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**Review**

# Diagnostic Immunohistochemistry in Cutaneous Neoplasia: An Update

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**Key Words**
Immunohistochemistry · Skin cancer · Cutaneous neoplasia · Biomarkers

**Abstract**
Immunohistochemistry (IHC) is an important adjunct in the diagnosis of neoplastic skin diseases. In addition to the many established IHC markers currently in use, new markers continue to emerge, although their general acceptance and routine application requires robust validation. Here, we summarize the most well-established and commonly used biomarkers along with an array of newer ones reported in the past several decades that either demonstrate or hold high clinical promise in the field of cutaneous pathology. We also highlight recent applications of novel IHC markers in melanoma diagnosis including genetic mutation status markers [e.g. BRAF (v-raf murine sarcoma viral oncogene homolog B) and NRAS (neuroblastoma RAS viral oncogene homolog)] and an epigenetic alteration marker (e.g. 5-hydroxymethylcytosine). We specifically focus on the role of IHC in the differential diagnosis of cutaneous lesions that fall under the following categories: melanoma, epidermal tumors with an intraepidermal epitheliomatous pattern, spindle cell lesions of the dermis, small round blue cell tumors of the dermis, and cutaneous adnexal tumors. While IHC is a valuable tool in diagnostic dermatopathology, marker selection and interpretation must be highly informed by clinical context and the histologic differential diagnosis. With rapid progress in our understanding of the genetic and epigenetic mechanisms of tumorigenesis, new IHC markers will continue to emerge in the field of diagnostic dermatopathology. 

## Introduction

While the routine practice of dermatopathology relies predominantly on histologic findings and clinical context, immunohistochemistry (IHC) will remain an important adjunct tool for the diagnosis of difficult cases, tumor staging and identification of genetic variants of therapeutic significance. The utility of IHC is broad across cutaneous neoplasms but becomes

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**Table 1.** IHC staining patterns in normal skin

| Antigen | Antibodies | Internal control | Figure |
|---|---|---|---|
| Pan-cytokeratin | AE1/3 (AE1-acidic CK; AE3-basic CK), Pan-K | suprabasal keratinocytes | 1a, b, f |
| HMWCK | 34βE12 (CK1, 5, 10, 14, 15), CK5/6 | suprabasal keratinocytes and adnexal epithelia | 1c, d |
| LMWCK | CAM5.2, CK7 | secretory portion of eccrine and apocrine glands | 1e |
| Muscle markers | SMA, desmin | pilar smooth muscle | 2a–d |
| Eccrine and apocrine glands | CEA, EMA | sweat glands | 2e, f |
| Endothelial cell markers | CD31, CD34, vWF, ERG-1 | endothelial cells in vessels | 3a–d |
| Melanocytic markers | S100, MART-1, MITF, HMB-45, tyrosinase | epidermal basal layer melanocytes | 4 |
| Langerin | CD1a, CD4 | epidermal Langerhans cells | |
| Axon | NPF, S100 | nerve bundle | |

LMWCK = Low-molecular-weight cytokeratin; NPF = neuropeptide F; vWF = von Willebrand factor; Pan-K = pan-keratin.

particularly powerful when 'extracutaneous' lesions, such as metastatic carcinoma, soft tissue neoplasms and hematologic malignancies enter the differential. Overreliance upon or uninformed utilization of biomarkers, however, can be treacherous due to the diagnostic pitfalls they can create. Here, we summarize some of the most commonly used and newly emerged biomarkers for the diagnosis of cutaneous neoplasms.

## Staining Patterns of the Common IHC Markers in Normal Skin

Skin is rich in normal internal positive controls for the majority of antigens used as markers of neoplastic lesions, including keratinocytes, melanocytes, Langerhans cells and Merkel cells, as well as vessels, muscle and nerve bundles (table 1; fig. 1–3) [1]. For example, the cells of secretory coils of eccrine sweat glands are positive for low-molecular-weight cytokeratin, including CK7, cell adhesion molecule 5.2 (CAM5.2), carcinoembryonic antigen (CEA) and epithelial membrane antigen (EMA), while acrosyringeal cells of the intraepidermal portion of sweat glands are positive for high-molecular-weight cytokeratins (HMWCK). Careful attention to positive and negative internal controls is a critical first step in the interpretation of IHC staining.

## IHC Markers for Melanoma Diagnosis

Melanoma is the most lethal type of skin malignancy, causing approximately 75% of skin cancer-related deaths worldwide [2]. Optimal therapy and patient prognosis for melanoma critically depend on early detection and accurate diagnosis. Given the tremendous histologic diversity of melanoma, diagnosis can be challenging [3]. Melanocytic lesions are now the second highest source of litigation in surgical pathology, following only lesions of the breast [4, 5]. Utilization of a panel of melanocytic IHC markers can be an extremely valuable adjunct to hematoxylin and eosin (H&E) morphology for the diagnosis of melanoma, although what

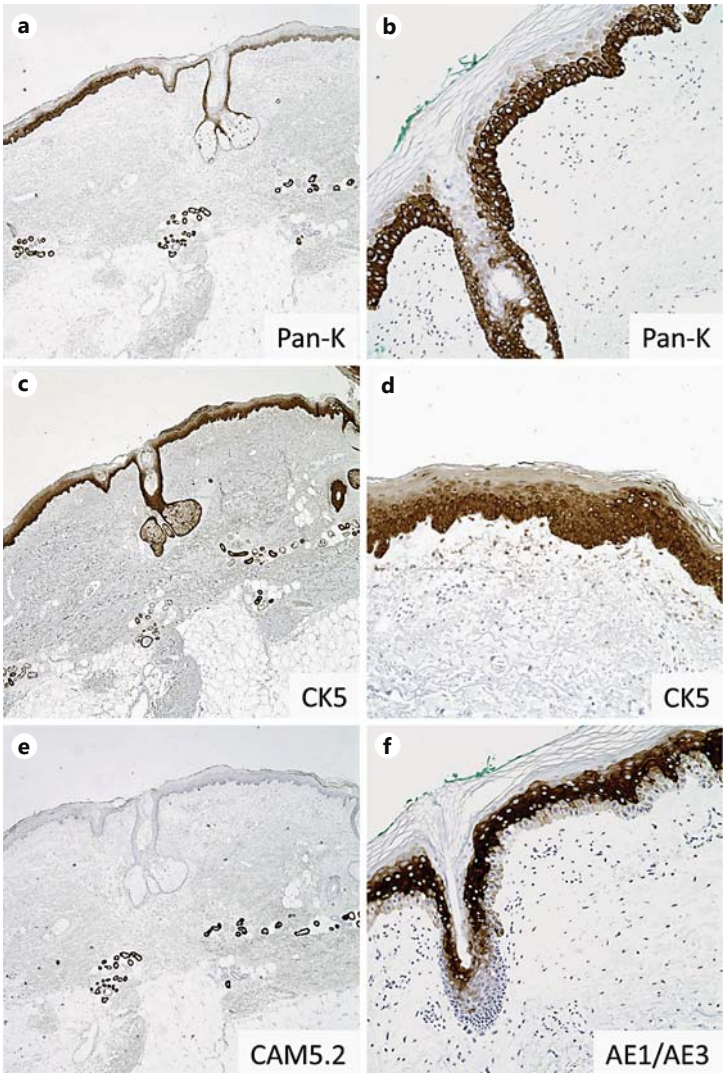


**Fig. 1.** Keratin expression in normal skin. **a**, **c**, **e** Staining patterns of pan-keratin (Pan-K), HMWCK (CK5) and low-molecular-weight cytokeratin (LMWCK; CAM5.2) in normal skin. Pan-K (**a**) and HMWCK CK5 (**c**) highlight epidermal and follicular epithelium as well as dermal eccrine myoepithelium; **e** LMWCK CAM5.2 stains eccrine myoepithelium but not the epidermis or follicular epithelium. **b**, **d**, **f** Staining patterns of Pan-K, CK5 and AE1/AE3 in epidermis. Basal layers of the epidermis and hair follicle strongly express Pan-K (**b**) and HMWCK CK5 (**d**), while more superficial cell layers show decreased expression with cell maturation. **f** By contrast, more superficial/mature layers of the epidermis and follicle show strong expression of AE1/AE3, while the basal layers show little expression.

appears to be routine use of such panels by some laboratories for a majority of melanocytic lesions is inappropriate [6, 7]. Accordingly, stringent and informed selection of cases that require IHC as a diagnostic adjunct is of utmost importance.

