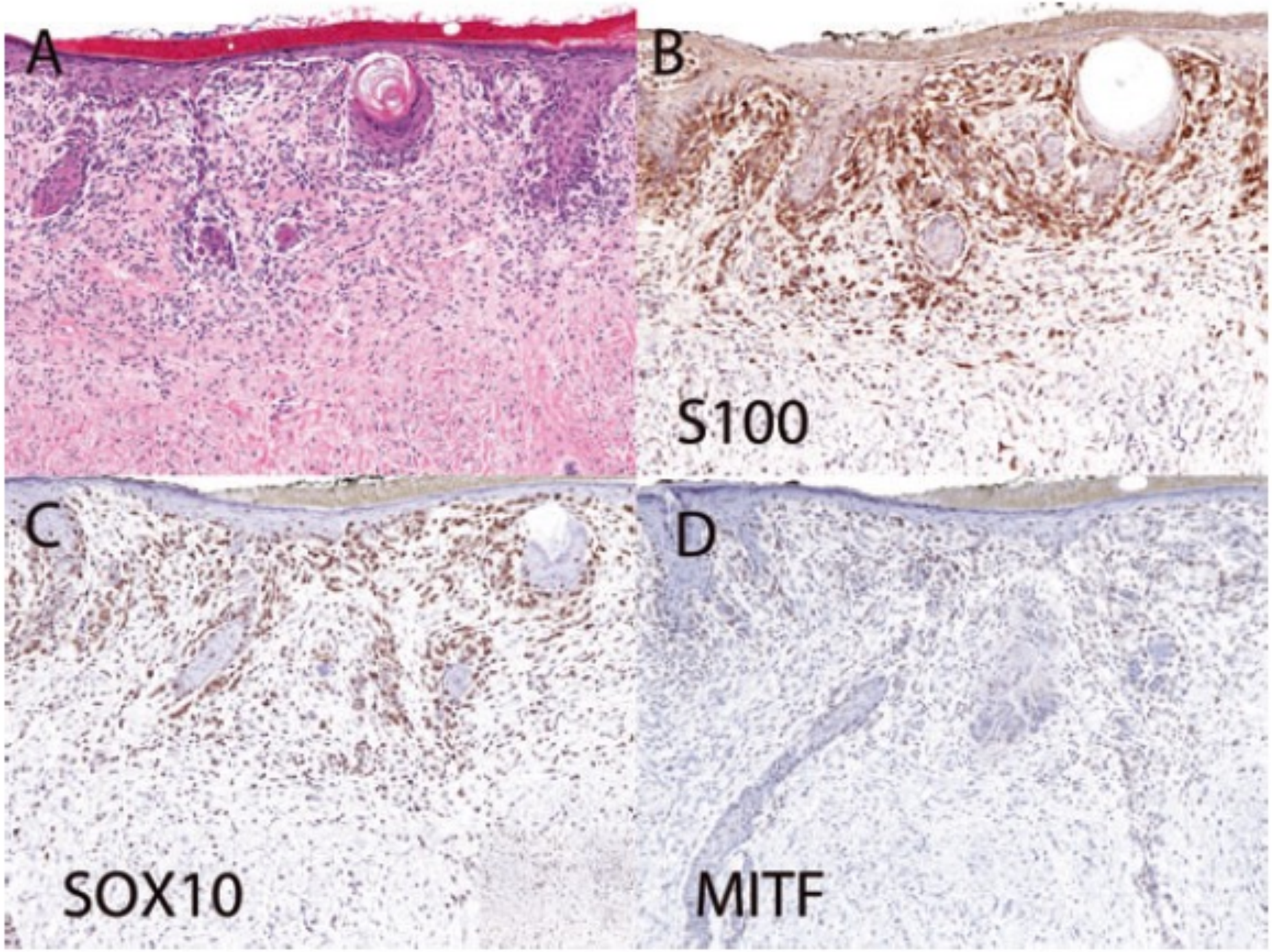
Table 3. Summary of the averaged immunohistochemical staining scores in cutaneous melanoma *vs.* scar

