Chapter 35
Skin

Tammie Ferringer

Abstract Correlation of the clinical history and histopathology are typically sufficient for accurate diagnosis in dermatopathology. However, in cases where this alone is insufficient, immunohistochemistry can further characterize lesions in the differential diagnosis. As with all immunohistochemical markers, none of those used in dermatopathology are completely sensitive and specific, therefore appropriate selection of a panel of antibodies maximizes the likelihood of making an accurate diagnosis.

The majority of studies evaluating immunohistochemical antibodies are limited to small numbers of cases with variable antibody sources, antigen retrieval methods, and definition of reactivity resulting in inconsistent results. The following chapter summarizes the general trends reported for several of the common conundrums in cutaneous pathology including differentiating spitzoid melanocytic lesions, small blue cell tumors, spindle cell lesions of the skin, sclerosing epithelial neoplasms, and lesions with pagetoid intraepidermal scatter.

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T. Ferringer (✉)
Department of Laboratory Medicine, Geisinger Medical Center, Danville, PA, USA
e-mail: tferringer@geisinger.edu

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Table 35.1 Summary of applications and limitations of useful markers

Antibodies	Staining pattern	Function	Key applications and pitfalls
AE1/AE3	C	Epithelial marker; cocktail of high and low molecular weight cytokeratins (CK 1–6, 8, 10, 14–16, 19)	Useful in the differential of cutaneous spindle cell neoplasm but does not stain all sSCCs (see Fig. 35.17)
CK7	C	Epithelial marker	Positive in Paget's, EMPD (see Fig. 35.27), metastatic breast and lung carcinoma; Usually negative in MCC
CK20	C	Marker of intestinal epithelium, urothelium, and Merkel cells	Positive in metastatic colon carcinoma; Positive in MCC (see Fig. 35.13)
CK903(34BE12)	C	High molecular weight cytokeratin (CK1, 5, 10, 14); expressed in suprabasal keratinocytes and adnexal epithelium	Positive in many poorly differentiated or sSCCs
CK5/6	C	High molecular weight cytokeratin; expressed in suprabasal keratinocytes and adnexal epithelium	Positive in many poorly differentiated or spindle cell SCCs; usually positive in primary cutaneous adnexal tumors while negative in most metastatic adenocarcinomas to the skin
CAM5.2	C	Low molecular weight cytokeratins (CK8, 18, 19); expressed in secretory portion of eccrine and apocrine glands	Useful to differentiate EMPD from SCCis
EMA	M+C	Epithelial marker; one of human milk fat globule proteins	Marks sebaceous and sweat glands and their neoplasms; positive in sclerosing perineuroma and rudimentary meningocele; labels plasma cells but not a problem distinguishing cytologically
CEA	C	Expressed in secretory portion of eccrine and apocrine glands and eccrine ducts	Marks sweat glands and their neoplasms as well as various adenocarcinomas
Ber-EP4	M+C	Epithelial marker; marks all epithelial cells except the superficial layers of epidermis	Positive in BCC but negative in SCC
AR	N	Transcriptional regulator; expressed in mammary secretory cells, follicular infundibulum, apocrine glands, and sebaceous glands	Helpful in differentiating sebaceous carcinoma from BCC and SCC; positive in metastatic breast carcinoma and mammary and EMPD
Adipophilin	M	Protein on the surface of intracellular lipid droplets	Membranovesicular pattern in sebaceous lesions (Fig. 35.1), xanthomatous lesions, and metastatic RCC but negative or focal and granular in clear cell BCC or SCC (Fig. 35.2)
MSH2, MSH6, MLH1, PMS2	N	Mismatch repair genes; MSH2 and MSH6 form a heterodimer; loss or dysfunction is associated with microsatellite instability as seen in Lynch and MTS	Loss of normal expression in sebaceous tumors may be a screening tool for MTS
p63	N	A p53 homolog required for epidermal development and stem cell maintenance	Expressed in normal basal and suprabasal epidermal layers and basal cells of sebaceous and sweat glands, as well as myoepithelial cells; positive in primary cutaneous adnexal tumors (see Fig. 35.45) but negative in metastatic adenocarcinoma (see Fig. 35.46) and EMPD; present in sSCC (see Fig. 35.18) but absent in most AFX
p40	N	One of the p63 isoforms	Similar sensitivity and possibly more specificity for poorly differentiated SCC than p63
Desmin	C	Intermediate filament in skeletal and smooth muscle except vascular smooth muscle	Useful in differential of spindle cell neoplasms of the skin; may weakly and focally stain myofibroblasts but usually not myoepithelial cells
SMA	C+M	Alpha-smooth muscle isoform of actin in smooth muscle, including vascular smooth muscle	Stains myofibroblasts, myoepithelial cells, pericytes, and glomus cells; myofibroblasts tend to have a parallel "tram-track" pattern (Fig. 35.3) in contrast to the diffuse cytoplasmic staining in smooth muscle cells
SMMS	C	Structural protein of contractile apparatus of smooth muscle cells	Also expressed in myoepithelial cells but does not consistently stain myofibroblasts
h-caldesmon	C	Cytoskeletal protein that regulates contraction in muscle cells; high molecular weight form is expressed in smooth muscle cells	Expressed in normal myoepithelial cells but not myofibroblasts thus useful to differentiate smooth muscle tumors from myofibroblastic lesions like nodular fasciitis

Table 35.1 (continued)

Antibodies	Staining pattern	Function	Key applications and pitfalls
calponin	C	Binds with actin in smooth muscle cells, myofibroblasts, glomus, and myoepithelial cells	Positive in glomus tumor and lesions composed of myofibroblasts and myoepithelial cells
CD34	M+C	Endothelial and hematopoietic progenitor cell marker; highlights dendritic dermal fibroblasts	Stains many vascular tumors and fibrohistiocytic tumors including DFSP (see Fig. 35.41), solitary fibrous tumor, superficial acral fibromyxoma, sclerotic fibroma, but also neurofibroma, spindle cell lipoma and others; absent in DF; positive in tumors with ORS differentiation such as trichilemmoma; loss of interstitial staining of the dermis is noted in morphea (Fig. 35.4)
Factor XIIIa	C	Dermal dendrocyte marker	Positive in DFs (see Fig. 35.42)
CD31	M	Endothelial marker	More specific vascular marker than CD34; can stain macrophages
ERG	N	Endothelial marker	Positive in vascular tumors, prostate adenocarcinoma, and Ewing sarcoma
FLI1	N	Endothelial marker	Positive in vascular tumors and Ewing sarcoma
D2-40 (podoplanin)	C	Lymphatic endothelial marker	Can help identify lymphatic invasion (Fig. 35.5) particularly in melanoma; positive in some vascular lesions including Kaposi sarcoma, targetoid hemosiderotic hemangioma, and a subset of angiosarcomas; reactivity in cutaneous adnexal tumors helps differentiate them from metastatic adenocarcinoma; expression noted in CNTs, DFs, and myoepithelial cells
c-MYC	N	MYC amplification is noted in post-radiation associated angiosarcomas	Positive in post-radiation angiosarcomas of the breast (see Fig. 35.44) but negative in AVLs of the breast; majority of primary angiosarcomas from other sites do not show expression and thus is not diagnostic of angiosarcoma
WT1	C	Proliferating endothelial cells	Reported in proliferative endothelial lesions such as infantile hemangioma, RICH, NICH, tufted angioma, pyogenic granuloma, cherry hemangioma but usually lacking in lymphatic and venous vascular malformations
GLUT1	C+M	Major glucose transporter at the blood brain barrier	Reactive in all phases of infantile hemangioma but absent in vascular malformations; neither RICH nor NICH express GLUT1; care is required in interpretation as there is normal reactivity in erythrocytes; perineural cells and perineuriomas are positive
Vimentin	C	Mesenchymal marker, including endothelial cells, all fibroblastic cells, macrophages, adipocytes, melanocytes, smooth muscle, and lymphocytes; found in all types of sarcoma and lymphoma	In the appropriate panel, positivity excludes most carcinomas
S100	N+C	Neural crest marker; highlights melanocytes, Langerhans cells, sweat glands, nerves, Schwann cells, lipocytes, myoepithelial cells	Sensitive melanoma marker, especially for sMM/dMM (see Fig. 35.24), but not specific; S100 may be weak or negative in benign and malignant junctional melanocytes of the nail matrix but is important in identifying invasive melanoma in this area; positive in granular cell tumor and RDD; negative in CNT (see Fig. 35.20) in contrast to nerve sheath myxoma
SOX-10	N	Nuclear transcription factor crucial for differentiation of Schwann cells and melanocytes; highlights melanocytes, Schwann cells, myoepithelial cells, and the secretory cells of the eccrine coil	Expressed in all types of nevi and melanoma (see Fig. 35.25); high specificity with reactivity in only a few other tumors including granular cell tumor, schwannoma, neurofibroma, myoepithelioma, and some ductal breast carcinomas; negative in RDD, CNT, and LCH; useful in junctional melanocytic proliferations due to the nuclear staining and in SLNs due to lack of background staining of follicular dendritic cells seen with S100
HMB-45	C	Recognizes the antigen gp100 expressed on stages 1–3 melanosomes (organelle, rather than lineage specific marker); indicates active melanosome formation, not present in resting adult melanocytes	Reveals a gradient with decreased staining in the deeper dermal component of benign nevi (see Fig. 35.31), with the exception of uniform staining in blue nevi (Fig. 35.33); not reliable in desmoplastic or spindled melanoma; negative in nodal nevi; positive in PEComas

(continued)

Table 35.1 (continued)

Antibodies	Staining pattern	Function	Key applications and pitfalls
MART1/Melan-A	C	Melanocytic marker	More specific melanocytic marker than S100 but less sensitive, especially for sMM/dMM (see Fig. 35.23); two antibodies detect the same protein at two different antigenic sites: A-103 (Melan-A) and MART1; Melan-A stains adrenocortical cells and steroid producing cells of the ovary and testis that MART1 does not; macrophages may aberrantly label with some antigen retrieval techniques, however, the staining is weak and granular; positive in most PEComas; beware staining of pseudomelanocytic nests in interface processes mimicking a melanocytic proliferation
MITF	N	Transcription factor involved in the development of melanocytes and regulation of melanin synthesis; melanocytic and Schwann cell marker	Nuclear staining avoids distraction of cytoplasmic staining of dendritic, overlapping melanocytes when evaluating junctional melanocytic proliferations; not reliable in dMM/sMM; positive in most PEComas and can stain histiocytes, lymphocytes, mast cells, and smooth muscle cells
S100A6 (calcyclin)	N+C	Belongs to family of S100 calcium binding proteins	Strongly and diffusely positive in Spitz nevi but weak, patchy, or negative in melanoma; stains fibrohistiocytic lesions such as AFX (see Fig. 35.15)
p16	N	Tumor suppressor protein encoded by CDKN2A; prevents progression into S phase of cell cycle	Surrogate marker for oncogenic HPV but not well studied in skin, however increased expression is typical in Bowen disease; complete loss of staining correlates with CDKN2A silencing mutations (homozygous loss of 9p21) and thus is potentially helpful in identifying this subset of melanomas; positive in many histiocytic and fibrohistiocytic lesions
VE1	C	Detects BRAFV600E mutations	Approximately half of melanomas have BRAF mutations and over 90% of these are in V600E; high concordance of staining with DNA based detection of this mutation; useful screening tool for BRAF inhibitor therapy eligibility especially in cases with low tumor content; does not identify other less common BRAF genotypes such as V600K
BAP1	N	Tumor suppressor	Presence of multiple BAP1 negative epithelioid melanocytic lesions suggests a familial cancer syndrome associated with uveal melanoma and mesothelioma; loss of nuclear staining in the epithelioid cells of the melanocytic lesion (Fig. 35.6) is a potential screen for BAP1 mutation and should be followed by confirmatory genetic testing
ALK	C	ALK gene rearrangements have been identified in a diverse array of neoplasms including ALK positive anaplastic large cell lymphoma, epithelioid histiocytoma, and some spitzoid neoplasms	Intersecting fascicles of amelanotic fusiform melanocytes are typical of ALK positive spitzoid lesions which can be benign or malignant
panTRK	C	Identifies tumors with NTRK gene fusions	Spitzoid tumors with NTRK1fusions have filigree-like, elongated, thin, and branched rete ridges and dermal melanocytes arranged in a rosette-like configuration; TRK expression correlating to NTRK fusions can be seen in melanoma
β-catenin	N	Protein coded by the CTNNB1 gene	Nuclear expression is noted in nearly half of DPNs but not blue nevi, Spitz nevi, and pigmented epithelioid melanocytomas
PRAME	N	Tumor associated antigen with low or no expression in normal tissues except for in testis and ovary	Data suggests that expression may be useful in suspected diagnosis of melanoma (Fig. 35.37, 35.39, and 35.40); rare isolated junctional melanocytes are also seen in solar lentigines and benign nonlesional skin
NSE	C	Neural and neuroendocrine marker	If neoplastic cells co-express keratin and NSE, neuroendocrine differentiation is probable; positive in MCC
NFP	C	Cytoskeletal element in nerve axons and dendrites	Positive in MCC, particularly MCPyV-positive MCCs, often in a paranuclear dot pattern; useful in differentiating from non-cutaneous small-cell neuroendocrine carcinomas
CD68/KP1	M+C	Expressed in monocytes, macrophages, myeloid precursors, neutrophils, mast cells; more specific to lysosomes than lineage specific	Less specific than CD163 for monocytes and macrophages; stains XG, AFX, and LCH

Table 35.1 (continued)

Antibodies	Staining pattern	Function	Key applications and pitfalls
CD163	M+C	Expressed in monocytes and macrophages	Negative in mast cells and Langerhans cells
CD1a	M	T cell surface antigen on antigen presenting cells	Positive in Langerhans cells and indeterminant cells; MTB1 clone reported to stain amastigotes of leishmania in some cases, particularly old world disease
Langerin (CD207)	M+C	Role in formation of Birbeck granules	Surrogate for identification of Birbeck granules of Langerhans cells without electron microscopy; indeterminant cells are CD1a positive but lack langerin
Tryptase	C	Secretory granule-derived proteinase contained in mast cells.	Useful mast cell marker
CD117 (c-Kit)	M+C	Stem cell factor important in mast cell and melanocyte functioning; expressed in sweat gland secretory cells	Expression reportedly helpful in differentiating porocarcinoma from lack of staining in SCC; expression associated with MCPyV-negative MCCs; Kit mutations are common in acral and mucosal melanoma
CD123	C	Stains plasmacytoid dendritic cells	Quantity and distribution vary in different inflammatory and neoplastic conditions; increased numbers and clusters of PDCs are seen in lupus (Fig. 35.7)
Mib-1 (Ki-67)	N	Nuclear proliferation marker; expressed in cells in the G1, M, G2, and S phase of the cell cycle (i.e., all phases except the resting G0 phase)	Useful in determining proliferation index in dermal component of melanocytic lesions and other tumors of uncertain malignant potential; not lineage specific so also stains proliferating lymphocytes requiring distinction by cytology or dual staining (see Figs. 35.34 and 35.35)
PHH3	Mitotic	Histone H3 is phosphorylated during mitotic chromatin condensation in late G2 and M phase of the cell cycle	Distinguishes mitotic figures (Fig. 35.8) from apoptotic, hyperchromatic, and pyknotic nuclei; not lineage specific; helpful in identifying the mitotic "hot spot"
Collagen IV		Collagen type in basement membrane	Detected more commonly above the subepidermal blisters than below in EBA and bullous SLE, unlike BP