Among all IHC markers, S100 is among the most sensitive for melanocytic lesions, although it lacks specificity. Melanoma antigen recognized by T cells (MART-1), micropthalmia-associated transcription factor (MITF) and/or human melanoma black-45 (HMB-45) are frequently used because they provide increased specificity and reasonable sensitivity for differentiating most conventional melanomas from nonmelanocytic histologic mimics. HMB-45 has additional utility in differentiating benign melanocytic lesions from malignant melanoma as benign lesions (e.g. dermal nevi) tend to show decreased expression with lesion depth/maturation, while melanoma often shows more consistent staining in the deeper component. However, numerous exceptions exist, particularly in the setting of certain nevic variants of melanoma. Thus, interpretation of HMB-45 staining is not always straightforward, and expression (or lack thereof) should never be a single or dominant criterion in the establishment of a benign versus a malignant lesion. IHC is also useful in gauging confluent (contiguous/continuous) junctional growth of intraepidermal melanocytic proliferations or extent of pagetoid spread to help rule

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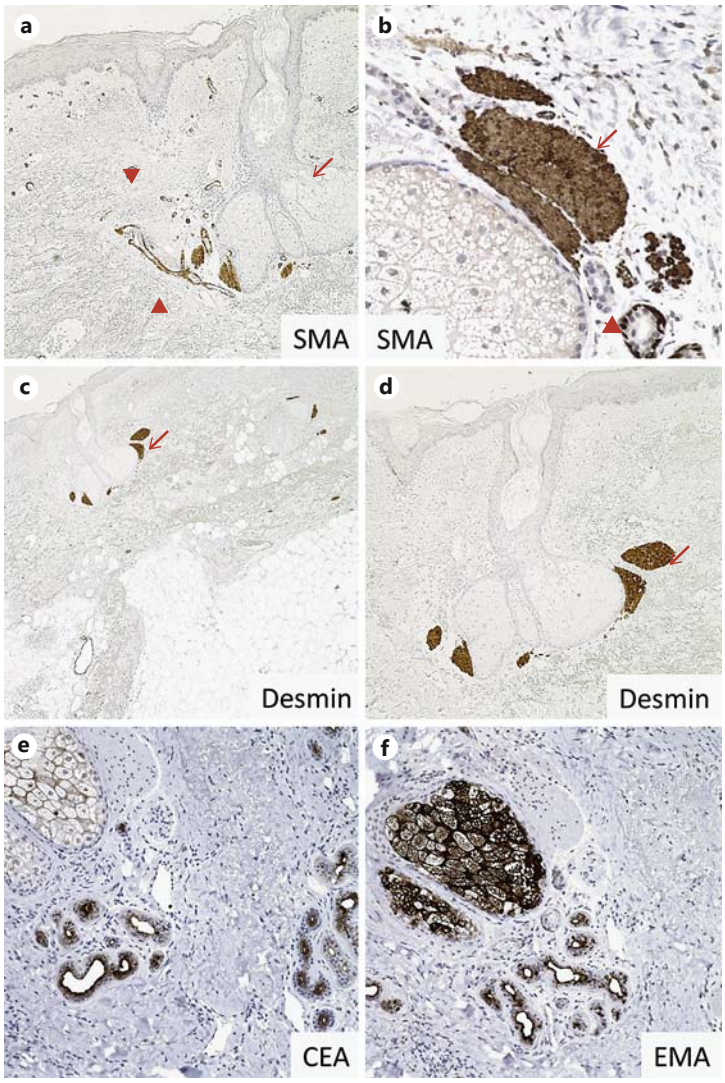


**Fig. 2.** Pilosebaceous unit IHC markers in normal skin. **a**, **b** SMA is strongly expressed in pilar muscle (arrows), eccrine myoepithelium (arrowheads) and vascular smooth muscle (not shown) in normal skin. **c**, **d** Pilar muscle also strongly expresses desmin (arrows). **e** Adnexal ducts are highlighted by CEA. **f** EMA immunostain highlights the luminal lining of adnexal ducts and sebaceous glands.

in or out a diagnosis of melanoma in situ or an in situ melanoma component of a worrisome compound melanocytic lesion. Although MART-1 is widely used for this purpose, the degree of confluent growth may be overestimated due to positive staining of melanocyte dendritic processes that wrap around keratinocytes and/or as a consequence of false-positive 'overstaining' [7–10] (fig. 4a–d). For these reasons, some prefer staining with the nuclear marker MITF when evaluating possible confluent lentiginous growth of the intraepidermal components of melanocytic lesions [7–10]. IHC for keratin may also be useful, as it provides the negative image of an intraepidermal melanocytic proliferation [11]. Of note, it is important to be aware of a few reports of melanomas with heterologous differentiation that express keratin, vimentin, EMA or smooth muscle actin (SMA), and such cases may create difficult diagnostic pitfalls, particularly in the setting of metastatic malignancy [3, 12–14], further emphasizing the value of assessing a complementary panel of well-selected biomarkers when faced with challenging neoplasms of potential melanocytic differentiation.

*Surrogate IHC Markers for Mitoses in Melanoma – Phosphorylated Histone H3 and Ki-67*

In the 7th edition of the American Joint Committee on Cancer (AJCC) Staging Manual, mitoses within the dermal/invasive component were added to the tumor staging criteria for

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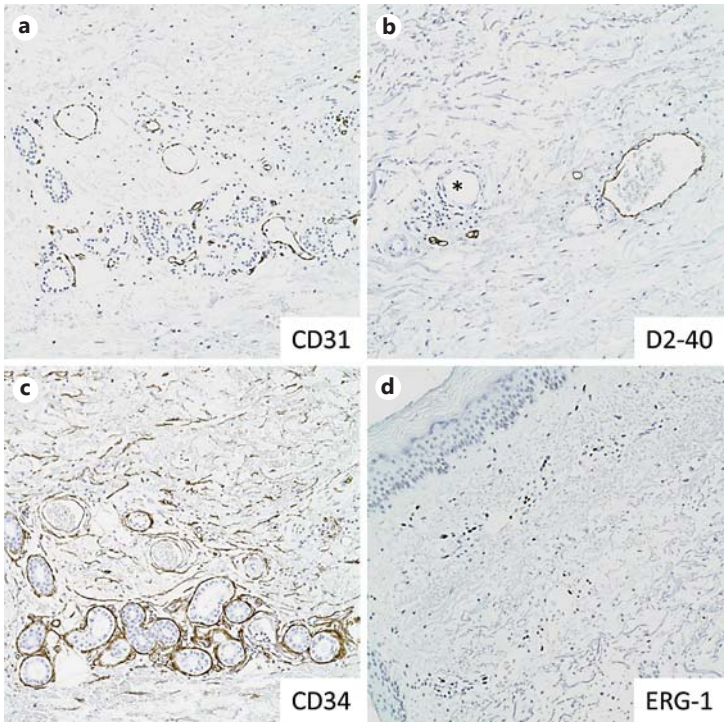


**Fig. 3.** Lymphovascular IHC markers in normal skin. **a** CD31 highlights endothelial cells of dermal vessels. **b** D2-40 highlights the lining of dermal lymphatic channels but does not stain vascular endothelium (asterisk). **c** CD34 highlights dermal vascular endothelium and dermal mesenchymal cells. **d** ERG-1 is a nuclear stain of vascular endothelium.

primary cutaneous melanoma [15] as their presence is believed to have significant prognostic value. While mitotic counts are a routine part of the practice of pathology, accurate evaluation in skin biopsies and excisions may be challenging due to the small sample size and as a result of histologic mimics, such as apoptotic tumor cells or mitoses in surrounding inflammatory or stromal cells. Studies have demonstrated a potential role for immunohistochemical markers of proliferation in the staging of primary cutaneous melanoma. Phosphorylated histone H3 (pHH3) is a general marker of cell proliferation whose utility in melanocytic lesions remains under active investigation. Histone H3 is phosphorylated during late G2/early M phases of the cell cycle coincident with chromatin condensation and is dephosphorylated between late anaphase and telephase, making pHH3 a useful proxy of cell division. Data suggest that pHH3 staining successfully highlights mitoses in cutaneous melanomas and reduces interobserver variability [16, 17]. Co-staining for pHH3 with one or more markers of melanoma, such as MART-1, may further improve accurate enumeration of mitoses restricted to cells of melanocytic lineage and reduce time spent on analysis [16, 18]. In these studies, a mitosis was counted if the cell lacked a nuclear membrane and the chromatin was condensed and positive for pHH3. Multiple studies have identified the pHH3 index to be a powerful independent prognostic factor that rivals, and in some cases exceeds, the predictive value of histologic mitotic counts [16, 19, 20]. Double staining for a melanoma marker and limiting analysis to a mitotic 'hot spot', instead of the entire slide or specimen, has the greatest prognostic value [20]. Currently, the pHH3 index has not been introduced into standardized practice guidelines, such as the AJCC, and has not achieved widespread use in routine dermatopathology. For now, pHH3/melanoma marker co-stains serve to increase confidence in staging difficult cases of cutaneous melanomas, particularly when H&E stains are equivocal.