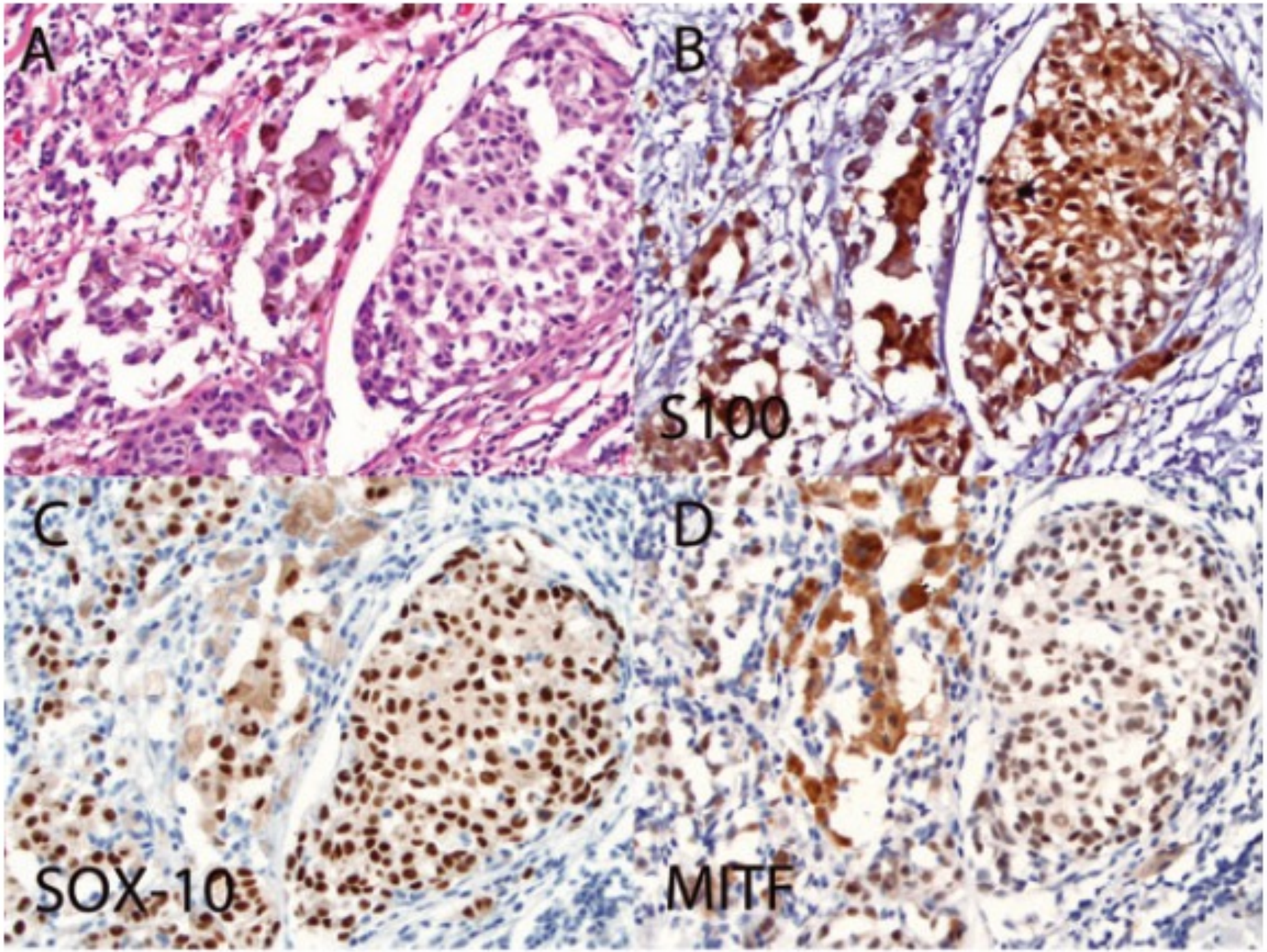
Diagnosis	SOX10	MiTF	S100	Melan-A	HMB-45
MMIS or intraepidermal component ($n = 14$)	2	2	1.5	2	1.7
Invasive melanoma ($n = 3$)	2	2	2	2	2
Desmoplastic melanoma ($n = 9$)					
Pure type ($n = 7$)					
Intraepidermal	2	1.7	1.8	2	1.5
Intradermal	2	0.25	2	0.5	0
Combined type ($n = 2$)					
Intraepidermal	2	2	2	2	1
Intradermal	2	1	2	0	0
Scar (n = 18)					
Fibroblasts	0.6	1.5	1.9	0	0.1
Histiocytes	0	1	0.3	0	0

MMIS, malignant melanoma *in situ*; 0, negative; 1, weak positive; 2, strong positive. The scores represent average numbers for all tested specimens.