Note: *C* cytoplasmic staining, *M* membranous staining, *N* nuclear staining, *SMA* smooth muscle actin, *EMA* epithelial membrane antigen, *ORS* outer root sheath, *DF* dermatofibroma, *AFX* atypical fibroxanthoma, *CNT* cellular neurothekeoma, *CEA* carcinoembryonic antigen, *PHH3* phosphor-Histone H3, *SCC* squamous cell carcinoma, *BCC* basal cell carcinoma, *DFSP* dermatofibrosarcoma protuberans, *ERG* Ets-related gene, *FLI-1* Friend leukemia integration-1, *NSE* neuron specific enolase, *MART1* melanoma antigen recognized by T-cells, *MITF* microphthalmia transcription factor, *GLUT1* glucose transporter, *PEComas* perivascular epithelioid cell tumors, *RICH* rapidly involuting congenital hemangioma, *NICH* non-involuting congenital hemangioma, *MCC* Merkel cell carcinoma, *AR* androgen receptor, *EMPD* extramammary Paget disease, *MTS* Muir Torre syndrome, *SMMS* smooth muscle myosin, *WT1* Wilms tumor 1, *BAP1* BRCA-1 associated protein-1, *ALK* anaplastic lymphoma kinase, *NTRK* neurotrophin receptor tyrosine kinase, *PRAME* preferentially expressed antigen in melanoma, *EBA* epidermolysis bullosa acquisita, *BP* bullous pemphigoid, *NFP* neurofilament protein, *DPN* deep penetrating nevus, *AVL* atypical vascular lesion, *SLN* sentinel lymph node, *SCCis* squamous cell carcinoma in situ, *CK* cytokeratin, *RDD* Rosai-Dorfman disease, *sMM* spindle cell malignant melanoma, *dMM* desmoplastic malignant melanoma, *sSCC* spindle cell squamous cell carcinoma, *RCC* renal cell carcinoma, *LCH* Langerhans cell histiocytosis, *HPV* human papilloma virus, *DNA* deoxyribonucleic acid, *XG* xanthogranuloma, *SLE* systemic lupus erythematosus

References: [1–91]

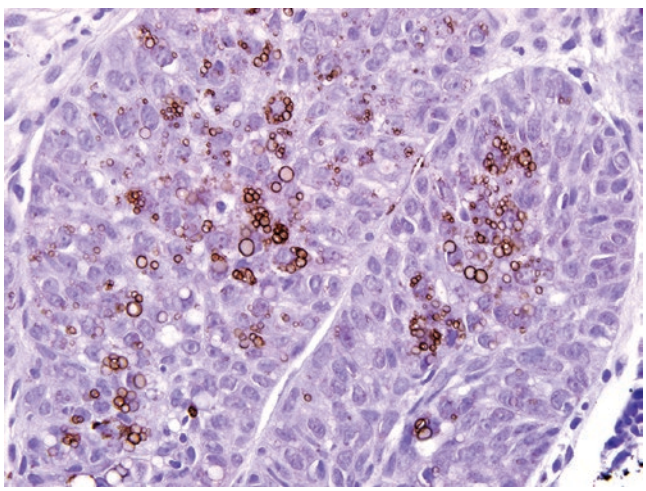

Fig. 35.1 Membranous and vesicular staining with adipophilin in sebaceous carcinoma

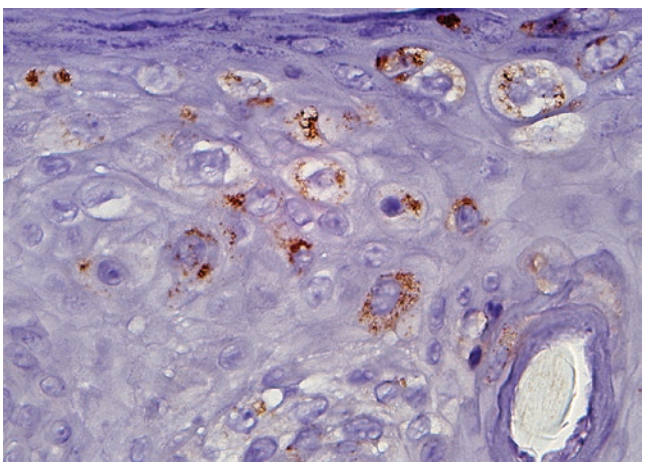

Fig. 35.2 Focal granular staining of adipophilin in a clear cell SCCs

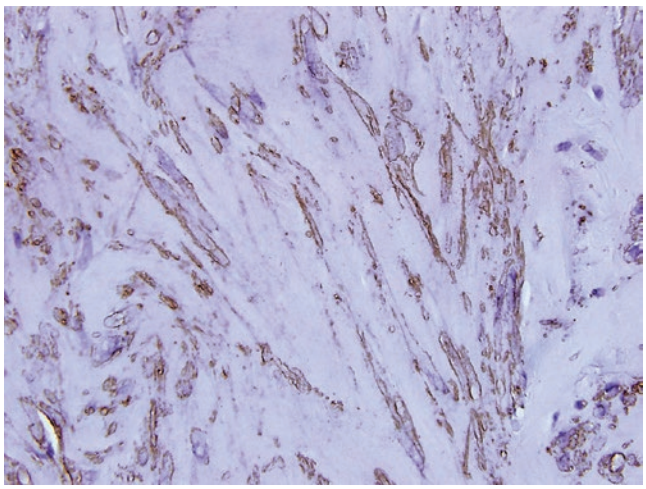

Fig. 35.3 Tram-track SMA in myofibroma

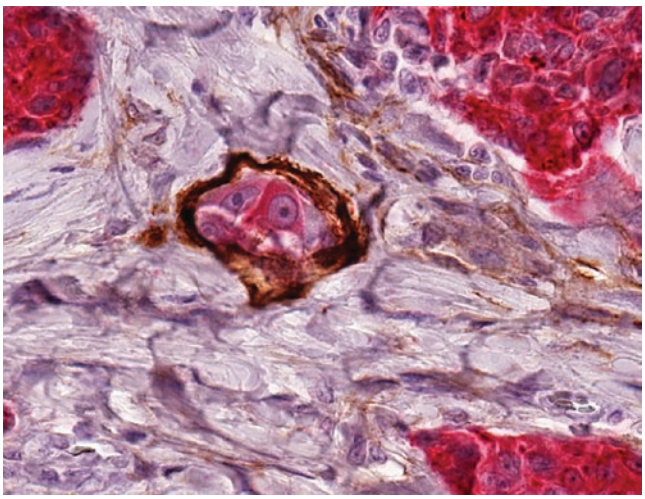

Fig. 35.5 Melanoma with dual MART1 (Fast red) and D2-40 (DAB) staining showing intravascular invasion

Fig. 35.4 Loss of interstitial staining with CD34 in morphea

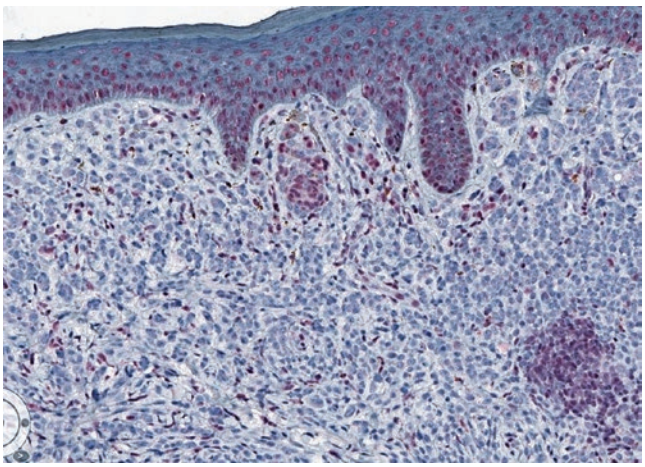

Fig. 35.6 Loss of nuclear BAP1 staining in the epithelioid melanocytes in a melanocytic lesion from a patient with BAP1 germline mutation

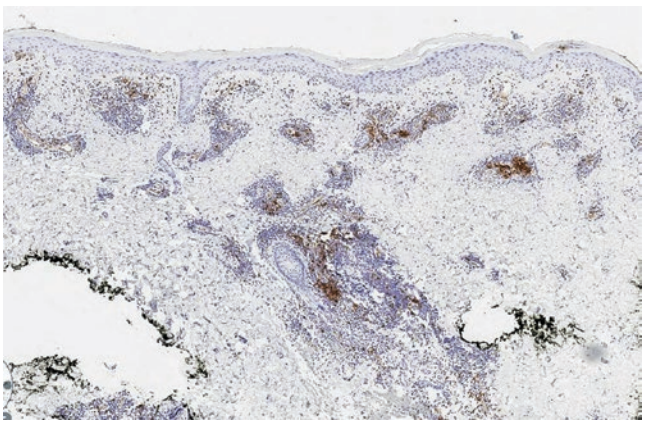

Fig. 35.7 Clusters of CD123 positive cells in lupus erythematosus

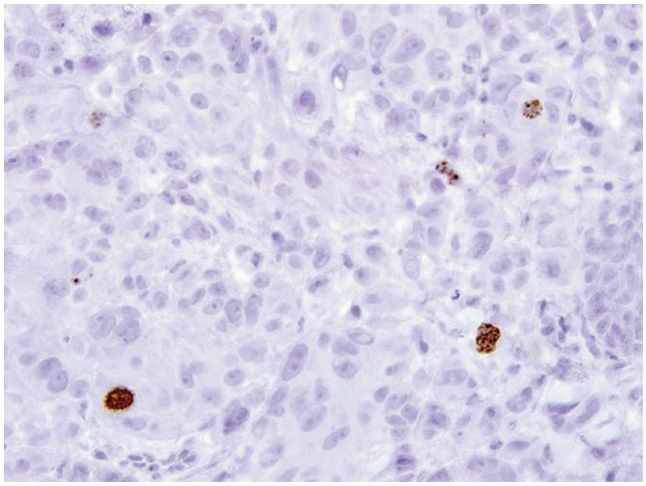

Fig. 35.8 PHH3 highlights mitotic figures in a spitzoid melanoma

Table 35.2 Markers for primary cutaneous melanoma

Antibodies	Literature	GML, %(*N*)
S100	+^	93.4% (91)
HMB-45	+	75% (88)
MART1	+	88.8% (89)
MITF	+	79.8% (89)
Tyrosinase	+^	94.3% (88)
NKI-C3	+^	95.5% (88)
MUM-1	+	75.6% (86)
SOX-10	+^	NA
VE1	+/-	NA
PRAME	+	NA

GML% Geisinger Medical Laboratories data, percentage of melanomas tested with greater than 25% reactivity of tumor cells, *N* number studied, *NA* not available

^: greater than 90% of cases are positive

Immunohistochemical markers are virtually never completely specific and sensitive. The published literature on immunohistochemistry of melanoma often is limited to small numbers of cases, and the types of melanoma tested (nodular, metastatic, spindle, desmoplastic) vary between studies. The definition of positive reactivity, the antibody source, antigen retrieval methods, and concentrations vary from study to study often resulting in inconsistent results.

While the great majority of melanomas are S100 positive, this marker lacks specificity and stains other tissue. Therefore, other antibodies are needed to confirm the melanocytic nature of a S100 positive neoplasm. SOX-10 is at least as sensitive as, and is more specific than S100. Tyrosinase has decreased sensitivity with increasing stage and in metastatic lesions. NKI-C3 has poor specificity.

Reactivity with melanocytic markers may be less in metastatic melanoma. SMM/dMM is often negative for HMB-45 and other specific melanocytic markers, including MART1. S100 and SOX-10 are the most sensitive markers for sMM/dMM.

MITF, MUM-1, and SOX-10 are nuclear markers. This avoids the overlapping cytoplasmic staining of dendritic melanocytes when evaluating junctional melanocytic proliferations (Fig. 35.9). MUM-1 is primarily used in the workup of hematologic malignancies and is not in routine use for melanoma.

Mib-1 highlights the nuclei of proliferating cells, including melanocytes. Combining the cytoplasmic MART1 and nuclear Mib-1 using contrasting chromogens can ensure that the proliferating cells are indeed melanocytic (see Fig. 35.34). There is increased expression from benign to malignant melanocytic lesions, particularly in the deeper dermal component.

PHH3 (see Fig. 35.8) improves reproducibility of mitotic counts, but similar to Mib-1, it is not lineage specific. pHH3 determined mitotic counts are often higher than those performed on standard sections.