Antigen KI-67 (Ki-67) is a nuclear protein expressed as two isoforms during the G1, S, G2 and M stages of cell division, making it a more sensitive (inclusive) marker of proliferation when compared with histologic mitotic counts or pHH3 staining approaches. Similar to pHH3,

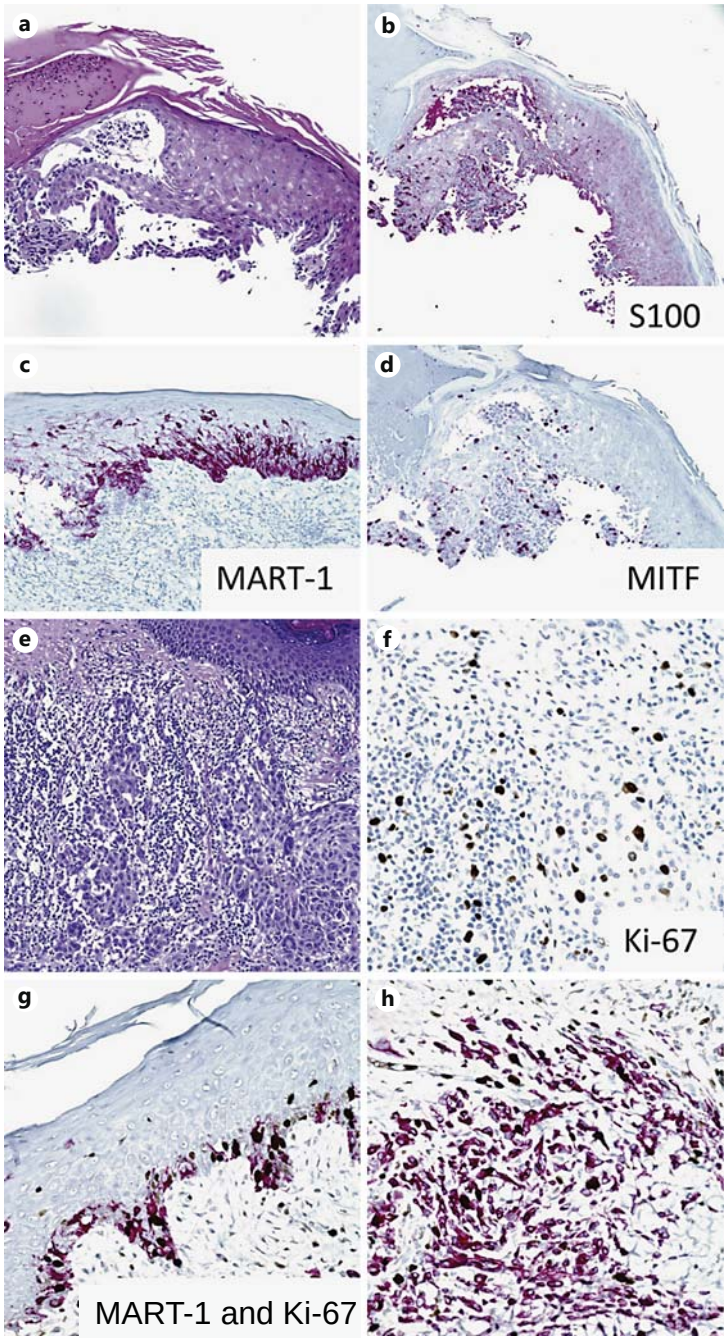


**Fig. 4.** Melanocytic markers. Melanoma in situ (**a**) highlighted by immunostains of S100 (**b**), MART-1 (**c**) and MITF (**d**). **e**, **f** Ki-67 immunostain in a melanoma with a brisk tumor infiltrating lymphocytic response, highlighting the difficulty in interpreting lineage of Ki-67-positive cells. **g**, **h** Double Ki-67 and MART-1 immunostains of melanoma, highlighting cell proliferation specifically in melanocytic lineages.

the Ki-67 index of cutaneous melanomas is a powerful, statistically significant, independent prognostic factor [20, 21]. Going forward, standardized Ki-67 indices would need to be established for melanoma by consensus prior to widespread use in staging. In melanomas with a brisk tumor-infiltrating lymphocyte response, single labeling with Ki-67 may lead to overestimation of the proliferative index due to the high density of mitotically active inflammatory cells (fig. 4e, f). In such cases, a Ki-67 and MART-1 double staining is recommended to clarify the histogenesis of proliferating cells (fig. 4g, h). Additionally, a recent report indicates that the mixed variant of desmoplastic melanoma (e.g. lesions also containing sarcomatoid or epithelioid regions) has a higher proliferative index based on Ki-67 IHC compared with the

pure variant [22, 23]. Studies with larger numbers of cases and a broader spectrum of melanocytic lesions to include nevi (especially traumatized and irritated lesions), Spitzoid lesions and borderline melanocytic lesions are needed to firmly establish the diagnostic and prognostic value of Ki-67 staining in melanocytic neoplasms.

*SRY (Sex-Determining Region Y)-Box 10*

SRY (sex-determining region Y)-box 10 (SOX10), a member of the Sry HMG box (Sox) family of transcription factors, is essential for maintenance of neural crest progenitor cells and their subsequent differentiation down melanocytic and glial lineages during embryogenesis [24]. Multiple studies have demonstrated that SOX10 is a highly sensitive immunohistochemical marker of both benign and malignant melanocytic lesions, making it a useful cell lineage indicator in the appropriate clinical context. Nearly 100% of primary melanomas display strong nuclear staining for SOX10 [25–27]. While SOX10 shows similarly high sensitivity for metastatic melanoma, staining intensity and the percentage of positive nuclei may be lower compared with benign melanocytic lesions and primary melanomas [25]. As with most IHC biomarkers, SOX10 should not be used in isolation for the diagnosis of metastatic lesions, particularly in the setting of unknown primary tumors, given that a subset of breast and salivary gland carcinomas stain positively for SOX10 [28–30], and expression has yet to be defined in many carcinomas. One area, however, where SOX10 may have particular utility is in differentiating desmoplastic melanoma from a variety of histologic mimics including fibrohistiocytic lesions, mesenchymal neoplasms, 'spindled' carcinomas and cellular excisional scars. Desmoplastic melanoma often does not stain for proteins considered to have higher specificity for conventional melanoma, such as MART-1, MITF and HMB-45. S100 is a highly sensitive marker of desmoplastic melanoma, but is also expressed by a number of mimics, including excisional scars, limiting its diagnostic utility. SOX10, however, is strongly expressed in 100% of desmoplastic melanomas [25–27, 31], but not in the majority of spindle cell mimics, including a variety of sarcomas, spindle cell squamous cell carcinoma (SCC), fibrohistiocytic lesions such as Rosai Dorfman, atypical fibroxanthoma (AFX), dermatofibroma, Langerhans cell histiocytosis (LCH), juvenile xanthogranuloma, cellular neurothekeoma, reticulohistiocytoma, and the most frequently encountered (and perhaps treacherous mimic) cellular scar [25, 26, 31]. Thus, SOX10 may be particularly useful in evaluating residual desmoplastic melanoma and assessing its proximity to margins in reexcision specimens. Of note, SOX10 is expressed in 100% of clear cell sarcomas, 100% of neurofibromas and schwannomas and approximately 50% of malignant peripheral nerve sheath tumors (MPNST). As such, SOX10 should not be utilized to differentiate these entities from melanoma. However, in most instances, histologic features alone should suffice (the diagnosis of spindled cell dermal tumors is further discussed in a subsequent section). In addition to positivity for SOX10, clear cell sarcomas frequently show at least partial positivity for other melanocytic markers including S100, MITF, Melan A and HMB-45 [32, 33]. Unlike melanoma, however, approximately 75% of clear cell sarcomas harbor a t(12;22)(q13;q12) that creates an EWS-ATF1 fusion protein known to activate the MITF promoter in a SOX10-dependent manner [34]. PCR-based methods and fluorescent in situ hybridization may be used to detect this chromosomal translocation [35], which has never been described to occur in melanoma.