- SOX-10 is more specific in detecting melanoma in scar compared to MITF and S100
- SOX-10 is more specific in detecting desmoplastic melanoma compared to Melan-A, MITF and HMB-45

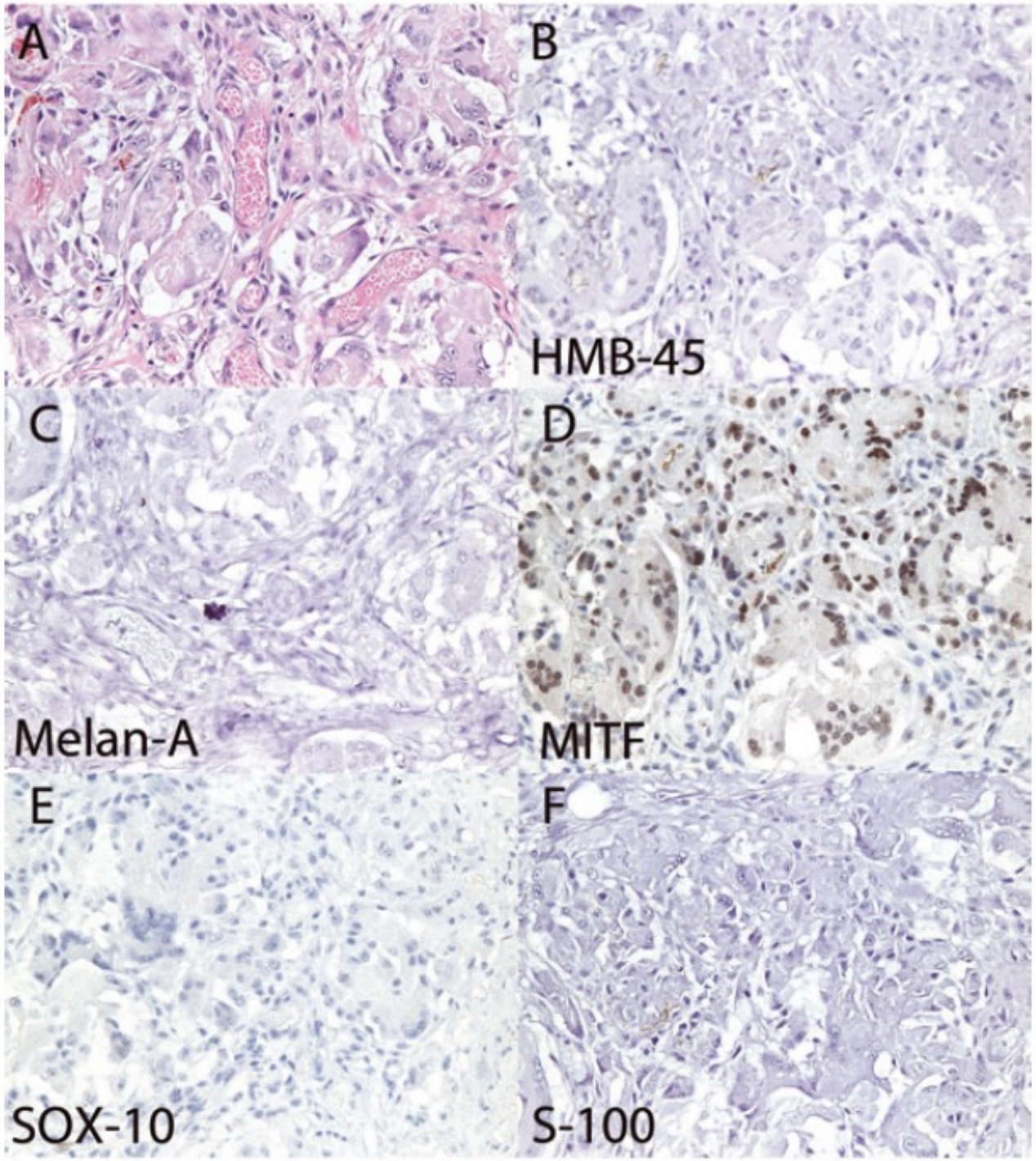
SOX-10 identifies melanoma in situ overlying desmoplastic melanoma