Pigmented melanocytes can be difficult to distinguish from pigmented keratinocytes and melanophages. The brown diethylaminobenzidine (DAB) chromogen can be difficult to identify in a background of dense melanin (Fig. 35.10). Alternatives include the following:

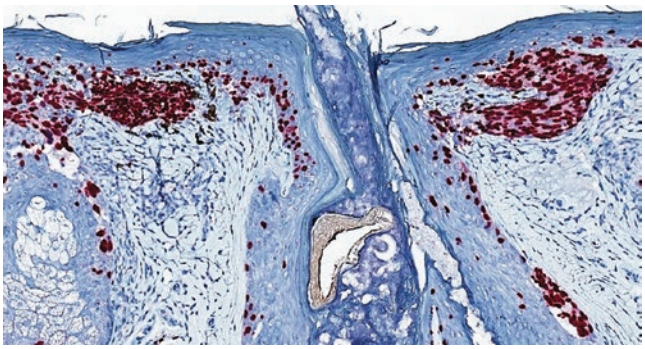

Fig. 35.9 Nuclear staining of melanocytes in MMIS with SOX-10

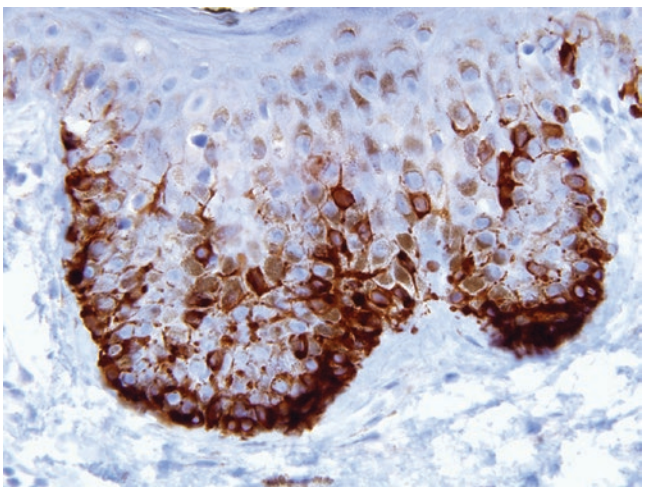

Fig. 35.10 Junctional dysplastic nevus stained with MART1 using DAB brown chromogen in background of heavy melanin pigmentation of the basal layer keratinocytes

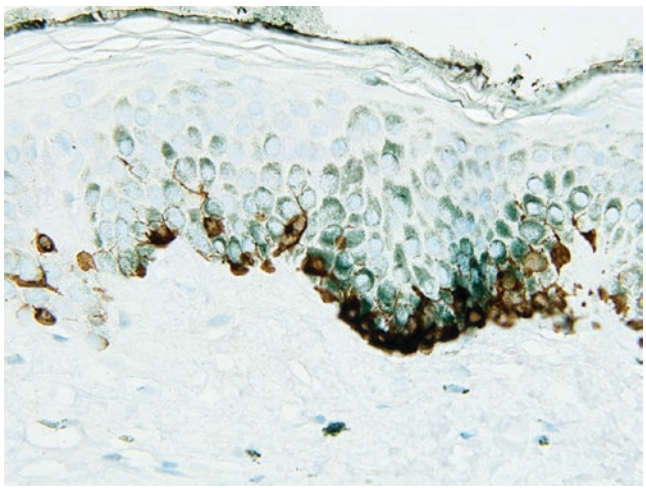

Fig. 35.11 Same heavily pigmented junctional dysplastic nevus as in Fig. 35.10 stained with MART1 using DAB brown chromogen and azure B counterstain. The melanin is now green-blue and contrasts easily with the DAB brown chromogen

1. Use of aminoethyl carbazole (AEC) resulting in a red product which is slightly easier to distinguish but can lack the longevity of DAB
2. Melanin bleaching may result in loss of antigenicity, incomplete melanin removal, or loss of cytologic detail
3. Kamino et al. were the first to report replacement of hematoxylin by azure B, which stains the melanin green-blue providing contrast from DAB staining of melanocytes (Fig. 35.11)

Rarely melanomas can exhibit aberrant expression including smooth muscle actin, CD138, MDM-2, GFAP (glial fibrillary acidic protein), CD30, and EMA. CEA reactivity can be seen in melanoma with the polyclonal antibody. Over half of melanomas express CD68. Cytokeratin expression occurs in up to 4% of melanomas with staining tending to be focal and sparse. CAM5.2 is the most frequently positive. There is increased aberrant expression of epithelial-associated markers in metastases.

The VE1 antibody reliably identifies melanomas with mutations in BRAF V600E. Patients with positive staining tumor cells are eligible for BRAF inhibitor therapy. Non-specific staining of histiocytes should be disregarded. Those with negative staining tumor cells should be further tested with DNA based techniques to identify the much less common other BRAF mutations, such as BRAF V600K. BRAF mutations are common in benign nevi and thus expression of VE1 is not diagnostic of melanoma.

Diffuse nuclear reactivity with PRAME was found in 87% of metastatic and 83.2% of primary melanomas. While true in most melanoma subtypes, only a third of dMM showed expression. Absence of staining in over 80% of nevi suggests potential benefit in the diagnostic armamentarium. Further study with additional cases is required as rare isolated junctional melanocyte immunoreactivity has been seen in solar lentigines and benign nonlesional skin.

References: [17, 23, 24, 31, 37, 51, 61–66, 72, 74, 80–83, 92–136].

MCC, also known as primary cutaneous neuroendocrine carcinoma of the skin, expresses neuroendocrine markers as well as low molecular weight epithelial markers. The small blue cell appearance of MCC results in a histologic differential diagnosis including metastatic small cell carcinoma from a primary in the lung or other site, lymphoma, and small cell melanoma. TTF-1 is a nuclear marker expressed in thyroid and pulmonary neoplasms, including small cell carcinoma of the lung and is only very rarely identified in MCC. Melanoma can be distinguished by S100 and lymphomas by CD45. The overlapping reactivity of MCC and some hematologic malignancies with ALK, CD99, TdT, PAX-5, CD56, Bcl-2, and CD117 can complicate diagnosis of these small blue cell neoplasms. ALK positivity in MCC ranges from 12% to 94% but does not correlate with ALK rearrangements. The etiology of expression is uncertain but tends to correspond with MCPyV positivity. Inclusion of epithelial and neuroendocrine markers in the immunohistochemical panel should avoid confusion.

Table 35.3 Markers for Merkel cell carcinoma

Antibodies	Literature
NSE	+^
Chromogranin	+/–
Synaptophysin	+/–
CK20	+^
TTF-1	–
Ber-EP4	+
CD56	+^
LCA	–
S100	–/+
CD99	+/–
NFP	+/–
CK7	–/+
FLI1	–/+
PAX-5	–/+
Bcl-2	+
TdT	–/+
CD117	+/–
MCPyV	+
ALK	+/–
p63	–/+
p53	–/+
EMA	+
CK5/6	–

MCPyV Merkel cell polyomavirus, *TTF-1* thyroid transcription factor, *LCA* leukocyte common antigen (CD45), CD56=NCAM (neural cell adhesion molecule)

Ewing's sarcoma/primitive neuroectodermal tumor (EWS/PNET) and neuroblastoma are very rare in the skin but have a similar histologic appearance. It is important to recognize that CD99 and FLI1, markers of EWS/PNET, can be positive in MCC. Ber-EP4 and Bcl-2 reactivity in MCC can be a pitfall if BCC is considered in the histologic differential diagnosis, as both are positive in BCC (Fig. 35.12).

CK20 is expressed in most MCCs but despite the typical CK20+/CK7− pattern, CK20−/CK7+ MCCs have been reported. It is important to be aware of the staining pattern of the primary tumor when evaluating SLNs. CK20 typically highlights aggregates of keratin near the nucleus in a characteristic paranuclear dot pattern (Fig. 35.13). However, in some cases of MCC, diffuse cytoplasmic staining predominates. NFP also often has a dot-like pattern in MCC.

Oncogenic MCPyV integration has been detected in 80% of MCCs and can be identified immunohistochemically. The remaining virus negative MCC cases are associated with high mutational load and are most likely caused by ultraviolet radiation. Other non-MCC skin neoplasms have shown MCV DNA by polymerase chain reaction (PCR) based techniques, but the viral load is considerably less and may not be detected by immunohistochemistry. Classic MCCs (CK20+, NFP+, chromogranin+, TTF-1-, CK7−) are usually MCPyV positive. NFP is less frequent, while CK7 and TTF-1 are more frequent in MCPyV negative MCCs.

p53, a tumor-suppressor essential in apoptosis, is usually undetectable in normal cells but mutations of this gene result in expression in 23–43% of all MCCs with such nuclear expression associated with low viral load. P63 positivity has been noted in 17–49% of MCCs. A recent meta-analysis found p63 expression correlates with a poor prognosis.

The protooncogene, c-kit, encoding the tyrosine kinase receptor KIT/CD117 is expressed in a variety of processes including acute myeloid leukemia, mast cell disease, melanoma, small cell lung cancer, gastrointestinal stromal tumors, and most MCCs.

References: [6, 11, 12, 30, 31, 41, 118, 137–178].

AFX is a pleomorphic spindle cell tumor that must be distinguished histologically from sMM/dMM, sSCC, and

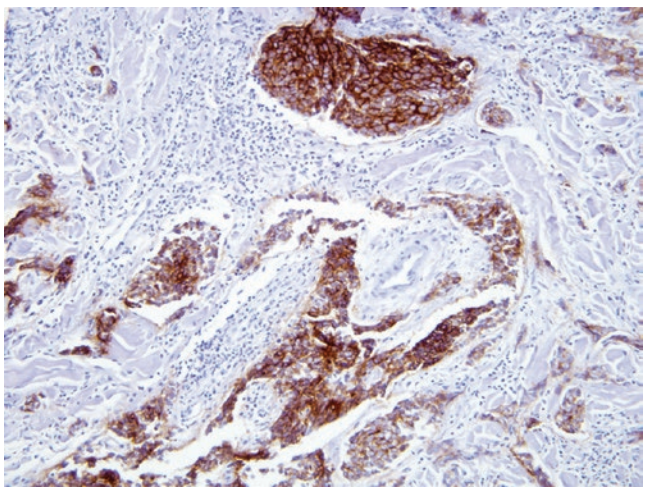

Fig. 35.12 MCC staining with Ber-EP4 can be a potential pitfall if BCC is considered in the differential diagnosis

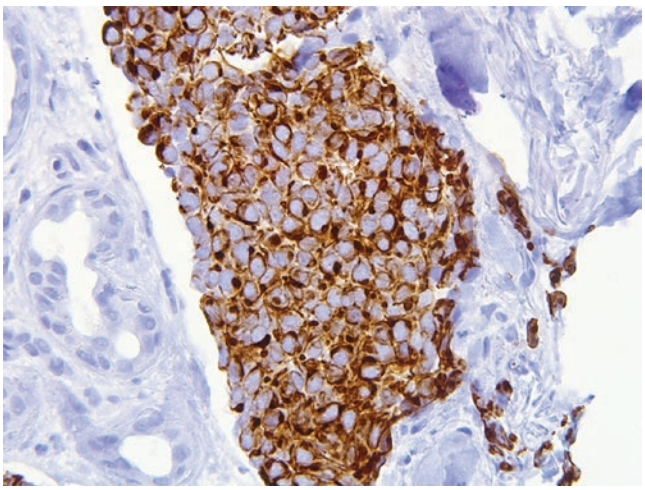

Fig. 35.13 MCC with the typical paranuclear dot pattern with CK20

Table 35.4 Markers for atypical fibroxanthoma

Antibodies	Literature	GML, %(*N*)
SMA	−/+	28% (35)
Vimentin	+^	100% (38)
S100	−	0% (35)
AE1/AE3	−	0% (36)
CK5/6	−	3% (36)
p63	−/+	24% (37)
Desmin	−	0% (33)
FLI1	−/+	NA
D2-40	−/+	0% (34)
CD31	−/+	NA
CD34	−	NA
ERG	−	NA
S100A6	+	74% (34)
CD10	+	85% (34)
Procollagen (PC-1)	+	79% (38)
CD68	+/−	72% (36)
CD99	+/−	14% (36)
CD163	+/−	NA
A1AT	+/−	NA
A1ACT	+/−	NA
NKI-C3	+/−	NA
EMA	−/+	NA
Factor XIIIa	−/+	44% (34)
Calponin	−/+	NA
p40	−	NA
CK903(34BE12)	−	NA

GML% Geisinger Medical Laboratories data, percentage of AFXs tested with greater than 25% reactivity of tumor cells, *A1AT* alpha-1 antitrypsin, *A1ACT* alpha-1 antichymotrypsin

leiomyosarcoma (LMS). While there are immunohistochemical stains that support the later diagnoses, the diagnosis of AFX is generally one of exclusion. A variety of markers have shown reactivity in AFX, including CD10 (Fig. 35.14), PC-1, and S100A6 (Fig. 35.15), but these antibodies often stain a variety of other neoplasms and are not specific. For example: CD10, S100A6, and PC-1 also highlight dermatofibromas. Rather than relying on one of these antibodies in isolation, a panel of markers is required to exclude the potential mimics (see Table 35.8). Therefore, AFXs have been defined in the past by the absence of S100 (Fig. 35.16), cytokeratins, and desmin. S100A6 (calcyclin) is a calcium-binding protein in the S100 family. While it is present in melanocytes, Schwann cells, and Langerhans cells, it is also positive in dermal dendrocytes supporting a fibrohistiocytic origin for AFX.

Focal or weak expression of myogenic markers, indicative of myofibroblastic differentiation, can be seen in AFX. Caution is required in interpreting S100 in atypical spindle cell neoplasms of the skin. There are often scattered S100 positive dendritic cells colonizing AFXs (possibly Langerhans cells) but the neoplastic cells are generally S100 negative (see Fig. 35.16).

CD117 reactivity has been reported in AFX; however, it typically highlights a small percentage of dendritic cells that are not highly atypical and many believe represent colonizing cells such as mast cells or Langerhans cells. Therefore, this is not a reliable marker for AFX.

Angiosarcoma at times needs to be differentiated from AFX with pseudoangiomatous features and this may be complicated by occasional expression of D2-40, FLI1, and CD31 in AFX. Reactivity to ERG is more sensitive in differentiation.