*Genetic and Epigenetic IHC Markers with Potential Clinical Implications*

The recent rapid progress in our understanding of the genetic and epigenetic mechanisms of melanomagenesis has heralded a new set of biomarkers of potential clinical importance. Recent studies demonstrate that IHC is a practical and easy method to detect the genetic mutational status of BRAF V600E (fig. 5a, b) and NRAS Q16R (fig. 5c) in melanoma. Genetic mutations in v-raf murine sarcoma viral oncogene homolog B (BRAF) and neuroblastoma

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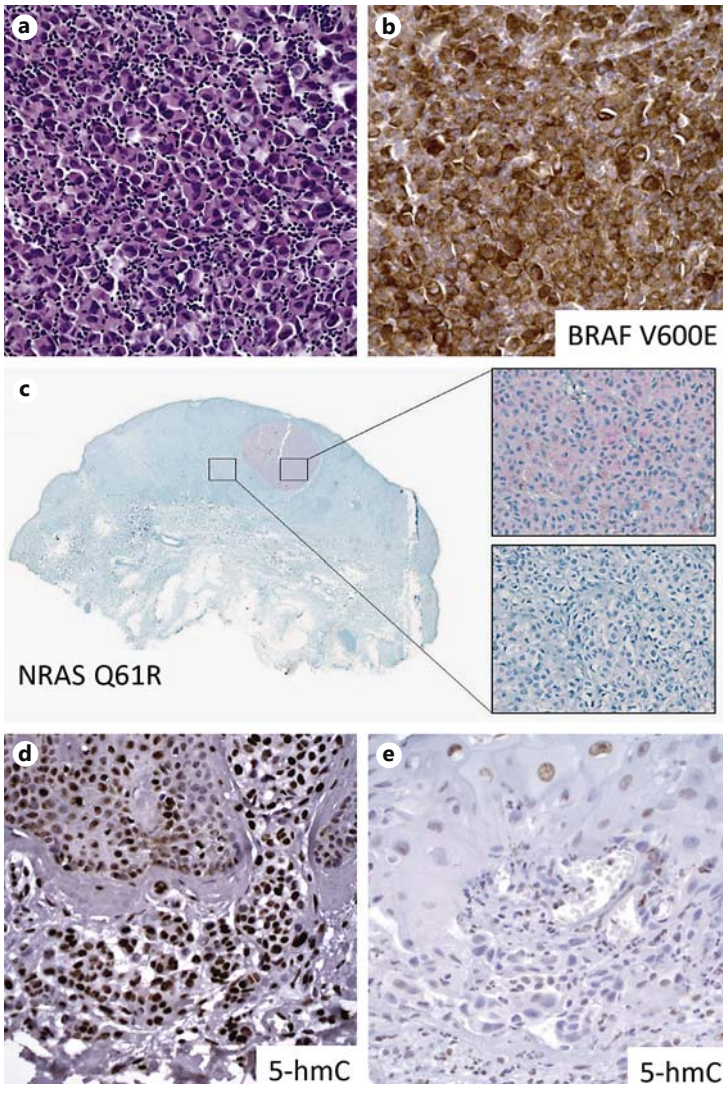


**Fig. 5.** IHC markers for genetic mutations and epigenetic alteration in melanoma. **a**, **b** Cytoplasmic positivity of BRAFV 600E immunostains highlights the melanoma cells with BRAF V600E mutation. **c** Intratumoral heterogeneity shown by NRAS (Q61R) immunostains correlates with the different NRAS Q16R mutational status confirmed by high-resolution melting analysis and sequencing of NRAS exon 3. Reprinted from *Modern Pathology* with permission from Nature Publishing Group. IHC for epigenetic DNA hydroxymethylation mark (5-hmC) shows significant loss of 5-hmC positivity in metastatic melanoma (**e**) compared with strong staining intensity in nevus (**d**).

RAS viral oncogene homolog (NRAS) are present in approximately 50 and 20% of melanomas, respectively [36, 37], and result in constitutive activation of MAPK pathways. The RAS-RAF-MAPK pathway has, in fact, proven to be a key therapeutic target for the treatment of metastatic melanoma, as multiple inhibitors either have achieved FDA approval, or are under investigation in clinical trials (e.g. BRAF inhibitor vemurafenib, MEK inhibitors). As such, accurate and rapid tests to assay mutational status are essential. Currently, molecular genetic testing is the preferred assay to determine BRAF inhibitor eligibility due to its superior sensitivity. Recent studies have shown that IHC for BRAF V600E and NRAS Q16R has excellent specificity that is highly concordant with molecular testing (e.g. PCR, pyrosequencing or next-generation sequencing) [38–41]. Other point mutations of BRAF (V600K, V600Q, and V600R) or NRAS (Q61K, Q61L, Q61H) melanomas do not stain positively with BRAF VE1 and NRAS Q61R antibodies [39, 41], respectively. In addition, studies indicate that germline mutation of BRAC1-associated protein (BAP-1) is associated with multiple cutaneous Spitzoid melanocytic neoplasms, as well as frequent somatic mutations in uveal melanoma [42–44]. The loss of BAP-1 in BAP-1 mutant melanocytic lesions can be detected by IHC [42–44].

In addition to genomic mutations, recent data demonstrate that epigenetic alterations play important roles in melanoma pathogenesis. Our group reported that detection by IHC of the loss of the DNA hydroxymethylation mark, 5-hydroxymethylcytosine (5-hmC), is a putative biomarker with diagnostic and prognostic value in melanoma [45] (fig. 5d, e). Additional studies by our group and others have demonstrated clinical application of immunohistochemical evaluation of 5-hmC, particularly with respect to differentiating micrometastases in sentinel lymph nodes from dermal nevic nests, and in the evaluation of melanocytic dysplasia [45–49].

Other markers under active investigation for their utility in the diagnosis and staging of melanoma include RUNX3 [50, 51], MAP-2 [52], nucleolin protein [53], KIT and p16 [54]. We also have noted that melanomas express the embryonic stem cell transcription factor SOX2 [55]. While not lineage specific, its expression appears to correlate with a more invasive phenotype [56], and IHC may be practically useful, when used in combination with detection of the intermediate filament protein nestin in verifying nodal melanoma metastases [57].

*IHC Biomarkers for Prediction of Response to Melanoma Therapy*

Given the recent progress of melanoma immunotherapy with regard to the blockade of immune checkpoints [e.g. CTLA-4 Ig and programmed cell death (PD-1) and programmed cell death ligand 1 (PD-L1)], there is urgent need to develop biomarkers to predict treatment responses. A recent study showed that PD-L1 IHC highlighted metastatic melanoma cells with membrane positivity in 30/81 (37%) of patients [58]. By multivariate analysis, Breslow thickness and PD-L1 membrane positivity were independent risk factors for melanoma-specific death [58]. However, interpretation of PD-1 and PD-L1 IHC stains requires caution given the expression of these epitopes on immune cells within the tumor microenvironment [59, 60]. Nonetheless, the ability to profile expression of potentially targetable immune checkpoints in melanoma tissue as a means of stratifying patients who may benefit most from specific therapies holds significant promise for personalized melanoma therapies. IHC to assess induction of metastasis infiltrating lymphocytes may also be used as one potential measure of immunotherapeutic treatment efficacy, as has recently been shown in a patient cohort treated with bevacizumab (VEGF inhibitor) and ipilimumab (CTLA-4 blocker) [61]. The importance of biomarker validation prior to clinical application has recently been emphasized in reference to a prominent report, based largely on in vitro data, implicating detection of hepatocyte growth factor in melanoma stroma as a means of predicting response to RAF inhibitors [62]. Detailed examination of this possibility using a large cohort and meticulously controlled reagents, however, failed to support this claim [63], further emphasizing the necessity for rigorous validation testing of any new biomarker that may potentially be employed in the care of patients.

## Epidermal Tumors with Intraepidermal Epitheliomatous Pattern

The differential diagnosis of intraepithelial lesions can be difficult given their frequent overlap in architectural and cytomorphologic patterns. Moreover, diagnostic pitfalls can be compounded by superficial and fragmented biopsies that only show part of the lesion. SCC, extramammary Paget's disease (EMPD), malignant melanoma, Merkel cell carcinoma (MCC), LCH and adnexal carcinoma (sebaceous, eccrine, and apocrine) can all exhibit pagetoid and nested patterns of intraepidermal growth in the presence or absence of an invasive/dermal component. And while most cases of these entities can be diagnosed by routine histology, IHC can be of considerable assistance in the diagnosis of problematic lesions, thus avoiding diagnostic pitfalls that may impact on patient care [64].