SOX-10 identifies dermal desmoplastic melanoma

MITF highlighted multi-nucleated histiocytes in dermal scar



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ORIGINAL ARTICLE

A quantitative comparison between SOX10 and MART-1 immunostaining to detect melanocytic hyperplasia in chronically sun-damaged skin

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Histologic differentiation of melanoma in situ (MIS) from solar keratosis on chronically sun-damaged skin is challenging. The first-line immunostain is usually MART-1/Melan-A, which can exaggerate the epidermal melanocytes, causing a diagnostic pitfall for MIS. By comparing MART-1 and SOX10 immunostaining, we scored the percentage of epidermal melanocytes per 2-mm diameter fields in pigmented actinic keratosis (n = 16), lichenoid keratosis (n = 7), junctional melanocytic nevus (n = 6), keratosis with atypical melanocytic proliferation (n = 17) and MIS (n = 10). These cases represented an older population (68 years median age) and the head and neck (50%) was the most common anatomic site. MART-1 score was significantly higher than SOX10 (P value <.05) in solar keratoses, but showed no difference in detecting melanocytic proliferations, demonstrating their equal detection rate of melanocytes. The sensitivity of both MART-1 and SOX10 was 100%, while their specificities were 17% and 96%, respectively. These results show that SOX10 is more specific than MART-1 in distinguishing epidermal melanocytes on sun-damaged skin by avoiding overdiagnosis of melanoma.

KEYWORDS

atypical melanocytic proliferation, benign lichenoid keratosis, junctional dysplastic melanocytic nevus, MART-1, Melan-A, melanoma in situ, pigmented actinic keratosis, SOX10