References: [32, 55, 166, 179–207].

sSCCs often fail to have an obvious origin from the epidermis or show evidence of keratinization. Due to similari-

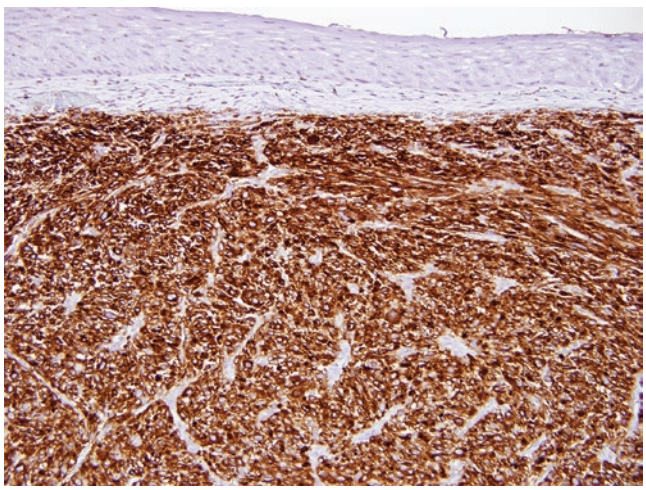

Fig. 35.14 AFX staining with CD10

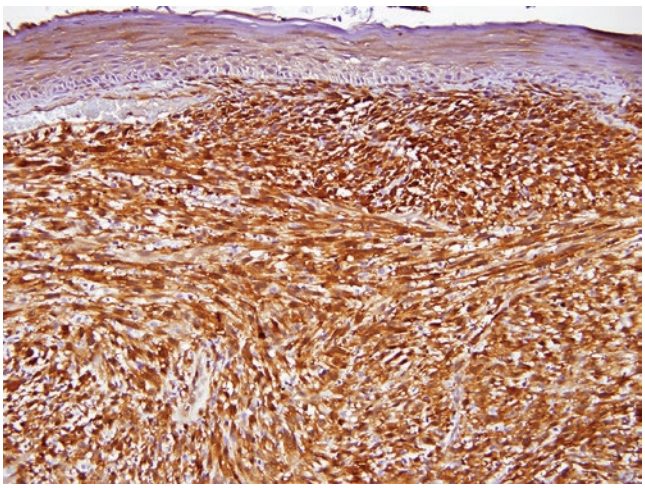

Fig. 35.15 AFX staining with S100A6

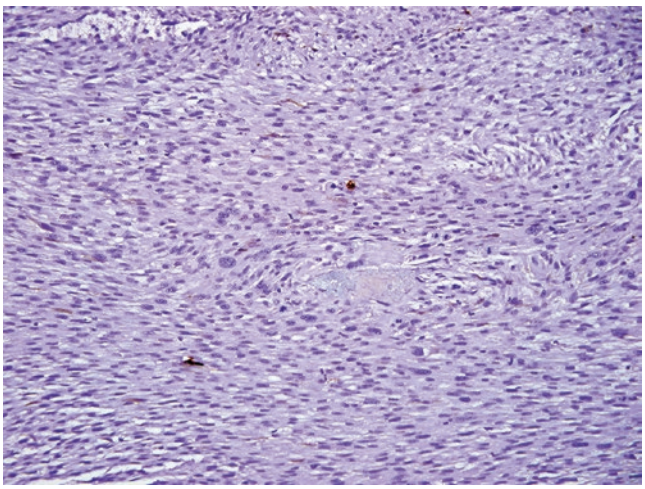

Fig. 35.16 In contrast to the diffuse S100A6 staining in Fig. 35.15, there is an absence of staining with S100 in AFX

Table 35.5 Markers for cutaneous spindle cell squamous cell carcinoma

Antibodies	Literature
AE1/AE3	+
CAM5.2	+/–
CK903(34BE12)	+
CK5/6	+
MNF116	+^
p63	+
p40	+^
S100	–
Desmin	–
CD99	–/+
D2-40	+/–
CD10	–/+
PC-1	–/+

MNF116: Antibody to cytokeratins 5, 6, 8, 17, and 19

ties with AFX, sMM/dMM, and LMS immunohistochemical confirmation may be required.

sSCCs are often negative or only focally positive with routine cytokeratin stains, including AE1/AE3 (Fig. 35.17) and may express only high molecular weight cytokeratins like CK903 and CK5/6.

While vimentin is a mesenchymal marker, co-expression with keratins can be seen in some epithelial tumors including sSCCs, possibly due to reduced cell-to-cell contact.

p63, a member of the p53 gene family, is a transcription factor involved in the proliferative capacity of epidermal stem cells. It is normally expressed in keratinocytes of the basal and lower spinous layers but is generally not expressed in mesenchymal cells and their neoplasms. This nuclear marker is useful for sSCC but is not completely specific (Fig. 35.18). P40 is one of the p63 isoforms that may have better specificity.

References: [32, 42, 54, 180, 181, 199–201, 208–210].

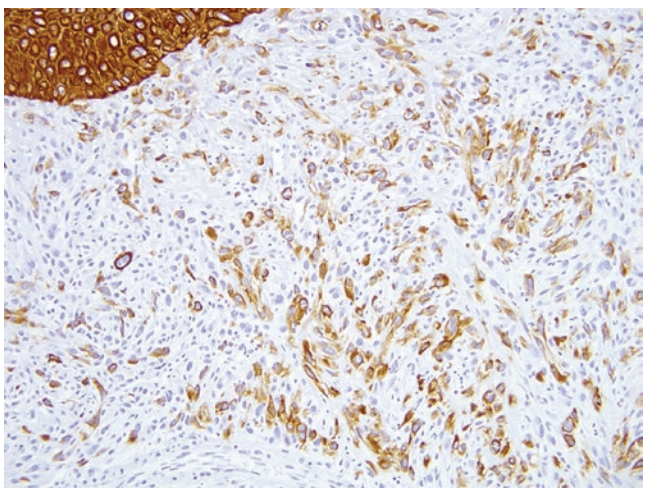

Fig. 35.17 sSCC focally staining with AE1/AE3

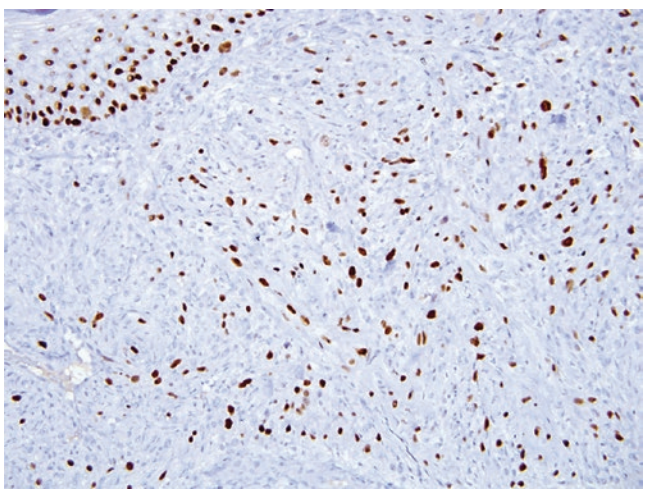

Fig. 35.18 Nuclear staining with p63 in sSCC

In the skin, smooth muscle is found in association with vessels, in genital skin (vulva, areola, dartos) and as arrector pili muscles. Smooth muscle tumors can occur in any of these sites. Immunohistochemistry can be helpful in identification but many of the markers are also expressed in myofibroblasts and or myoepithelial cells.

Unlike SMA and calponin, h-caldesmon can be helpful in differentiating smooth muscle from myofibroblasts in which it is negative, as in nodular fasciitis. While SMA is positive in myofibroblasts, it tends to show a parallel subplasmalemmal pattern of expression in a "tram-track" pattern unlike the diffuse cytoplasmic staining of smooth muscle cells (see Fig. 35.3).

Table 35.6 Markers of smooth muscle

	Smooth muscle	Skeletal muscle	Myofibroblasts	Myoepithelial cells
MSA	+	+	+	+
Desmin	+ except vascular	+	−/+	−
SMMS	+	−	−/+	+
h-caldesmon	+	−	−	Normal myoepithelial cells
SMA	+	−	+ Tram track	+
Calponin	+	−	+	+

MSA muscle specific actin

Table 35.7 Markers for cellular neurothekeoma

Antibodies	Literature
S100	−
S100A6	+^
MART1	−
SOX-10	−
SMA	−/+
MSA	−/+
CD68	+/−
CD163	−
CD10	+^
HMB-45	−
NKI-C3 (CD63)	+^
MITF	+
PGP9.5	+/−
D2-40 (podoplanin)	+^
NSE	+
CD99	+
p63	−/+
Desmin	−
Calponin	−/+
CD34	−
Vimentin	+^
CD117	−
GFAP	−
NFP	−

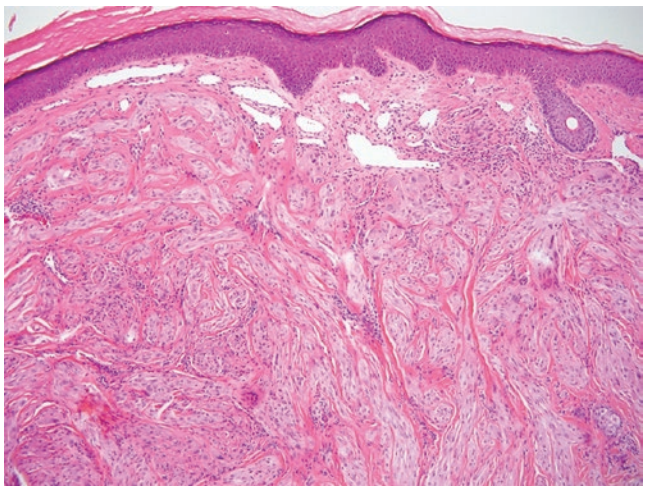

Fig. 35.19 Hematoxylin and eosin–stained sections of a CNT

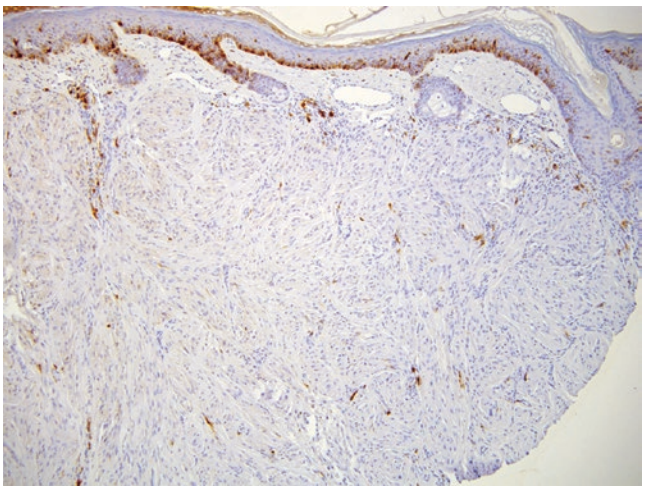

Fig. 35.20 In contrast to the diffuse S100A6 staining in Fig. 35.21 there is an absence of staining with S100 in CNT

Desmin is an intermediate filament found in skeletal, cardiac, and smooth muscle cells but does not reliably stain vascular smooth muscle. It is usually negative in myopericytes, myoepithelial cells and only focal or weakly reactive in myofibroblastic lesions.

Calponin and SMA are commonly used to identify myoepithelial cells. Immunoreactivity for both these antibodies has been reported in some neurothekeomas and atypical fibroxanthoma.

Myogenin and MyoD1, transcription factors involved in striated muscle differentiation, are negative in smooth muscle tumors. If focal staining is present, it likely is due to entrapped or regenerating skeletal muscle fibers.

References: [30, 31, 211–217].

There are three subtypes of neurothekeoma: myxoid, cellular (Fig. 35.19), and mixed. While myxoid neurothekeoma (nerve sheath myxoma) is S100 positive, CNTs are negative, suggesting that they are not of peripheral nerve sheath or melanocytic histogenesis; however, the true lineage is uncertain. The absence of S100 is important in differentiating CNT from a melanocytic lesion (Fig. 35.20). Typical melanocytic markers, including S100, SOX-10, HMB-45, and MART1, are negative in CNT, while other less specific melanocytic markers like MITF and NKI-C3 have been identified. Most CNTs express NKI-C3 but expression has also been seen in nevi, melanomas, granular cell tumors, and some fibrohistiocytic lesions. PGP9.5 also suffers from low

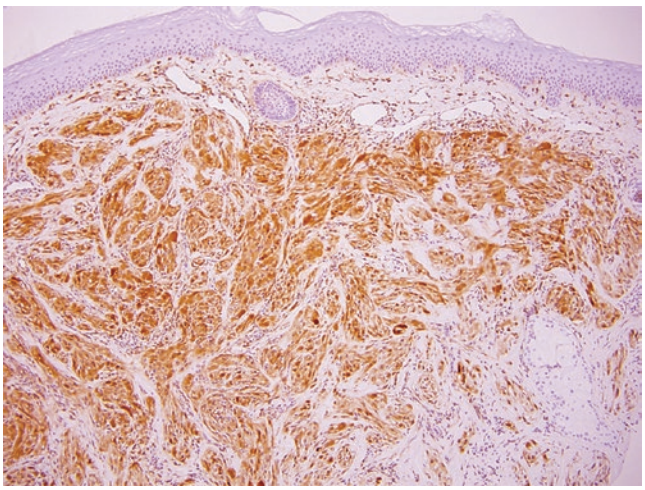

Fig. 35.21 Diffuse S100A6 reactivity in CNT

specificity, also showing variable expression in nerve sheath tumors including granular cell tumor; fibrohistiocytic lesions, including XG; vascular tumors and other tumors like leiomyoma. In contrast to S100, CNTs are S100A6 positive (Fig. 35.21) but so are nevi and other melanocytic lesions. Similar to S100A6, CD10 and D2-40 have been expressed in the great majority of those studied; however, none of these markers are specific for CNT.

References: [31, 214, 218–229].

Markers for Differential Diagnosis

Table 35.8 Markers for cutaneous spindle cell neoplasms

Antibodies	AFX	sMM/dMM	sSCC	LMS	Angiosarc
AE1:AE3	–	–	+	–/+	+/–
CK903	–	–	+	–	NA
p63	–/+	–	+	–/+	–/+–
S100	–	+^	–	–/+	–
P75/NGFR	–	+^	–/+	–	NA
SOX-10	–	+^	–	NA	NA
desmin	–	–	–	+	–
h-caldesmon	–	NA	NA	+	NA
calponin	–/+	–	–	+	NA
SMA	–/+	–	–	+^	–
vimentin	+^	+^	–/+	+^	+
S100A6	+	+^	+^	+	NA
PC-1	+	–/+	–/+	+	NA
CD163	+/–	–/+	–	–/+	NA
CD10	+	–/+	–/+	–/+	NA
CD99	+/–	–/+	–/+	NA	NA
p40	–	–	+^	NA	NA
MITF	+	–/+	–/+	NA	NA
MART1	–	–/+	–	–	NA
CK903(34BE12)	–	–	+	–	NA
CK5/6	–	NA	+	NA	NA
CD68	+/–	–	–	–	–
ERG	–	NA	–	–	+^
CD31	–	NA	NA	–	+
CD34	–	–	–	–	+
HMB-45	–	–/+	–	–	–

The differential diagnosis of atypical spindle cell neoplasms on sun-damaged skin includes AFX, sMM or dMM, sSCC, LMS, and if hemorrhagic, possibly angiosarcoma. Due to potential overlapping reactivity and rare anomalous expression, a panel prevents misdiagnosis.

Some melanocytic markers, including HMB-45 and MART1, are often negative in spindle/desmoplastic melanomas (Figs. 35.22 and 35.23). S100 (Fig. 35.24) and SOX-10 (Fig. 35.25) are the most sensitive markers for sMM/dMM. MART1 and Weak HMB-45 expression in the multinucleate giant cells of AFX can be another pitfall in diagnosis.

Desmoplastic melanoma may require differentiation from scar tissue, especially in the context of a re-excision specimen or possible recurrence. Based on the high sensitivity, S100 is often used in this context. Care is required in interpretation as scars often contain S100 positive spindle cells but unlike in melanoma, are focal and predominantly in a horizontal pattern (Fig. 35.26). SOX-10 positive spindled cells, possibly regenerating schwannian cells, and histiocytes have also been reported in scars unrelated to melanocytic neoplasms.