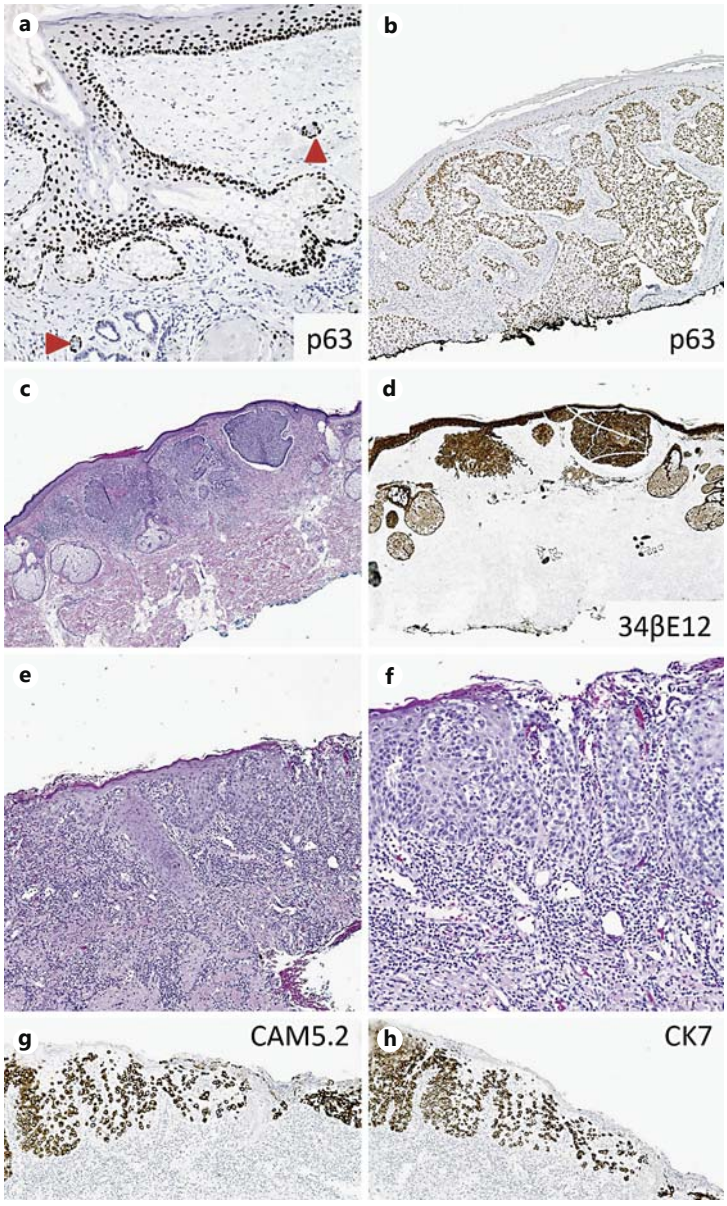


**Fig. 6.** IHC markers for epidermal tumors with intraepithelioma-tous pattern. **a**, **b** p63 expression in normal skin and squamous cell carcinoma. The epidermis, hair follicle and basal layers of the se-baceous unit express p63, with the strongest expression present towards the basal-most layers. p63 highlights myoepithelial cells of the eccrine units/ducts (arrow-heads). Squamous cell carcinoma intensely expresses p63. **c**, **d** IHC for HMWCK 34βE12 highlights basal cell carcinoma. **e**, **f** HE sec-tions of EMPD show Paget tumor cells in epidermis and extend into dermis. LMWCK immunostains CAM5.2 (**g**) and CK7 (**h**) highlight tumor cells in EMPD.

In situ SCC and melanoma, as well as EMPD are among the most frequently encountered entities demonstrating pagetoid growth patterns [65–68], and both occasionally will closely mimic pagetoid radial growth in melanoma. Historically, immunohistochemical positivity for CK7 and Cam5.2 has been utilized to favor a diagnosis of EMPD over SCC, and it also assists in excluding pagetoid radial growth phase melanoma. However, while invasive SCC does not frequently express these markers, recent data suggest pagetoid/'Bowenoid' SSCIS is frequently positive for CK7 and CAM5.2 [66, 69, 70]. p63, encoded on chromosome 3q27–28, is a p53 homolog required for epidermal development and stem cell maintenance [71, 72]. Due to its nuclear pattern of positivity, many regard this stain as easier to interpret, compared with cytokeratin reactivity. p63 is strongly expressed in normal basal and supra-basal epidermal layers and basal cells of sebaceous and sweat glands [73], and is not

**Table 2.** IHC panels for epidermal tumors with intraepitheliomatous patterns

| | MMIS | SCCIS | MCC | Seb CIS | LCH | EMPD | BCC |
|---|---|---|---|---|---|---|---|
| Screening | S100 | p63, EMA | CK20 | EMA, AR, adipophilin | CD1a, langerin | LMWCK | Ber-EP4 |
| EMA | 5% [161] | 79–96% [66, 83, 170, 171] | 100% [81] | 91–100% [83, 85, 171] | 0% [93] | 100% [172] | 0–6% [83, 170, 171] |
| Androgen R | 0% [173] | 0–10% [83, 84] | – | 83–100% [83–85] | – | 52–80% [86, 87] | 33–60% [83, 85] |
| Ber-EP4 | 0% [78] | 0–2% [66, 83, 170] | 75% [79] | 6% [83] | – | 100% [66, 78] | 80–100% [83, 170, 174] |
| CEA | – | 20–30% [83, 170] | 0% [175] | 42% [83] | – | 100% [172] | 0–20% [83, 170, 176] |
| Adipophilin | – | 0–10% [83, 88] | 0% [89] | 92–97% [83, 88, 89] | – | – | 0% [83, 88] |
| CD1a | 0% [91, 177] | Negative [178, 179] | – | – | 94–100% [180] | – | – |
| Langerin | – | – | – | – | 99–100% [92, 180] | – | – |
| CK7 | 0% [66] | 0–40% [174] | 50% [79] | 75% [83] | – | 100% [66, 181] | 0–70% [174, 176, 182] |
| CK20 | 0% [82] | 0% [183] | 83–100% [80–82, 170] | 0% [83] | – | 0% [181] | 0% [176, 182] |
| Cam5.2 | 0–10% [66, 161] | 0–10% [66, 171, 174] | 100% [79, 184] | 73% [171] | – | 100% [66, 69] | 20–95% [170, 171, 174, 176] |
| p63 | 0% [75] | 87–100% [73, 74] | 33% [185] | 100% [186, 187] | – | 0–17% [76, 77] | 100% [73] |
| S100A | 100% [82] | 0% [188] | 0–17% [82, 175] | N/A | 93–99% [93, 180] | 0% [189–191] | 0% [188] |
| MART-1 | 94% [188] | 0% [188] | – | – | – | – | 0% [188] |
| HMB 45 | 100% [78, 82] | 0% [188] | 0% [82] | – | – | 0% [78] | 0% [188] |

MMIS = Malignant melanoma in situ. Numbers in square brackets indicate references.

expressed in terminally differentiated cells (fig. 6a). Thus, the majority of SCC and basal cell carcinoma (BCC) express p63 immunostains (fig. 6b–d; tables 2, 3), including intraepidermal epitheliomatous variants, while staining is generally negative for EMPD [73–77]. On the other hand, Ber-EP4 is a highly sensitive marker of EMPD and BCC that is not expressed by pagetoid/Bowenoid SCC or melanoma [66, 78] (fig. 6c, d). Therefore, a panel of Ber-EP4, p63, and a specific melanoma marker such as MART-1 would be effective in differentiating these entities (table 2; fig. 6).

Epidermotropic/in situ MCC is a rare entity that frequently expresses Ber-EP4 [79], making this marker a poor choice to differentiate it from EMPD, although cytomorphologic features of these two entities are quite distinct from one another. Amongst intraepidermal lesions, CK20 is the most specific marker of MCC, and this can be added to the panel of diagnostic markers in the appropriate clinical setting or in difficult cases [80–82]. We have seen cases where squamous cell carcinoma in situ (SCCIS) and MCC in situ coexist, a rare and diagnostically challenging event that is easily resolved by the use of appropriate immunohistochemical panels.

**Table 3.** IHC panels for spindle cell neoplasms

| | Desmoplastic melanoma | SCC (PD/ sarcomatoid) | AFX | Angiosarcoma | Kaposi's sarcoma |
|---|---|---|---|---|---|
| Screening | S100 | p63 | CD10 | CD34 | HHV-8 |
| S100 | 83–100% [26, 27, 192, 193] | 0% [192] | 0% [104, 192, 194, 195] | 6% [108] | 0% [196] |
| HMB45 | 0% [26, 197] | 0% [198] | 0% [194, 195] | 0% [108, 109] | – |
| SOX10 | 100% [25–27, 31] | 0% [31] | 0% [25, 31] | N/A | – |
| AE1/AE3 | 0% [192] | 67–100% [105, 192, 199, 200] | 0% [105, 192, 194, 200] | 3–45% [108, 113] | – |
| Pan-K | 0% [201] | 40% [201] | 2% [201] | 35% [108] | – |
| p63 | 5% [70, 102] | 70–100% [102, 105, 199, 200, 201, 202] | 0–20% [102, 105, 195, 200–202] | 0–22% [70] | 0% [70] |
| CD10 | 0–44% [102, 104, 192, 201] | 14–50% [102, 192, 201] | 83–100% [102, 104, 192, 201, 203] | – | – |
| CD34 | See text [204–206] | – | 0% [195] | 21–74% [108, 110, 111] | 89–100% [120, 207] |
| ERG | – | 0% [113] | 0% [113, 195] | 100% [113] | 92–100% [208, 209] |
| CD31 | – | – | Up to 43% [195] | 33–100% [108–112] | HIV: 100% [207] Non-HIV: 83% [207] Not specified: 84% [120] |
| MYC | 5% [210] | – | – | Secondary: 100% Primary: 0–45% [114–117] | 43–54% [211, 212] |
| HHV-8 | – | 0% [198] | – | 0% [118, 213, 214] | 95–100% [118–120] |

Numbers in square brackets indicate references. Pan-K = Pan-keratin.