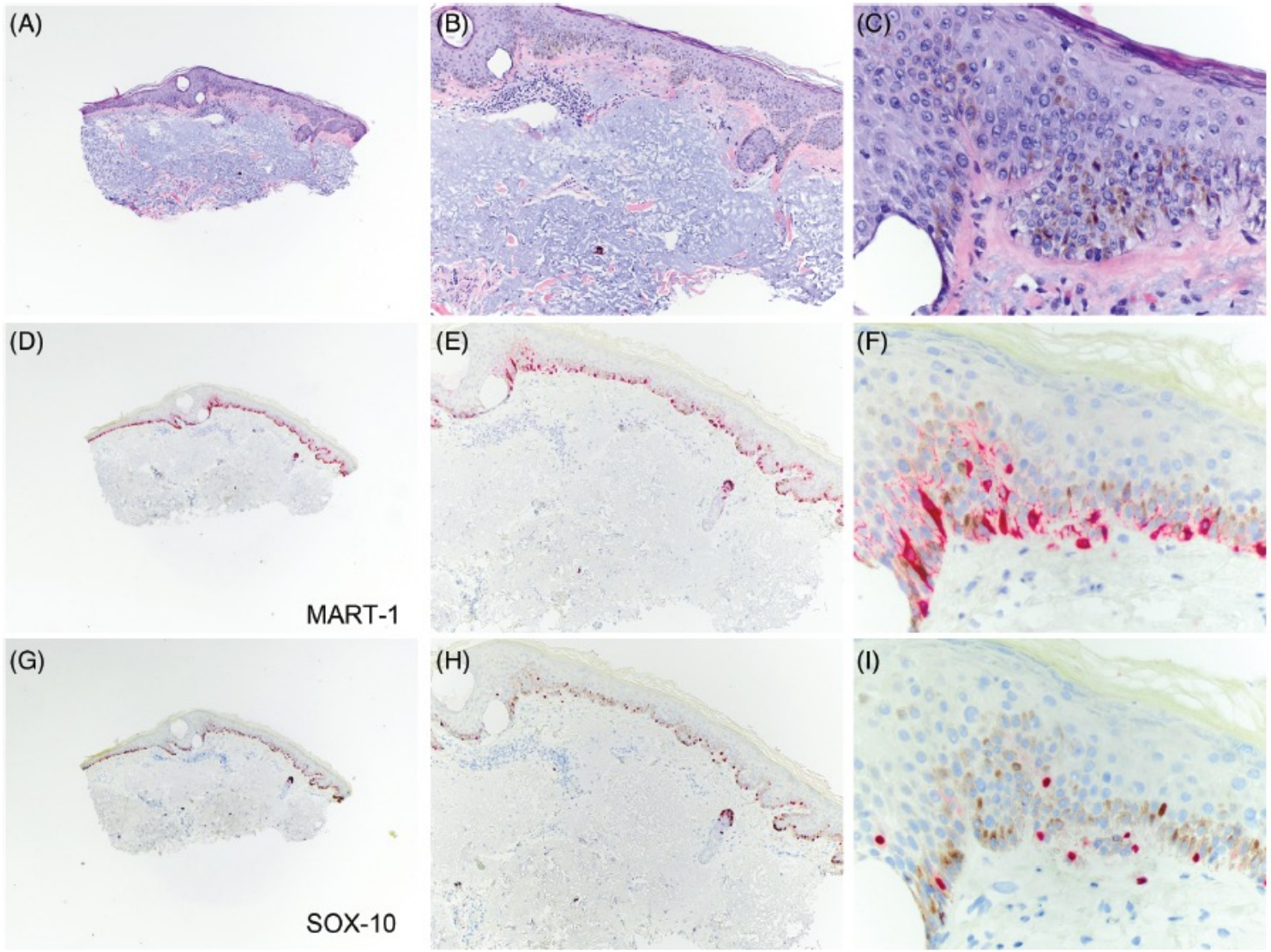


FIGURE 1 Contrast between MART-1 and SOX10 immunohistochemistry (IHC) in chronically sun-damaged skin. (A-C) Histopathology of a pigmented patch on the forehead of an 81-year-old male shows pigmented actinic keratosis overlying dermal solar elastosis, focally suggestive of atypical melanocytic proliferation. (D-F) MART-1 (red) IHC is suspicious for nearly confluent melanocytic hyperplasia, concerning for melanoma in situ, at the basal layer of epidermis and highlighting the dendritic process of melanocytes. (G-I) However, SOX10 (red) demonstrates the nuclei of a few scattered melanocytes, as seen in a pigmented actinic keratosis. Original magnifications: A, D and G (×20); B, E and H (×100); and C, F and I (×400)