P75, also known as nerve growth factor receptor (NGFR), expression is strongest in dMM with less consistent reactivity in other types of melanoma. However, p75 is not specific to dMM and is seen in other malignant spindle cell tumors

P40 has similar sensitivity and possibly more specificity for poorly differentiated SCC than p63. Most LMS are positive with SMA and calponin but these markers can also be positive in AFX. Desmin and h-caldesmon are less consistent in LMS but negative in AFX.

Some combination of S100 and SOX-10 for sMM or dMM, high molecular weight keratin and p63 or p40 for sSCC, desmin for LMS, and if hemorrhagic ERG for angiosarcoma can be refined in the setting of atypical spindle cell neoplasms of the skin. AFX is the diagnosis of exclusion.

References: [30–35, 42, 53–55, 63, 71, 72, 80, 125, 180–185, 187–193, 199, 200, 202–205, 207–210, 230–246].

Small blue cell tumors are composed of round closely packed cells with a high nuclear-cytoplasmic ratio. The histologic differential diagnosis includes neoplasms of vastly different lineages. The most common small blue cell tumor involving sun-damaged skin is MCC. In addition to neuroendocrine markers like NSE, MCCs are typically positive with CK20 in a paranuclear dot and/or cytoplasmic pattern while CK7 is only rarely identified.

Other neoplasms that can have similar cytology include MM, metastatic SCCL, lymphoma, and less commonly involving the skin; Ewing sarcoma/primitive neuroectodermal tumor (EWS/PNET), metastatic neuroblastoma, and rhabdomyosarcoma.

Desmin and myogenin identify rhabdomyosarcoma. Lymphoma can be distinguished by lymphoid markers: CD79a, CD3, CD19, and leukocyte common antigen (CD45). EWS/PNET can express S100, NSE, chromogranin, and synaptophysin. CD99 is a marker for EWS/PNET but is not spe-

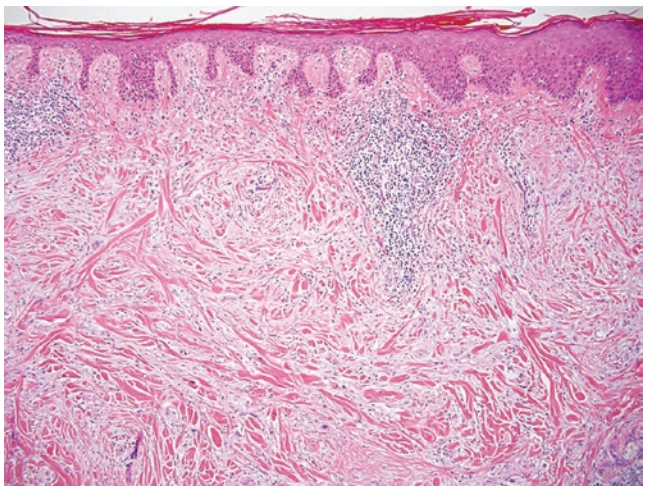

Fig. 35.22 Hematoxylin and eosin–stained sections of dMM

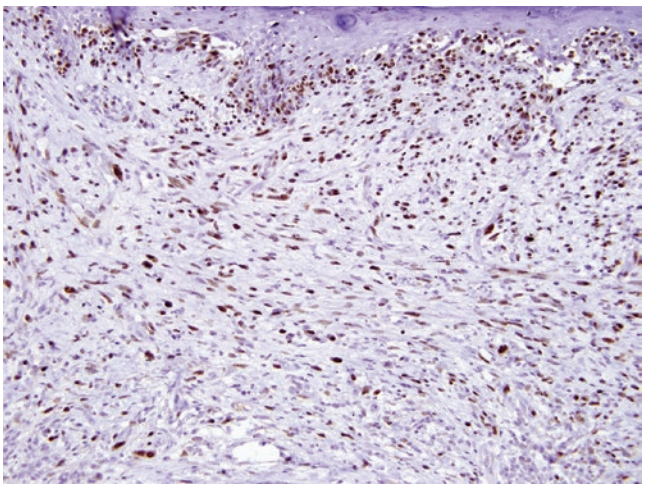

Fig. 35.25 dMM staining with SOX-10

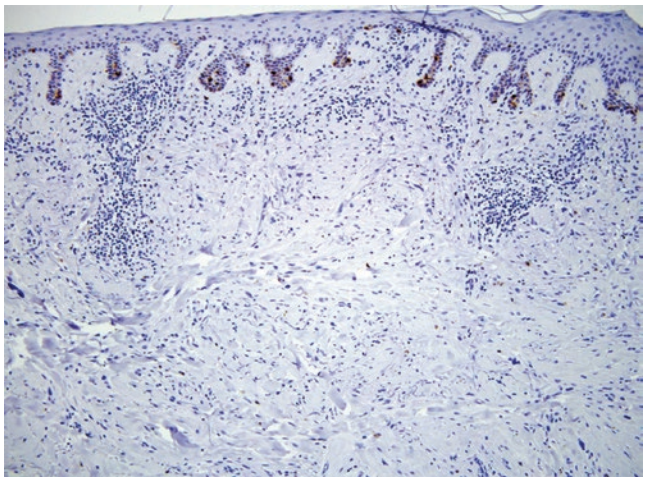

Fig. 35.23 dMM is often negative with MART1

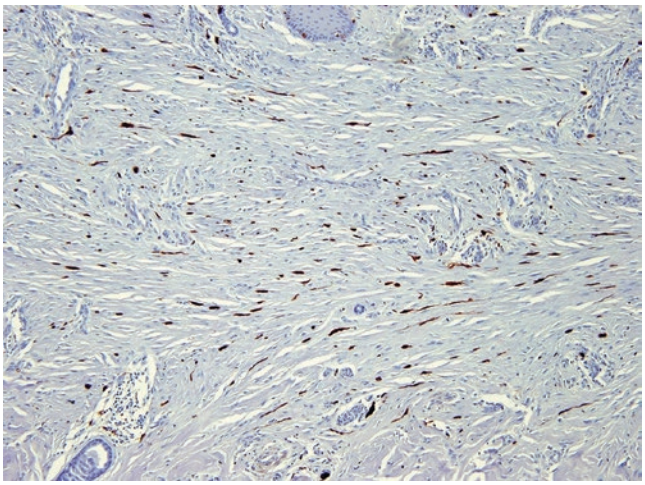

Fig. 35.26 S100 highlighting sparse horizontally oriented spindle cells within a scar. This should not be confused with dMM

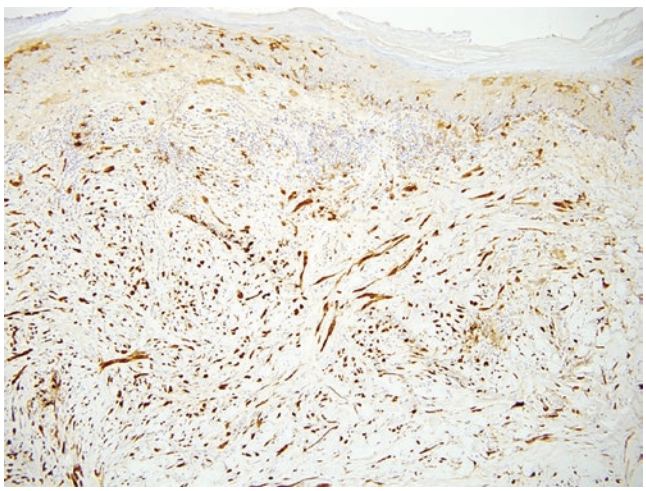

Fig. 35.24 dMM staining with S100

Table 35.9 Markers for cutaneous small blue cell tumors

Antibodies	MCC	MM	Mets SCCL
S100	–/+	+^	–
NSE	+^	–/+	+/–
CK20	+^	–	–
TTF-1	–	–	+^
NFP	+/–	–	–
FLI1	–/+	–/+	–/+
CK7	–/+	–	+
MCPyV	+	–	–

MM malignant melanoma, *Mets SCCL* metastatic small cell carcinoma of the lung

cific and is also seen in lymphoblastic lymphoma, select rhabdomyosarcomas, and small numbers of MCC and MM. FLI1 antibody is a useful nuclear marker for EWS/PNET, as well as an endothelial marker, but is also expressed in a subset of lymphoma, MCC, SCCL, and MM. Keratin reactivity, particularly CK20, is usually absent in EWS/

PNET. Currently EMS/PNET is confirmed through cytogenetic identification of the t(11;22) translocation involving EWS and FLI1 genes. Neuroblastoma can express NSE, NFP, synaptophysin, and chromogranin but is usually negative with CD99, CD45, S100, keratins, and skeletal muscle markers.

The presence of TTF-1 reactivity is not completely specific to SCCL and can be seen in metastatic small cell carcinoma of extra-pulmonary sites; however, it is negative in most MCCs. CK7 expression supports a diagnosis of SCCL but rare CK20–/CK7+ MCCs have been reported.

Ber-EP4 and bcl-2 reactivity in MCC can be a pitfall if BCC is considered in the histologic differential diagnosis (see Fig. 35.12) and on occasion, BCC can express chromogranin and synaptophysin. BCCs are negative with S100, CK20, and TTF-1.

Insulinoma-associated protein 1 (INSM1) is a sensitive nuclear marker of neuroendocrine differentiation found in most MCCs but is also positive in extracutaneous neuroendocrine carcinomas.

References: [11, 12, 30, 31, 35, 41, 54, 102, 118, 141, 145, 146, 148, 149, 153, 157–159, 167, 171, 173–176, 221, 247–255].

EMPD, SCCis, and MMIS are the most common causes of an atypical intraepidermal pagetoid pattern. Typically, the correct diagnosis can be made on morphology alone. However, in some cases a panel of immunohistochemical markers is required. The presence of CEA or Ber-EP4 favors EMPD. The percentage of reactivity varies between polyclonal and monoclonal CEA and between EMPD and Paget's disease of the nipple. EMPD is rarely S100 positive but expression has been reported in Paget's disease of the nipple.

Positivity with CK7 supports a diagnosis of EMPD (Fig. 35.27); however, CK7 positive SCCis has been reported. In addition, CK7+ Toker cells and occasionally CK7+ Merkel cells can be seen in the normal epidermis complicating interpretation.

Nuclear p63 staining is reported in pagetoid SCCis but not EMPD. Isolated studies have reported CD23 and CD5 reactivity in EMPD, in contrast to absent expression in both MMIS and SCCis.

EMPD is a heterogeneous entity that encompasses cases that are limited to the skin and others that are associated with underlying malignancy. This can result in variations in immunohistochemical expression. CK20 is negative in the majority of primary cutaneous EMPD but can be positive in cases with underlying regional malignancy. Similarly, CDX-2 expression suggests an association with underlying rectal carcinoma. Like Paget disease of the nipple, not all cases of primary cutaneous EMPD are positive with GCDFP (gross cystic disease fluid protein). Positive expression can help differentiate EMPD or Paget disease from SCCis, which has not shown reactivity with GCDFP.

Other processes with an intraepithelial component that can mimic those discussed above include mycosis fungoides (MF), LCH, adnexal carcinomas (sebaceous, eccrine, and apocrine) and MCC. While intra-epidermal involvement of MCC and sebaceous carcinoma (especially on the eyelid) are not uncommon, isolated in situ disease is rare. CK20 is useful in suspected MCC and membranovesicular staining with adipophilin can be helpful in identification of sebaceous carcinoma. However, be cautious of the pattern of immunoreactivity as granular adipophilin is not uncommon in SCCis. Another pitfall is coexistence of SCCis and MCC in the same biopsy. The Pautrier microabscesses of MF express pan T cell markers like CD3 while CD1a and langerin are characteristic of LCH. It is important to recognize that both the cells of interest in MF and LCH are CD4 positive.

Differentiation of a clonal seborrheic keratosis from SCCis is a common challenge for dermatopathologists. Morphology remains the gold standard but immunohistochemical aids have been studied. Increased Ki-67 positive cells and presence of over 75% p16 positive cells favors SCCis while CK10 negative clonal nests favor seborrheic keratosis.

References: [27, 31, 35, 36, 43, 67, 256–277].

Table 35.10 Markers for intraepidermal or pagetoid scatter

Antibodies	EMPD	SCCis	MMIS	Sebaceous Carcinoma	MCC
CEA	+^	–	–	–/+	–
S100	–	–	+^	NA	–/+
CK7	+^	–/+	–	+	–/+
EMA	+^	+/–	–	+^	+
CAM5.2	+	–/+	–	+	+
Ber-EP4	+	–	–	–/+	+
p63	–	+	–	+	–/+
AR	+/–	–	–	+^	NA
adipophilin	NA	–/+ (granular)	NA	+^ (vesicular)	–
CK20	–	–	–	–	+^
MART1	–	–	+^	NA	NA
HMB-45	–	–	+	NA	NA

MMIS malignant melanoma in situ

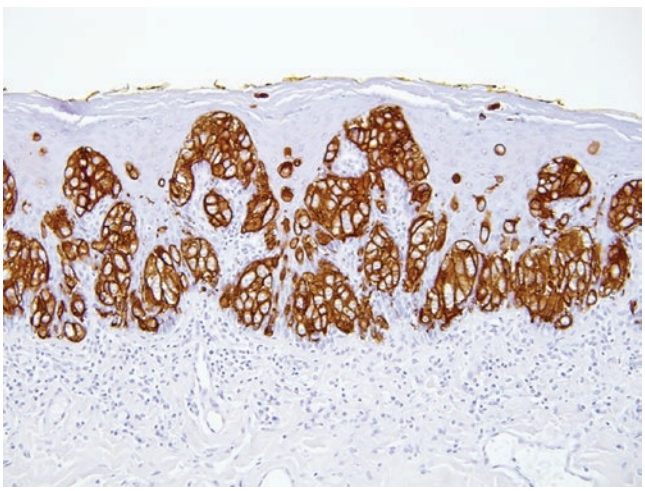

Fig. 35.27 EMPD stained with CK7

Table 35.11 Markers for sclerosing epithelial neoplasms

Antibodies	mBCC	DTE	MAC
FAP(peritumoral stroma)	+	–	NA
PHLDA1	–	+	+/–
P75/NGFR	–	+	–/+
CD10	Neoplasm	Stroma, if at all	–/+ (neoplasm)
CD34 (stroma)	–/+	+	–
Bcl-2	+	+ Periphery of islands	–+ Centrally in islands
CK20 *	–	+^	–
Mib-1 rate	20–40%	0–13%	<5%
AR	+/–	–	–
CK15	–	+^	+/–
SMA	+/–	–	+
Stromelysin-3 (stroma)	+	–	NA
Ber-EP4	+^	+/–	–/+
CK7	–/+	–	+ Centrally in islands
EMA	–	–/+	+/–
p53	+	–	–/+
CEA	–	–	–/+
p63	+ Diffuse	+ Diffuse	+ Scattered cells at periphery of islands, especially deep
MYB	+	–/+	–

mBCC morpheaform basal cell carcinoma, *DTE* desmoplastic trichoepithelioma, *MAC* microcystic adnexal carcinoma, *FAP* fibroblast activation protein

* CK20 highlights sparse Merkel cells colonizing DTE (Fig. 35.28), not the stroma or basaloid neoplastic cells. Merkel cells associated with pre-existing vellus follicles must be excluded and multiple sections may be required for identification. Merkel cells are not typically identified colonizing mBCC (Fig. 35.29) or MACs

Partial samples of sclerosing epithelial neoplasm can be difficult to classify. Differentiation is not only of academic interest but is paramount to clinical management. Numerous markers have been evaluated in this context, but the great majority evaluated very small numbers of tumors in this differential. Although trends have been identified, the clinical and histopathologic features remain the current gold standard.