Sebaceous carcinomas (SC) can have cytomorphologic and architectural overlap with SCC, BCC, melanoma and their variants. SC, when invasive, is a more aggressive tumor than BCC and most SCC, although surgical management can be curative, making accurate diagnosis of high clinical importance. Androgen receptor (AR) is a highly sensitive marker of SC that is useful for differentiating SC from SCC or melanoma. BCCs and EMPD [83–85], however, frequently express AR, making it a poor choice to differentiate SC with a similar intraepithelial pattern from these entities [83, 85–87]. More recent studies have identified adipophilin as a sensitive marker of SC, with high specificity among intraepithelial lesions, although expression in melanoma and EMPD has not been described [83, 88, 89]. Adipophilin is expressed in a membranous and vesicular pattern due to its association with membrane-bound and vesicle-laden lipids. A granular pattern of staining, sometimes present in other intraepidermal carcinomas like SCC, is not considered positive. Clear cell variants of SCC and BCC are negative for adipophilin, supporting the utility of this marker in differentiating intraepidermal carcinomas with clear cell features. The luminal cells recapitulating ductal differentiation in sweat gland neoplasms can be highlighted by CEA and/or EMA IHC stains [90], which can be helpful to distinguish the in situ component of eccrine, apocrine, and sebaceous neoplasms from EMPD or SCCIS.

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Because LCH in the adult is rarely limited to the skin, it is frequently overlooked in the differential diagnosis of intraepidermal lesions. Case reports describe instances in which LCH was mistaken for malignant melanoma due to an epithelioid cytomorphology and positivity for S100 [91], and we have also seen a case of Langerhans cell proliferation within the epidermis associated with a delayed hypersensitivity reaction (so-called Langerhans cell granulomas) mistaken for Pautrier microabscesses of mycosis fungoides, and when on nipple skin, for mammary Paget disease. Both CD1a and langerin are sensitive markers of LCH, and their use should be considered in the diagnosis of intraepidermal lesions. CD1a appears to have greater sensitivity for LCH among histiocytoses, and langerin, which correlates with the expression of Birbeck granules required to differentiate a Langerhans cell from an indeterminate cell, is of greater specificity [92, 93]. A panel approach is recommended that includes appropriate markers of epithelial and melanocytic lineage, when the differential diagnosis includes SCCIS, EMPD, and/or Pagetoid melanoma. Because both LCH cells and malignant T cells may express CD4, pan T cell markers (e.g. CD3) should be employed when the differential diagnosis includes mycosis fungoides.

## Spindle Cell Tumors in the Dermis

The differential diagnosis for spindle cell lesions in the dermis is quite broad, making IHC invaluable for classifying the many entities that may have overlapping histomorphologies. Here, we present markers used to diagnose some of the most commonly encountered tumors affecting the skin, including desmoplastic melanoma, poorly differentiated/sarcomatoid SCC, AFX, angiosarcoma (AS), and Kaposi's sarcoma (KS). Less common spindled cell tumors involving the dermis include cellular neurothekeoma with spindle cell differentiation, amelanotic cellular blue nevus [26, 94], cutaneous leiomyosarcoma/atypical intradermal smooth muscle neoplasms [95] and pleomorphic liposarcoma. In addition, exuberant formation of scar tissue is also common in the differential diagnosis, and it is worth noting that both desmoplastic melanoma and cellular scar tissue may contain cells that are immunoreactive for S100 [26, 96, 97], and neither may stain with antibodies that generally are associated with melanocytic lineage, such as HMB-45 [26]. Markers of high utility in the accurate diagnosis of dermal spindle cell tumors (table 3), when used in the proper clinical context and in the form of well-selected panels, include keratins (pan-keratin, HMWCK), p63, melanocytic markers (S100, MART-1, and HMB-45), desmin, SMA, and endothelial markers (CD31 and CD34).

Dermatofibroma is one of the most frequently encountered spindle cell lesions of the dermis, and when cellular, deep, or incompletely sampled, may pose vexing diagnostic challenges. CD34 is helpful in distinguishing dermatofibrosarcoma protuberans (DFSP) from DF and its variants. While DFSP often shows diffuse, strong positivity for CD34 [98, 99], DF may have focal staining at the periphery and is positive for factor XIIIa (fig. 7a–d) [99]. However, it is the CD34 negativity that is most helpful in establishing a diagnosis of an unusual or worrisome dermatofibroma because FXIIIa expression lacks specificity (and may even be expressed by stromal cells in desmoplastic melanoma [100], making overinterpretation based on its expression potentially hazardous).

In the absence of an intraepidermal component, desmoplastic melanoma can be easily overlooked or mistaken for biopsy/excisional scar, making it a frequent cause of melanoma-related litigation. The utility of SOX10 in diagnosing desmoplastic melanoma due to the paucity of sensitive and specific markers is discussed elsewhere in this article (fig. 7e–h). Although MPNST, schwannomas, and neurofibromas are positive for SOX10, data published to date suggest that most other soft tissue and dermal spindle cell tumors, including spindle

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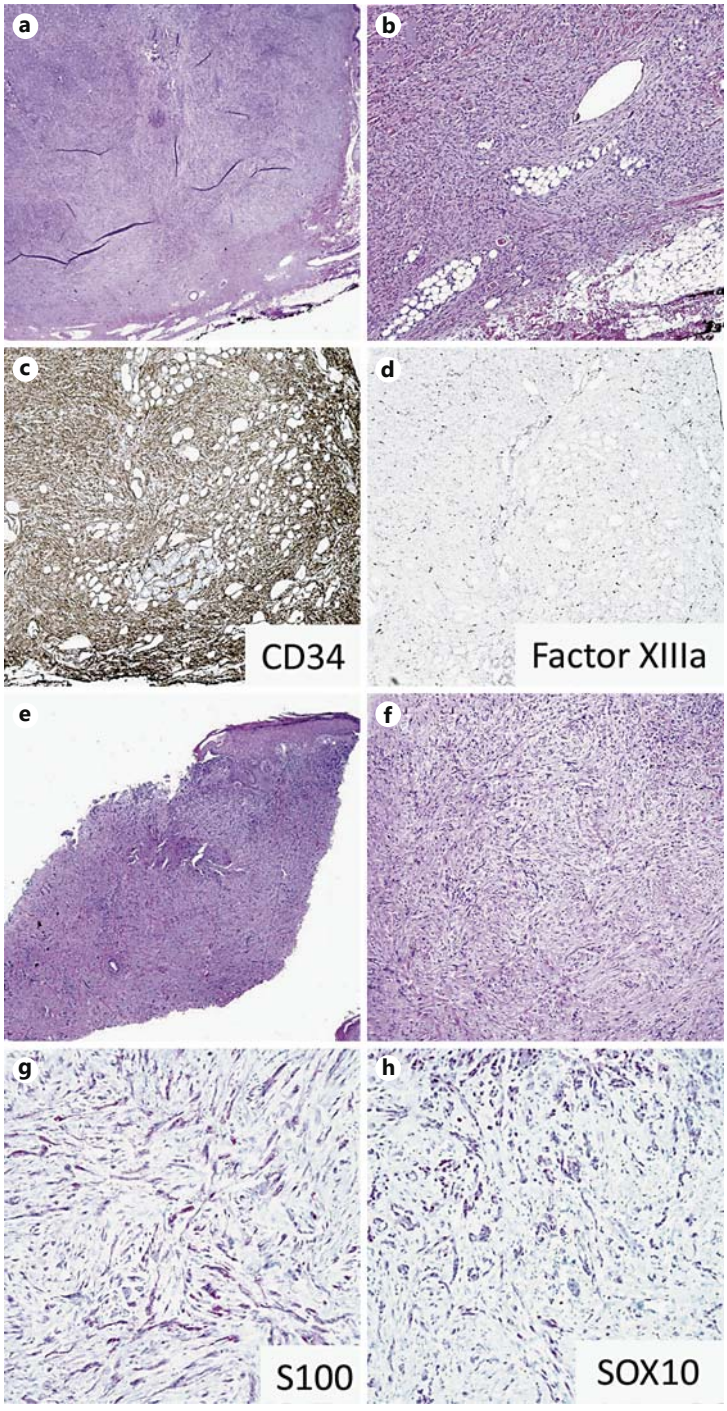


**Fig. 7.** IHC markers for dermal spindle cell neoplasms. **a–d** DFSP tumor cells are positive for CD34 (**c**) and negative for factor XIIIa (**d**). **e–h** Desmoplastic melanoma cells are positive for S100 (**g**) and SOX10 (**h**).

cell SCC, AFX, and DFSP are negative for SOX10 [31, 101]. Expression of SOX10 in AS and KS remains undescribed.