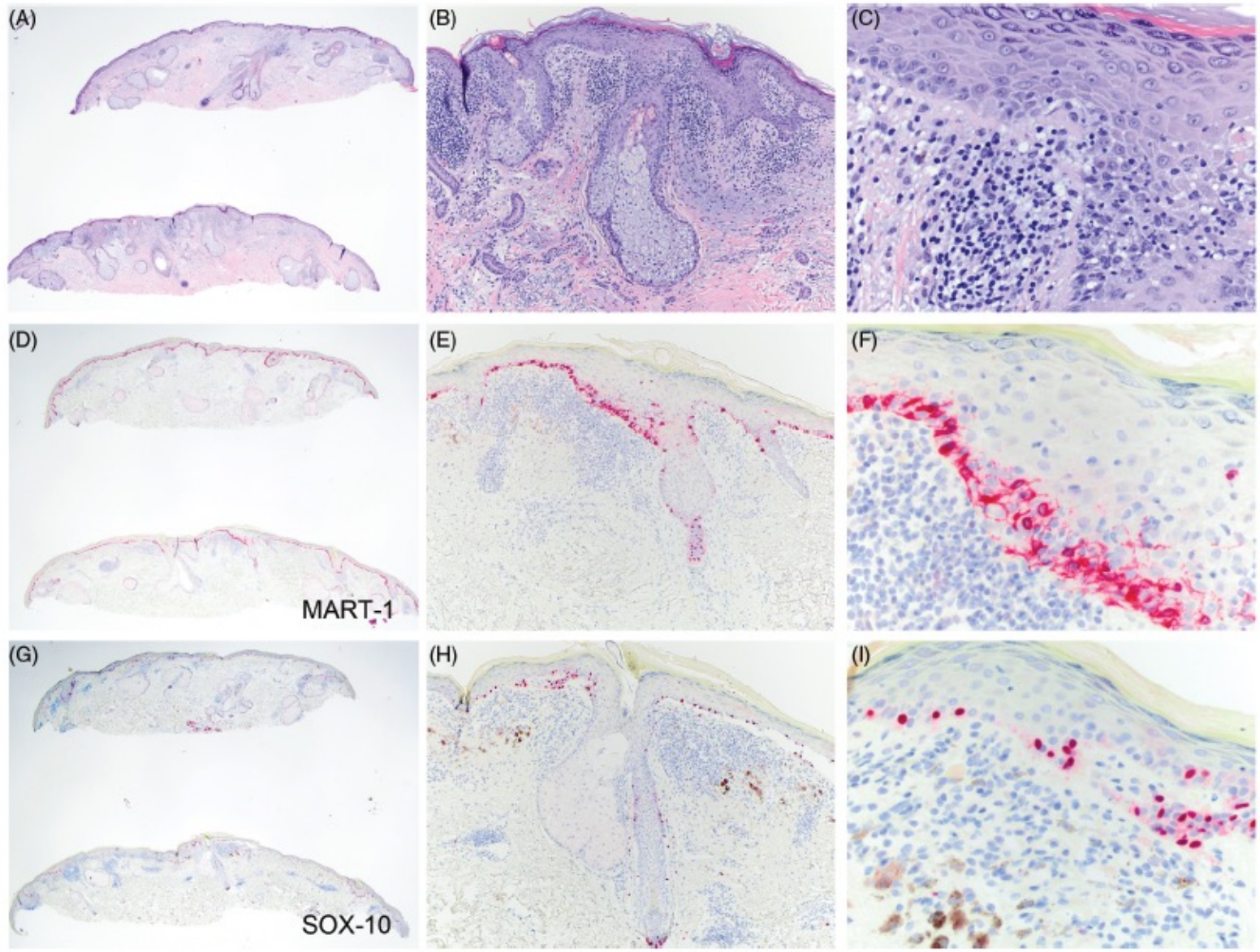
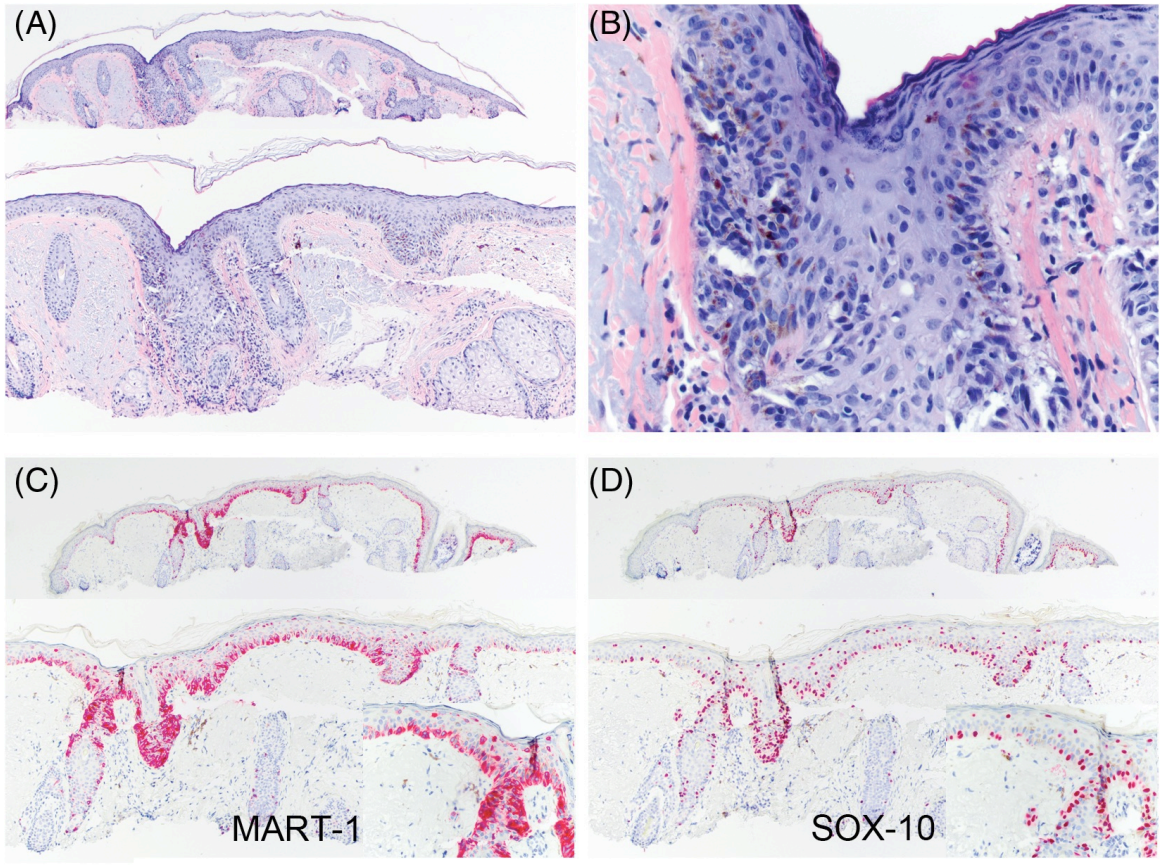
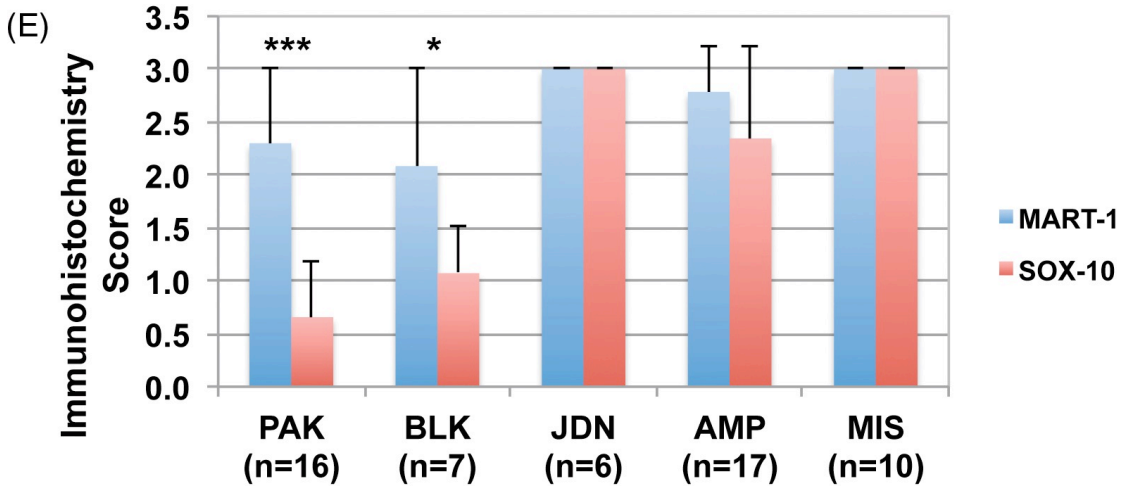


FIGURE 2 Contrast between MART-1 and SOX10 IHC in chronically sun-damaged skin with a band-like lymphocytic inflammation. (A-C) Histopathology of a patch on the right forehead of a 68-year-old male demonstrates benign lichenoid keratosis with melanin incontinence. (D-F) MART-1 (red) IHC is concerning for melanoma in situ, by highlighting the dendritic process of melanocytes, with possible inflammatory regression. G-I, SOX10 (red) highlights the nuclei of only few scattered melanocytes. Original magnifications: A, D and G (×20); B, E and H (×100); and C, F and I (×400)





SOX-10 associated with less false positive reaction in sun-damaged skin

- MART-1 and SOX10 IHC are equally efficient in confirming the diagnosis of junctional dysplastic nevus and melanoma in situ

- MART-1 over-stained epidermal melanocytes

SOX-10 expression in eccrine glands not in ducts