When present, CEA positive ductal lumina strongly favor MAC over DTE or mBCC. The pathologist must distinguish expression within the tumor from expression in background sweat ducts.

The pattern of reactivity of bcl-2 differs between DTE and mBCC. The tumor islands are diffusely positive in BCC whereas, typically only the periphery of the basaloid islands is positive in DTE. However, the small basaloid islands typical of these tumors may make distinction difficult. Focal positivity with bcl-2 has been reported in MAC.

Stromelysin-3 is a member of the metalloproteinase family, which is expressed in the stroma of carcinomas. Positivity is highest in the stroma of morpheaform and deeply invasive BCCs. SMA reactivity is greatest in the epithelial component of the more aggressive forms of BCC, including morpheaform, micronodular and infiltrative subtypes.

Although there is conflicting data, CD10 staining of the basaloid cells favors mBCC over DTE, while expression in the peritumoral stroma favors DTE.

CD34 stains the stroma of most DTEs differentiating them from the negative stroma of mBCC and MAC. In contrast, the peritumoral stroma of several epithelial cancers is positive for FAP, as in mBCC, but not DTE. FAP is a glycoprotein present in granulation tissue of healing wounds.

AR expression typically is lacking in DTEs, distinguishing them from the positively staining mBCCS, but conventional trichoepitheliomas may also show reactivity.

MBCCs tend to lack or only show focal and weak p75, in contrast to the strong expression in DTEs. However, this will not assist in differentiating from partially sampled MACs that are strongly positive in nearly half of cases. The hair follicle stem cell marker, PHLDA1, is not surprising positive in most tumor cells of the follicular derived DTE but is absent or minimally reactive in mBCCs.

References: [31, 35, 43, 49, 138, 273, 278–309].

Ber-EP4, in conjunction with EMA can be useful to differentiate BCC (EMA-/BerEP4+) from SCC (EMA+/Ber–EP4–). However, sebaceous carcinoma can show the same pattern as SCC. Unfortunately, poorly differentiated SCC and sebaceous carcinoma can show only focal expression with EMA complicating interpretation. In addition, BCCs can show squamoid areas that stain like SCC. EMA alone is only helpful in differentiating BCC, which is negative, from sebaceous carcinoma and SCC.

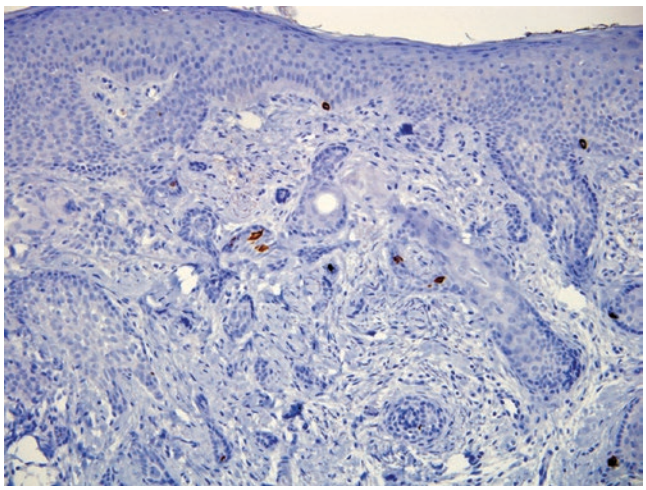

Fig. 35.28 CK20 highlights Merkel cells colonizing DTE

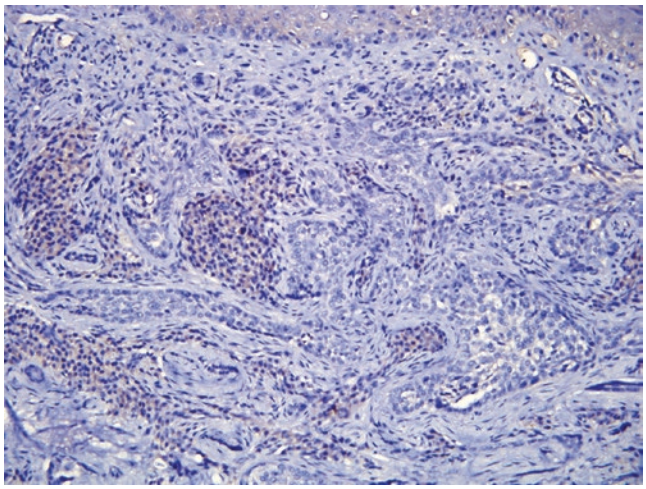

Fig. 35.29 CK20 positive Merkel cells are not identified in mBCC

Table 35.12 Basal cell carcinoma versus squamous cell carcinoma versus sebaceous carcinoma

Antibodies	SCC	BCC	Sebaceous carcinoma
EMA	+	–	+^
Ber-EP4	–	+^	–/+
Bcl-2	–	+	+/–
CK7	–/+	–/+	+
Factor XIIIa	–	–	+
AR	–	+/–	+
Adipophilin	– (50% granular)	– (75% granular)	+^ (membranovesicular)

Ber-EP4 is not diagnostic of BCC. In addition to occasional sebaceous carcinomas, MCC and porocarcinoma can show Ber-EP4 expression.

When sebaceous carcinoma is considered, AR and adipophilin may be helpful. Adipophilin highlights intracellular lipid droplets, as seen in sebocytes (see Fig. 35.1). Adipophilin positive membranovesicles can be only focal in sebaceous carcinoma and most BCCs and SCCs (see Fig. 35.2) only show granular if any staining. Attention to the pattern of staining is paramount to differentiation.

Table 35.13 Nevus versus melanoma

Antibodies	Nevus	MM
PRAME	–	+
HMB-45	Gradient	No gradient
Mib-1	<2%	>10%
p16	>40%	<20%

While most sebaceous carcinomas are isolated tumors, like other sebaceous neoplasms, they can be harbingers of MTS. MTS is most commonly caused by germline mutations in MSH2, followed by MLH1 and MSH6. Albeit imperfect, immunohistochemistry can serve as a screening tool for these mutations. The positive predictive value of loss of normal nuclear expression varies from 33% to 88% for MHL1, 55% to 66% for MSH2, and 67% for MSH6. Since MSH2 and MSH6 form a heterodimer, loss of both does not increase the positive predictive value. In other words, retained normal expression of all mismatch repair genes is reassuring but lack of expression should be followed by evaluation for additional similar lesions and family and personal history of associated malignancies. Genetic testing is required to confirm the immunohistochemical screening, given the significantly lower sensitivity and specificity of these markers in sebaceous lesions, as compared to colorectal cancers, consensus is not reached about routine immunohistochemical screening in many sebaceous lesion scenarios. Immunohistochemical screening is considered "usually appropriate" in patients of all ages with multiple sebaceous tumors, keratoacanthomas with sebaceous differentiation, cystic sebaceous lesions and patients with known MTS associated neoplasms. It is also considered "usually appropriate" in patients who are 60 years or under with a sebaceous lesion that is located outside the head and neck.

References: [24, 31, 36, 138, 282, 310–313].

Differentiating nevus from nevoid melanoma can be problematic, even for experts in the field. Misdiagnosis of melanoma as nevus is one of the most common causes of malpractice lawsuits in pathology. Many immunohistochemical markers have been investigated to aid in distinction without identification of a consistent and reliable method. While overlap exists, general trends have been identified with some markers. Expression of a single marker should never be a single or dominant criterion for designation as benign or malignant.

HMB-45 stain melanocytes at the junction and upper dermis but not the deeper melanocytes in nevi (Figs. 35.30 and 35.31) with the exception of blue nevi that are strongly and diffusely positive throughout (Fig. 35.33). This gradient suggests maturation. In contrast, melanomas reveal more heterogeneous, weak, and focal staining with HMB-45. Caution is required in interpreting HMB-45 in lesions that contain a blue nevus component. This component of combined nevi fails to show evidence of a gradient and is strongly positive throughout (Figs. 35.32 and 35.33) which should not be confused

with lack of maturation typical of melanoma. Another potential pitfall is the presence of HMB-45 expression in dermal melanocytes within and below the scar of traumatized nevi.

A proliferation index, as determined by nuclear Mib-1 staining of melanocytes, over 10% favors melanoma while a proliferation index below 2% favors nevus. However, great overlap exists between some nevi, like Spitz nevi and melanoma. The pattern of staining is also important. Mib-1 positive cells tend to be throughout the dermal component in melanoma, whereas they are superficial or absent in nevi. Mib-1 is not lineage specific and also stains proliferating lymphocytes. When a lesion is heavily inflamed, distinction by cytology or dual staining with a cytoplasmic melanocytic marker is required (Figs. 35.34 and 35.35).

The cell-cycle inhibitor protein p16 is expressed in a greater percentage of nevi (Fig. 35.36) but is deleted or mutated in a proportion of melanomas resulting in loss of nuclear and sometimes also cytoplasmic staining. Nevi are not always diffusely positive with p16 but typically show approximately 50% staining in a "patchwork" or "checkerboard" pattern. A recent study suggests that p16 is less helpful in heavily pigmented lesions. Loss of 9p21 that encodes p16 has been identified in spitzoid melanoma and correlates with loss of expression of p16 immunohistochemically. Some studies report a scoring system based on the results of p16, Ki-67, and HMB-45 to be helpful in classifying spitzoid lesions.

Immunohistochemistry for elastin typically shows preserved elastic fibers between nests and often around individual melanocytes in nevi, in contrast to melanomas that have markedly decreased elastic between and within the nests of melanocytes, often with compression at the base of the tumor or in areas of regression. This contrasts with scars that also show loss of elastic fibers in the fibrosis but lack the compression. Although exceptions are reported, identification of the elastic fiber pattern is potentially used in differentiating scar from regression and identifying the depth of melanoma invasion in a nevus.

PRAME (preferentially expressed antigen in melanoma), a tumor-associated antigen originally identified from patients with metastatic melanoma, has subsequently been found in ocular melanoma and various non-melanocytic malignancies. It is part of a 12-gene prognostic assay for uveal melanoma included in the National Comprehensive Cancer Network guidelines and a component of a 23-gene diagnostic assay for cutaneous melanoma, as well as one of the two genes evaluated in a noninvasive molecular assay used by clinicians to assist in determining the need for biopsy of a melanocytic lesion. Emerging studies show the value of immunohistochemistry for PRAME in diagnosis of melanocytic lesions. Diffuse nuclear expression is seen in a high proportion of primary and metastatic melanomas, excluding dMMs, while the majority of benign nevi are negative or show expression only in a minor subpopulation of cells (Fig. 35.37). Large numbers of equivocal melanocytic lesions have not yet been studied. Sparsely scattered PRAME positive melanocytes have been seen in solar lentigines and nonlesion skin suggesting a potential pitfall.

S100A6 and p21 have been studied in spitzoid lesions; however, use in non-spitzoid melanocytic lesions has not been studied or shown less consistent results. S100A6 (calcyclin) is a S100 subtype that stains Spitz nevi in a strong and diffuse pattern while only one-third of melanomas express S100A6 and usually in a weak and patchy pattern with minimal to no reactivity at the junction. It is important to recognize that nevi other than Spitz, including pigmented spindle cell nevi, react with S100A6 in a weak or negative pattern similar to melanoma and S100A6 also stains fibrohistiocytic lesions. The tumor suppressor, p21, is the main downstream effector gene mediating p53-induced cell cycle arrest. A high level of p21 nuclear expression suggests Spitz nevus over melanoma, especially when coupled with a low proliferation index.

Low levels of cyclin D1, bcl-2, and p53 are seen in Spitz, in contrast to higher expression in melanoma; however, significant overlap exists limiting their usefulness.

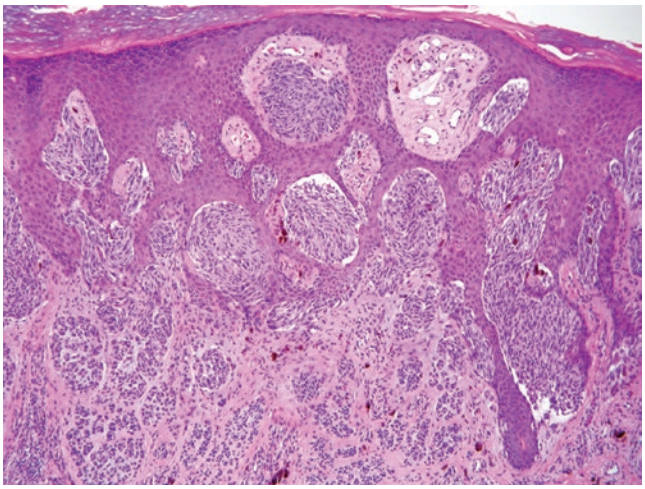

Fig. 35.30 Hematoxylin and eosin–stained sections of Spitz nevus

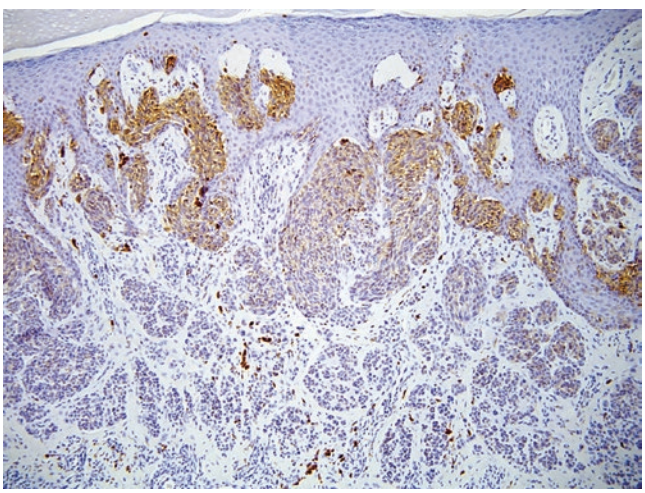

Fig. 35.31 Gradient of decreased expression of HMB-45 with increased depth into the dermis of a Spitz nevus