Immunohistochemical studies for p63 are widely regarded as useful in confirming squamous differentiation, with particular utility in the diagnostic differentiation of poorly differentiated/spindle cell variants of invasive SCC from AFX and melanoma, as well as from some mesenchymal neoplasms [70]. However, a comprehensive analysis of p63 expression

in soft tissue neoplasms demonstrated a total lack of immunoreactivity in AS, lipomatous neoplasms, DFSP, solitary fibrous tumor, schwannoma, neurofibroma, and leiomyosarcoma [70]. Nuclear p63 reactivity was found in a subset of soft tissue neoplasms including myoepithelioma, cellular neurothekeoma, soft tissue perineurioma, Ewing's sarcoma/peripheral neuroectodermal tumor, diffuse-type giant cell tumor, and giant cell tumor of soft parts. Infrequent, weak, or focal p63 positivity was observed in low-grade fibromyxoid sarcoma, MPNST, extraskeletal myxoid chondrosarcoma, myxofibrosarcoma, proximal-type epithelioid sarcoma, synovial sarcoma, embryonal rhabdomyosarcoma, desmoplastic small round cell tumor (DSRCT), AFX, and spindle cell melanoma.

When a differential diagnosis includes melanoma, sarcomatoid SCC, and AFX, a panel of S100 and/or SOX10, cytokeratins, and p63 are useful. Within the context of this differential diagnosis, S100 is very sensitive and specific for melanoma (but not specific when other soft tissue entities enter the diagnosis). While some spindle SCCs are negative for cytokeratins, the vast majority retain expression of p63. AFX is a diagnosis of exclusion based on strict histologic criteria and negativity for keratin(s), p63, and melanocytic markers. As previously indicated, a small number of studies suggest weak focal p63 staining in AFX and melanoma [102, 103], although this is in sharp contrast to strong, diffuse staining seen in most SCCs. Early studies suggested that CD10 may be a sensitive marker of AFX [102, 104]; however, this marker lacks specificity and it is not recommended for inclusion in the panel listed above [105, 106]. Of note, KS does not express S100 or p63, although a small percentage of AS may show weak/focal positivity.

KS and AS are occasionally encountered cutaneous soft tissue malignancies [107] that may display diagnostically ambiguous spindled morphology and frequently express a variety of vascular markers including CD31, CD34, and erythroblast transformation-specific related gene (ERG). While these markers are not specific for these tumors, they may be helpful in narrowing the lineage differential among spindled cell dermal lesions. A wide range of sensitivities of CD31 and CD34 have been reported for AS; this likely relates to studies combining data for both radiation-induced and primary tumors from a variety of sites [108–112]. Limited data suggest ERG is a highly sensitive marker of both primary (non-radiation-associated) and radiation-associated AS [113]. MYC is a highly sensitive marker of radiation-associated AS that can effectively differentiate it from a primary (non-radiation-associated) AS and from atypical postradiation vascular proliferations [114–117]. KS frequently expresses ERG (92–100%) and may also express MYC; however, it may be differentiated from AS, and from all other spindle cell and vascular neoplasms for that matter, based upon HHV-8 positivity, which is generally expressed in patch and plaque lesions, and is 100% specific, among solid tumors (HHV-8 positivity is also associated with some forms of lymphoma and Castleman's disease) [118–120]. There are limited data regarding the expression of vascular markers and MYC in SCC, AFX and melanoma, save for rare CD34 positivity in melanoma. However, it must be recalled that tumors showing the phenomenon of vasculogenic mimicry, including melanoma, may contain tumor cells that transcribe proteins encoded by certain aberrantly expresses endothelial genes, such as CD144 (VE cacherin) and TIE-1, but not CD31 [121, 122]. Indeed, multiple studies have demonstrated CD34 expression in desmoplastic melanoma, although in >90% of cases, <30% of tumor cells were positive.

## Cutaneous Adnexal Tumors

Sclerosing adnexal tumors, particularly microcystic adnexal carcinoma (MAC), desmoplastic trichoepithelioma (DTE) and morpheaform BCC (mBCC), pose frequent diagnostic challenges due to their overlapping histologic characteristics. Differences in tumor behavior

**Table 4.** IHC panels for adnexal neoplasms

| | MAC | DTE | mBCC | SCC |
|---|---|---|---|---|
| CEA | 44–58%<br>[215, 216] | 0%<br>[215, 216] | 0%<br>[216] | 0–30%<br>[170, 215] |
| D2-40 | – | 64%<br>[124] | 6%<br>[124] | 100%<br>[187] |
| Ber-EP4 | 0–38%<br>[135, 216, 217] | 57–75%<br>[135, 216, 217] | 100%<br>[123, 135, 216, 217] | 0%<br>[170] |
| EMA | 58%<br>[215] | 60%<br>[215] | 0%<br>[123] | 95%<br>[170] |
| 34bE12 | – | – | – | 100% [170] |
| CK7 | 100%<br>[123] | 0%<br>[123] | 0%<br>[123] | 22–40%<br>[174, 218] |
| Cam5.2 | – | – | – | 0%<br>[174] |
| CK5/6 | 100%<br>[125] | 100%<br>[219] | 100%<br>[219] | 70%<br>[220] |
| CK20 | – | 100% [131–133]<br>(intratumoral Merkel cells) | 0–3% [132, 133]<br>(intratumoral Merkel cells) | – |
| PHLDA1 | 40%<br>[135] | 88–100%<br>[134–136] | 0%<br>[134–136] | – |
| Androgen R | 0%<br>[125] | 0–13%<br>[131, 132] | 65–100%<br>[131, 132] | 0–10%<br>[83, 85] |
| p63 | 100%<br>[75, 125, 126] | 100%<br>[126] | 100%<br>[126] | 99–100%<br>[75, 187, 221] |
| Bcl-2 | 99–100%<br>[123, 124] | 0–89%<br>[123, 131] | 98–100%<br>[123, 124 127, 128] | 10–67%<br>[127, 129, 130] |
| CK15 | 10–92%<br>[135, 216] | 94–100%<br>[124, 135, 216] | 0–64%<br>[124, 135, 216] | 0–3%<br>[216] |
| CK17 | 100%<br>[125, 222] | 94–100%<br>[222] | 100%<br>[223] | – |
| CK19 | 45–89%<br>[135, 222] | 10–11%<br>[135, 222] | 35%<br>[135] | 17%<br>[224] |

Numbers in square brackets indicate references.

(locally aggressive vs. benign) and management (wide local excision vs. conservative management) make accurate diagnosis essential, especially given the predilection of these tumors for head and neck regions where over- or undertreatment can have devastating consequences. Further, other entities, such as cutaneous SCC and metastatic carcinomas with a marked desmoplastic stromal response, enter into the differential diagnosis, with a diagnosis of the latter having critical implications for prognosis and management.

To date no immunohistochemical markers of sclerosing adnexal tumors have been described to provide sufficient sensitivity and specificity for diagnosis when the differential diagnosis is broad. Therefore, when diagnosing sclerosing adnexal tumors, or their mimics, it is best to narrow the differential diagnosis based on histologic and clinical features prior to enlisting the use of markers. Further, data regarding the utility of these markers have been inconsistent across studies. This may be partially due to instances of misdiagnosis, although it more likely relates to differences in the interpretation of 'positivity' versus 'negativity' due to variations in staining patterns, degree (percentage of labeled cells), and intensity amongst different tumor types and within a single tumor (table 4).

A number of markers may aid in the distinction of MAC from other sclerosing lesions based on the staining pattern instead of straightforward positivity/negativity. Bcl-2 and CK7 are expressed in the central areas of individual MAC tumor nests, while peripheral cells are negative for these markers and positive for p63 [75, 123–126]. DTE, mBCC, and SCC do not display this pattern of staining and instead show either diffuse, patchy, or limited expression of these markers [127–130]. Of note, the pattern of peripheral p63 expression in MAC is more prominent with increasing tumor depth, and accordingly, the utility of this marker may be limited in superficial biopsies.