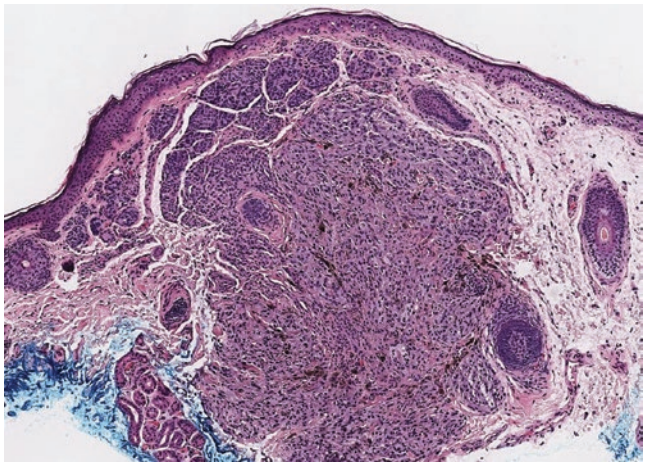

Fig. 35.32 Hematoxylin and eosin–stained sections of a combined nevus

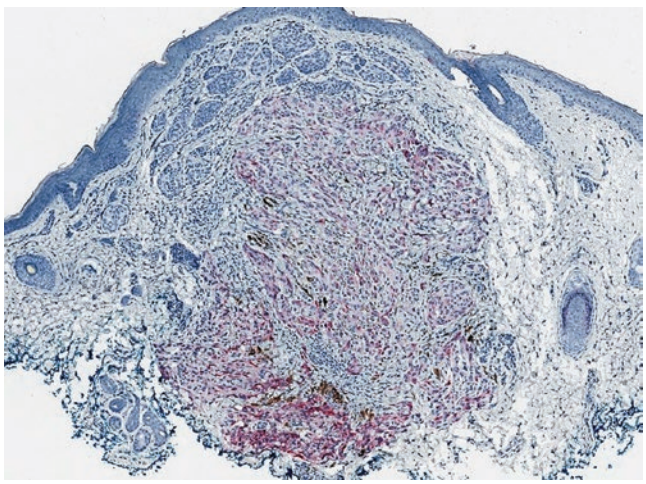

Fig. 35.33 HMB-45 staining the blue nevus component in the dermis

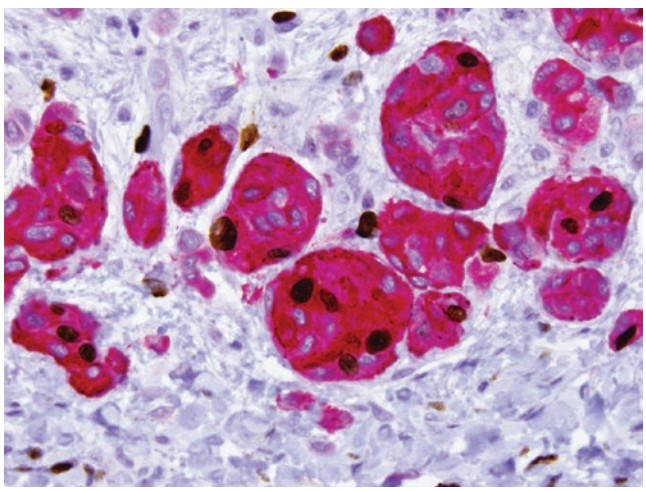

Fig. 35.34 Melanoma with dual MART1 and Mib-1 staining. MART1 with Fast red as the chromogen was used to stain the cytoplasm of the melanocytic cells at the same time that Mib-1 with DAB was used to highlight the nuclei of proliferating cells. This allows identification of the frequent proliferating melanocytes that have red cytoplasm and brown nuclei in melanoma

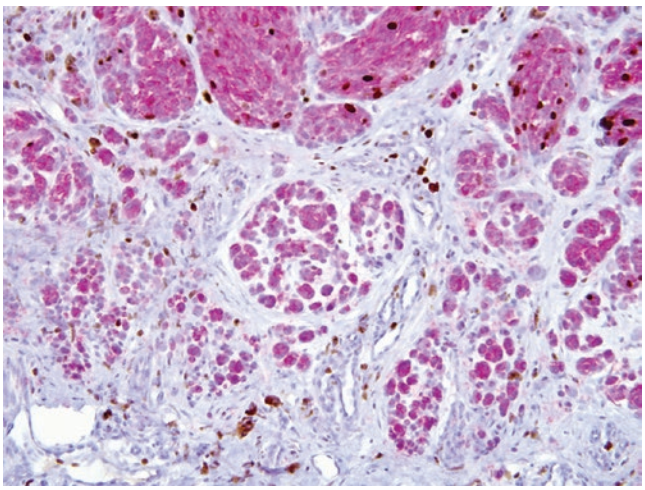

Fig. 35.35 Spitz nevus with MART1(Fast red) and Mib-1(DAB) revealing a gradient of Mib-1 positive Spitz cells with very few proliferating cells in the deeper dermis

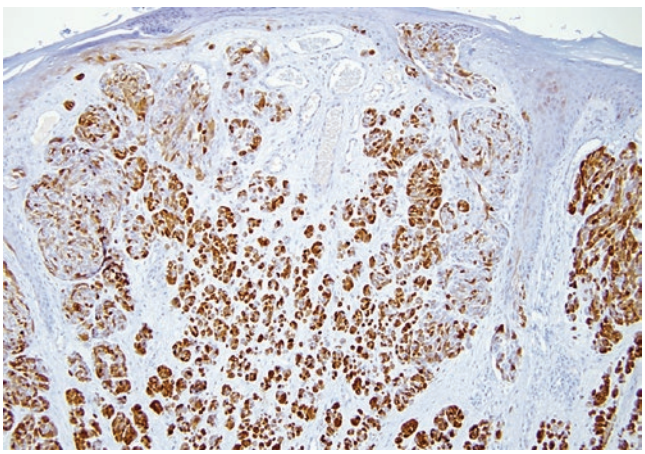

Fig. 35.36 p16 checkerboard staining of a Spitz nevus

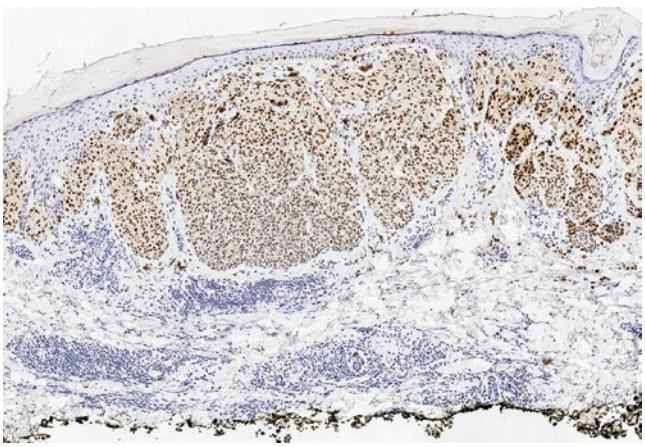

Fig. 35.37 Melanoma developing in a nevus with PRAME positive nuclei in the melanoma but lack of staining in the nevi of the pre-existing congenital nevus at the base

The majority of nevi have no chromosomal abnormalities, whereas melanoma shows various aberrations providing great potential in the field of molecular testing in diagnosis of difficult melanocytic lesions. Once identified molecularly, specific markers have and will continue to be developed to immunohistochemically identify the identified target in a faster, cheaper, and more accessible way.

References: [17, 29, 48, 52, 81, 105, 314–343].

Nodal nevi are present in lymph nodes from patients with divergent primary malignancies but most commonly from patients with melanoma, at a frequency as high as 22%. Differentiation of nodal nevus and metastatic melanoma can typically be determined based on presence or absence of cytologic atypia, histologic comparison with the primary melanoma, and location, capsular/trabecular or subcapsular/parenchymal, respectively.

Protocols for melanoma SLNs vary from institution to institution with differing use of immunohistochemical stains. S100 is highly sensitive but is also expressed in dendritic cells complicating interpretation of potential small foci. MART1 fails to show this distraction but on occasion, pigmented macrophages will weakly label. SOX-10 is highly sensitive and lacks these limitations. Nerves and small slightly elongate perivascular nuclei, possibly of pericytes or schwannian cells, are highlighted with SOX-10 in normal

Table 35.14 Nodal nevus versus metastatic melanoma

Antibodies	Nodal nevus	Nodal metastasis
S100	+	+
SOX-10	+	+
MART1	+	+
HMB-45	–	+/–
Mib-1	–	+
p16	+	–
PRAME	–	+

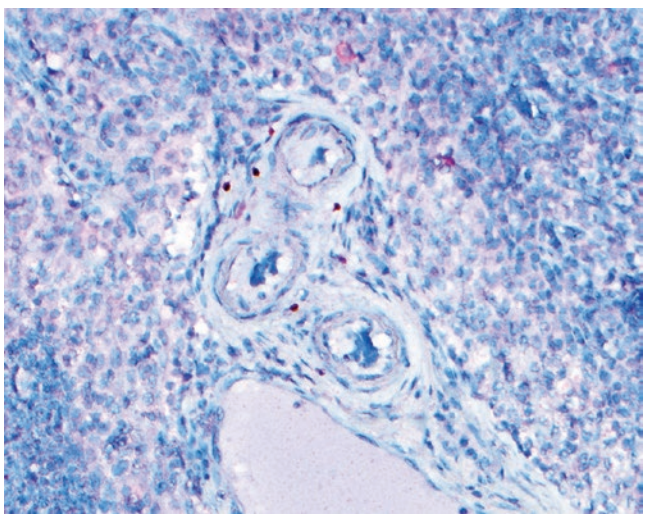

Fig. 35.38 Perivascular small SOX-10 positive nuclei in a negative sentinel lymph node

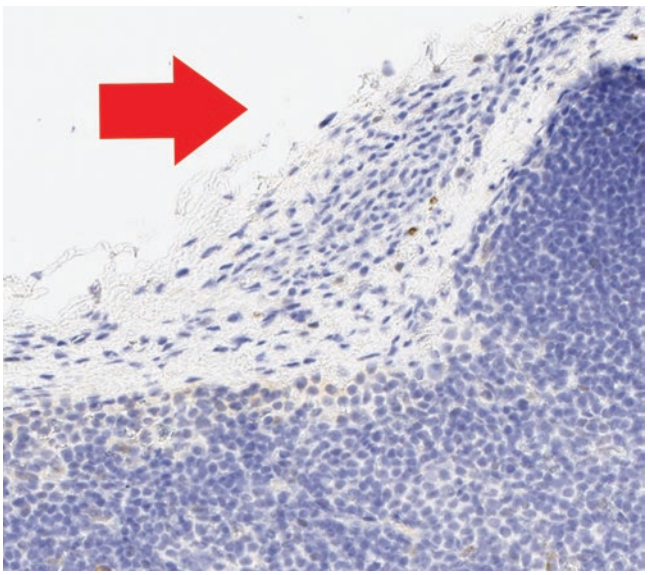

Fig. 35.39 PRAME negative nodal nevus

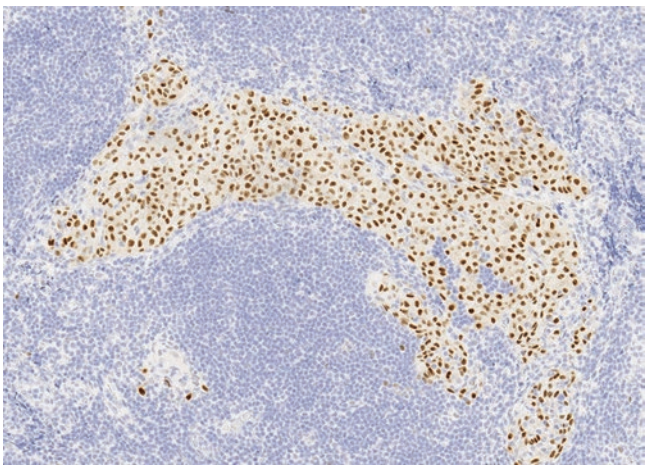

Fig. 35.40 PRAME positive nuclei in metastatic melanoma of the lymph node

Table 35.15 Dermatofibroma versus dermatofibrosarcoma protuberans

Antibodies	DF	DFSP
CD34	–/+	+^
Factor XIIIa	+	–/+
Stromelysin-3	+	–
CD99	+^	+/– but weak and deep
S100A6	+^	–
p53	–	+/–
Tenascin (at DEJ)	+^	–
Nestin	–/+	+^
CD10	+^	–/+
CD163	+^	–/+
CD68	+	–

DEJ dermal epidermal junction

lymph nodes (Fig. 35.38). This dot-like reactivity is smaller than the size of typical lymphocyte, shows little to no associated cytoplasm, is variably elongate, and is perivascular aiding in differentiation from metastases.

HMB-45 is expressed by approximately 60% of metastatic melanomas, whereas, similar to the dermal component of benign cutaneous nevi, ordinary nodal nevi fail to express HMB-45. This can be useful in differentiation, however, like cutaneous blue nevi, nodal blue nevi are HMB-45 positive.

Similar to nevi and melanoma of cutaneous sites p16, Mib-1, and PRAME (Figs. 35.39 and 35.40) appear to be helpful in differentiation. Additional studies have suggested the pattern of reticulin expression and presence or absence of fatty acid synthase (FAS), acetyl-CoA carboxylase (ACC), and 5-hydroxymethylcytosine (5-hmC) may be of assistance with FAS and ACC expression limited to metastases and 5-hmC nuclear expression preserved in nevi.

Dual staining of some of the non-melanocytic markers in conjunction with a melanocytic marker, like MART1, can ensure reactivity is involving only the cells of interest.

References: [16, 29, 31, 47, 344–354].

Most DFs are easily distinguished from DFSP in adequate samples; however, morphologic differentiation can be difficult in deep or cellular DFs. Classically, the dermal dendritic cell marker, Factor XIIIa has been used with CD34 to differentiate. However, there is overlap and lack of specificity. While CD34 is positive in DFSP (Fig. 35.41) it is not specific and it highlights vascular endothelium, hematopoietic progenitor cells, solitary fibrous tumor, spindle cell lipoma, superficial acral fibromyxoma, sclerotic fibroma, Kaposi sarcoma, trichilemmoma, scleromyxedema, nephrogenic systemic fibrosis, neurofibromas, among others. Caution is required in interpretation of DFSP margins with CD34, since CD34 disappears from scars but proliferates in peri-cicatricial tissue. DFs are often only weakly positive or reactive at the periphery with Factor XIIIa but staining is more diffuse in cellular DFs (Fig. 35.42). Some DFs exhibit focal staining with CD34, especially at the periphery of cellular and deep DF (Fig. 35.43).