AR expression is highly specific for BCC within this differential diagnosis, but the reported sensitivity for morpheaform variants ranges from 65 to 100% [131, 132]. Thus, a negative result cannot rule out mBCC. One study suggests that AR in combination with CK20 may have utility in differentiating mBCC from DTE, as CK20-positive Merkel cells frequently infiltrate DTE but are absent in mBCC [133]. However, we are unaware of the regular or reproducible utility of this panel in routine practice. Until recently, Ber-EP4 was accepted as a reliable marker for differentiating mBCC, which is nearly always positive, from MAC, which were putatively negative. More recent data, however, suggest that up to 38% of MACs are positive for Ber-EP4, calling into question the utility of this marker in differentiating these two morphologically similar entities. Pleckstrin homology-like domain, family A, member 1 (PHLDA1), a protein highly expressed in the hair follicle, is a more recently described marker of DTE that is not expressed in BCC, making it useful for differentiating these two entities [134–136]. Of note, up to 40% of MACs express PHLDA1, and expression in cutaneous SCC has not been described, making interpretation difficult, if not impossible, when the differential diagnosis includes these entities. Further, mBCC may express PHLDA1 near sites involved by ulceration, making interpretation challenging in superficial biopsies showing this feature. There has been increasing interest in the use of stem cell keratins (CK15 [137, 138], CK17 [125] and CK19 [139]) for the diagnosis of sclerosing adnexal tumors, although the data remain limited and variable, and thus these markers should be used with caution.

Finally, metastatic carcinomas may histologically mimic sclerosing adnexal tumors, and the expression of IHC markers, especially keratins, in the former, varies greatly depending on tumor type (i.e. primary site/histogenesis) and degree of differentiation, creating potential diagnostic pitfalls in the diagnosis of cutaneous carcinomas. For example, cutaneous neoplasms with eccrine differentiation are often positive for estrogen receptor (ER) and/or progesterone receptor (PR) [140], and IHC is performed to predict response to hormonal therapy. The differential diagnosis of cutaneous eccrine neoplasms and metastatic breast cancer largely requires clinical and radiological correlation, since both can be positive for ER and PR [141]. Therefore, interpretation of IHC marker expression in cutaneous adnexal neoplasms should be guided by clinical and histologic features to avoid diagnostic pitfalls that could result in clinical harm.

## Cutaneous Small Blue Cell Neoplasms

The differential diagnosis for small round blue cell tumors of the skin and subcutis includes primary cutaneous neoplasms (e.g. small cell variants of melanoma and adnexal carcinomas, as well as MCC), certain soft tissue neoplasms, metastatic carcinoma – particularly small cell lung carcinoma, and lymphoma. Prior to utilizing IHC to aid in the diagnosis of these entities, a differential diagnosis based on patient age, lesion location, cancer history and imaging must be formulated, given the significant overlap in marker expression within this category (table 5).

**Table 5.** IHC panels for small round blue cell neoplasms

| | Ewing's sarcoma/ PNET | Merkel cell | Melanoma | Metastatic lung SCC | DSRCT |
|---|---|---|---|---|---|
| Keratin | 0–50% [146, 149, 160, 225] | 80–100% [79, 147, 226, 227] | 0–10% [154, 161–163, 228] | 100% [226] | 69–100% [31, 32, 153, 159] |
| CK20 | 0% [146] | 75–100% [79, 82, 168, 226, 227, 229] | 0% [82, 228] | 0% [80] | 0% [159] |
| EMA | 16% [160] | 95% [168] | 0–7% [154, 161–163] | – | 90–96% [151, 152, 159] |
| S100 | 38% [3] | 17–22% [79, 82] | 95–100% [82, 154, 161, 228] | – | 0–13% [151, 152] |
| LCA | 0% [230] | 0% [79] | – | – | – |
| Synapto | 23–25% [3, 160] | 75–96% [79, 168, 226, 227] | – | 100% [226] | 15–75% [151, 152, 159] |
| NSE | 36–88% [3] | 100% [82] | 30% [82] | 58–100% [231–233] | 72% [159] |
| PAX5 | 0% [234] | 67–94% [226, 235, 236] | 0% [235, 237] | 0–73% [226, 236] | – |
| CD99 (MIC2) | 91–100% [3, 142–149] | 55–100% [168, 229] | 57–60% [238, 239] | – | 0–57% [145, 151–154] |
| FLI-1 | 71–100% [147–150] | 90–100% [155, 168] | 50–60% [155, 239] | – | 0–87% [150, 155] |
| TTF-1 | – | 0–12% [80, 147, 226, 227] | 0% [228] | 90–100% [80, 169, 226] | – |
| NKX2.2 | 93% [157] | 0% [157] | 33% [157] | 25% [157] | 0% [157] |

Numbers in square brackets indicate references.

Within the pediatric and young adult populations, small cell melanoma, Ewing's sarcoma/primitive neuroectodermal tumor (PNET), DSRCT, and rhabdomyosarcoma are frequently in the differential diagnosis of small round blue cell tumors that may be present in the skin and subcutis. Unlike desmoplastic melanoma, a substantial portion of most other morphologic variants of melanoma retain expression of the more specific lineage markers MART-1, MITF, and HMB-45, making them useful in view of the lack of specificity of S100 when small cell variants of melanoma are suspected in the differential diagnosis of small round blue cell tumor. CD99 [142–149] and Friend leukemia virus integration 1 (FLI-1) [147–150] are the most sensitive markers of Ewing's sarcoma/PNET, although a substantial portion of melanomas, and by some reports, DSRCT, may express one or both of these markers [145, 150–155]. Further, lymphoblastic lymphoma, a hematopoietic malignancy observed in young adults, expresses CD99 and is frequently negative for leukocyte common antigen (LCA). Molecular analysis to confirm the presence of an EWS-FLI-1 fusion or the associated t(11;22)(q24;q12) translocation is more definitive, although a number of histologically distinct tumors are now known to be associated with this translocation, and not all Ewing's sarcoma/PNET are positive [156]. Of note, NK2 homeobox 2 (NKX2.2) is a recently described sensitive marker of Ewing's sarcoma/PNET with greater specificity compared with CD99 and FLI-1 [157]. Most DSRCTs express EMA [152, 158, 159], while Ewing's sarcoma/PNET and melanoma are generally negative [154, 160–163], making this a useful marker in a narrowed differential diagnosis. Finally, when rhabdomyosarcoma enters the differential diagnosis, particularly in slightly younger patient populations, myogenin and myogenic differentiation 1 are sensitive markers of this tumor, although other malignancies with rhabdoid features may also express

these markers [164–166]. In particular, loss of SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily B, member 1 (INI-1) expression can aid in distinguishing malignant rhabdoid tumor from rhabdomyosarcoma [167].

Among older patient populations, MCC, metastatic carcinoma, lymphoma and melanoma are in the differential diagnosis of cutaneous small round blue cell tumors. Although MCC and metastatic small cell carcinoma both express neuroendocrine markers [79, 168], they may be differentiated in most instances based on paranuclear dot-like expression of CK20 in MCC [79, 80, 82, 168] and TTF-1 expression in metastatic SCLC [80, 169]. While lymphomas may have a variety of immunohistochemical profiles, most cases are distinguishable from other small round blue cell tumors based upon their expression of LCA. Of note, there are reports of lymphomas that have lost expression of LCA, again signifying the importance of utilizing a multimarker panel. Further, PAX5 (BSAP) and terminal deoxynucleotidyl transferase (TdT), two markers of some variants of lymphoma, are expressed in a portion of MCCs and thus represent a potential diagnostic pitfall [226, 227].

Finally, although rare, some sweat gland tumors may enter this differential diagnosis. While the immunophenotype among different variants of sweat gland tumors is variable, many express p63 [125], while melanoma, small cell carcinoma and soft tissue neoplasms typically do not. Of note, studies suggest some sweat gland tumors may express PAX5 [125], creating a diagnostic dilemma if lymphoma or MCC are in the differential diagnosis.

## Conclusion

Herein, we have summarized the existing and more recent literature concerning the use of IHC markers in the diagnosis of cutaneous neoplasms, with specific emphasis on melanoma, epidermal tumors with intraepitheliomatous growth patterns, dermal spindle cell neoplasms, sclerosing adnexal tumors, and dermal small round blue cell tumors. IHC markers will continue to emerge in the field of diagnostic dermatopathology, especially as a result of recent rapid progress in our understanding of the genetic and epigenetic mechanisms of tumorigenesis. However, IHC must always be interpreted within an informed clinical context, a narrowed histologic differential diagnosis, a complementary panel of probes, and rigorous antibody and tissue controls to exclude false-positive and -negative interpretations.

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