Stromelysin-3 is a member of the metalloproteinase family that is involved in tissue remodeling, including tumor invasion. Expression is seen in the fibroblastic cells surrounding the epithelial portion of most cancers while most benign tumors, other than DF, are typically negative.

Tenascin, an extracellular matrix glycoprotein involved in embryogenesis, carcinogenesis, and wound healing, is noted within the lesion in both DFs and DFSPs and does not assist in differentiation. However, strong tenascin expression is identified at the DEJ overlying DF but not over DFSP.

Nestin, a neuroectodermal and mesenchymal stem cell marker, is strongly expressed in DFSP with no or only rare focal expression in DFs. Unlike CD34 that may lose expression in fibrosarcomatous areas of DFSP, nestin remains unaltered.

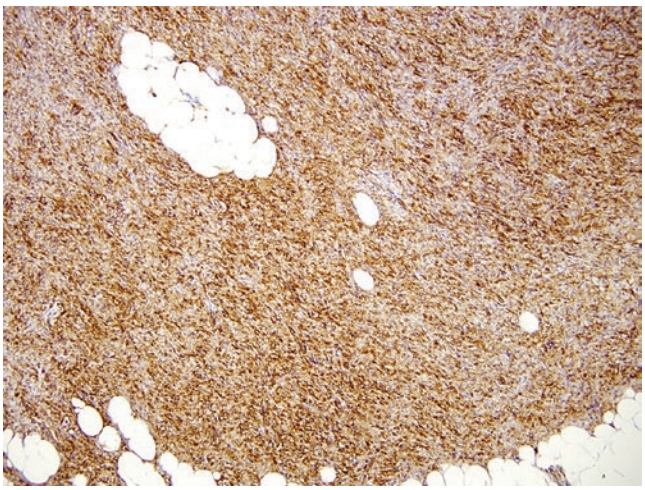

Fig. 35.41 DFSP staining with CD34

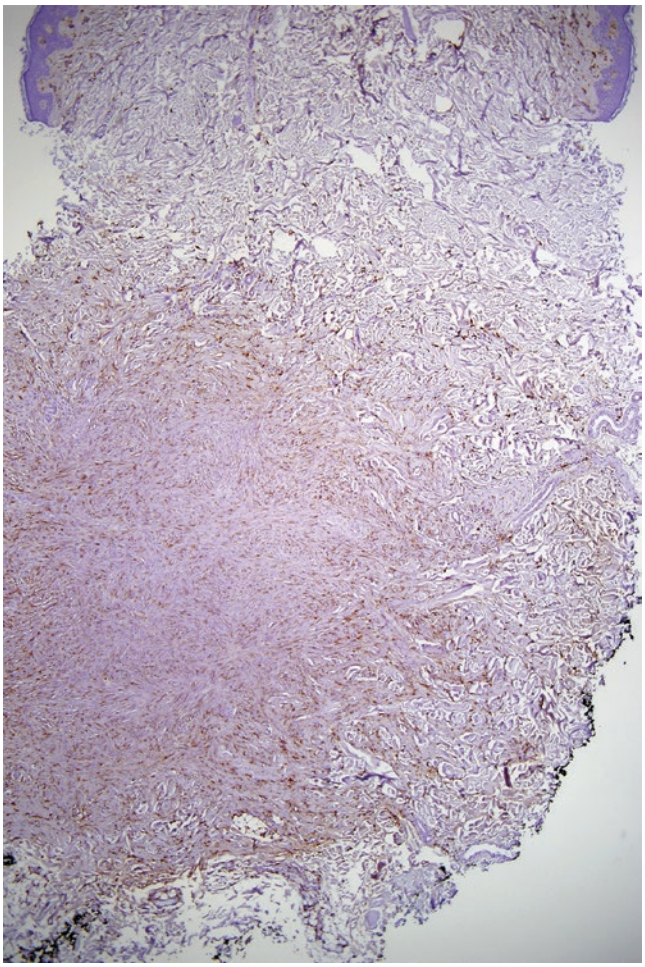

Fig. 35.42 Cellular DF staining with Factor XIIIa

The vast majority of DFs are reactive with S100A6 and CD10, whereas CD10 expression is seen in approximately half of DFSPs. Studies on D2-40 show variable expression in DFs and DFSPs, typically higher in DFs.

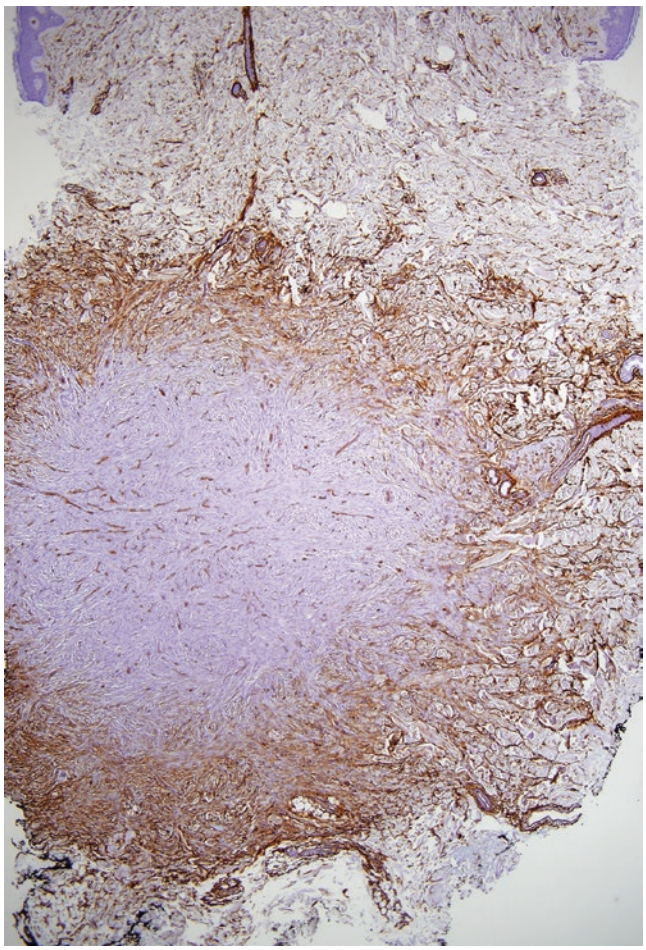

Fig. 35.43 Cellular DF with focal CD34 reactivity at the periphery of the lesion

Table 35.16 Markers of histiocytic processes of the skin

Antibodies	LCH	XG	Reticulohistiocytoma	RDD
CD1a	+	–	–	–
Langerin(CD207)	+	–	–	–
CD68	–/+	+/–	+/–	+
CD163	–/+	+	+	+
S100	+	–	–	+
Factor XIIIa	–	+	+/–	–
VE1	–/+	–	NA	–

DFs are more likely to show diffuse CD99 staining than DFSP and when staining is present in DFSP it tends to be patchy and weak in the deeper parts of the lesion without reactivity superficially.

Expression of p53 in DFSPs ranges from 15% to 92% depending on the study. It has been suggested that presence of a p53 mutation is associated with tumor progression to fibrosarcoma.

Table 35.17 Atypical vascular lesion versus secondary angiosarcoma

Antibodies	AVL	Secondary Angiosarcoma
CD34	+	+/–
CD31	+^	+
D2-40	+	–/+
c-MYC	+^	–

Table 35.18 Primary cutaneous malignant adnexal tumors versus metastatic adenocarcinoma to the skin

Antibodies	CAT	Met Adeno
p63	+	–
CK5/6	+	–/+
D2-40 (podoplanin)	+/–	–
CK15	–/+	–
p40	+	–

CAT cutaneous adnexal tumor, *Met adeno* metastatic adenocarcinoma

Contrary to intuition, DFs have a higher Ki-67 proliferation index and mitotic count than most classic DFSPs, especially superficially.

In rare cases that cannot be distinguished by morphology and immunoprofile, FISH can be used to identify the t(17;22) translocation fusing COL1A1 and PDGFB in DFSPs.

References: [46, 55, 188, 293, 339, 340, 355–375].

Histiocytic disorders of the skin tend to be classified as LCH and non-Langerhans cell histiocytoses, which includes XG, reticulohistiocytoma, and RDD. All show variable expression of the histiocytic markers CD163 and CD68. Only LCH and RDD are also S100 positive. Langerhans cells are distinguished by the presence of CD1a and Langerin that signifies the presence of Birbeck granules. BRAF V600E mutations, as characterized by the immunohistochemical marker, VE1, are present in approximately half of cases of LCH. Indeterminate cells are also S100 and CD1a positive but lack Birbeck granules typical of Langerhans cells and thus are negative with langerin.

References: [23, 72, 205, 207, 376–380].

Cutaneous angiosarcoma occurs in 3 settings: primary disease usually on the head and neck of elderly sun-damaged patients, secondary due to chronic lymphedema, and secondary due to radiation, most commonly in breast cancer patients. Several studies have shown that the majority of secondary angiosarcomas harbor MYC amplification which has good concordance with immunohistochemistry (Fig. 35.44). Differentiation of AVLs from secondary angiosarcoma of the breast can be problematic, particularly in small biopsy specimens. Although c-MYC immunohistochemistry is helpful in this distinction, primary angiosarcomas are not characteristically positive (0–45%). Margin analysis of secondary angiosarcoma can be assisted with c-MYC immunohistochemistry.

References: [24, 31, 35, 381–383].

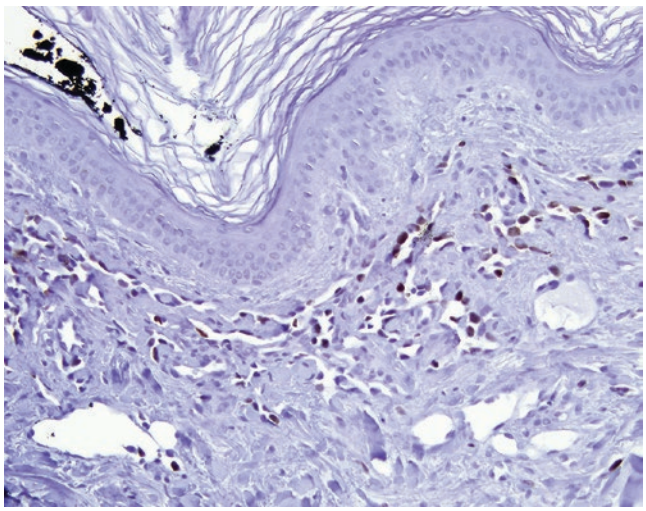

Fig. 35.44 Nuclear c-MYC in a biopsy of a vascular proliferation from the breast of a woman who had prior radiation for breast cancer. Wider excision revealed angiosarcoma

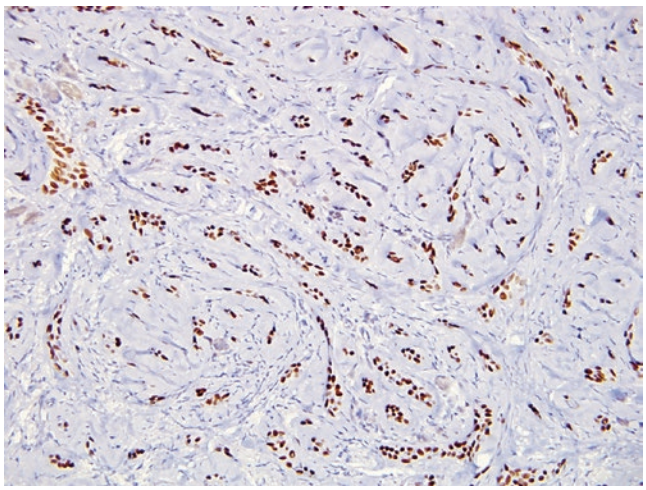

Fig. 35.45 MAC with strong p63 expression

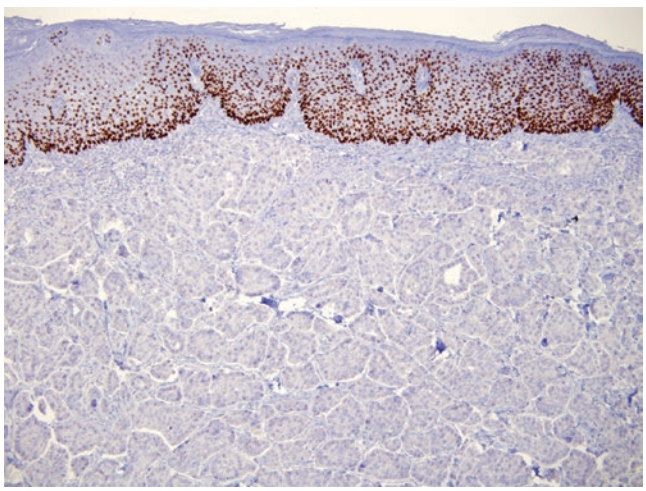

Fig. 35.46 Metastatic breast carcinoma to the skin fails to stain with p63

Table 35.19 Identification of unknown primary

	Lung	Breast	Colon	Kidney	Thyroid	Ovary
CK7	+	+	–/+	–	+	+
CK20	–	–	+	–	–/+	–
TTF-1	+	–	–	–	+	–
CDX-2	–	–	+	–	–	–
GATA3	–	+	–	–	–	–
PAX8	–	–	–	+	+	+
GCDFP	–	+/–	–	–	–	–

The majority of primary benign and malignant CATs are positive for p63, p40, CK5/6, and D2-40 while expression is rare in metastatic adenocarcinomas (Figs. 35.45 and 35.46). These markers are helpful in distinguishing primary CATs from metastatic adenocarcinoma to the skin but should not preclude systemic evaluation for a primary source. This is not useful in the case of metastatic SCC or urothelial carcinoma to the skin. In addition, primary cutaneous mucinous carcinoma appears to be an exception and, although a primary CAT, does not reliably express p63, D2-40, or CK5/6 and like metastatic breast carcinoma, is often CK7, ER, PR, GATA3, and GCDFP positive. Metastases from malignant CATs generally retain p63 and D2-40 expression similar to their associated primary CATs.

The studies of high molecular weight CK5/6 are small and consist predominantly of benign CATs. In general, metastatic adenocarcinomas express CK5/6 in only one-third of cases, predominantly with weak intensity. However, metastatic breast carcinoma is reactive for CK5/6 in almost half of cases.

CK15 is specific in distinguishing CAT from cutaneous metastases but is not sensitive. In general, a panel of immunohistochemical stains provides the greatest sensitivity and specificity.

References: [23, 31, 66, 278, 384–397].

Tumors from the lung, breast, and colon are the most common source of cutaneous metastases. In general, a panel of CK7 and CK20 can differentiate metastases from above the diaphragm (CK7+ in breast and lung adenocarcinomas) and below the diaphragm (CK20+ in colon carcinoma). TTF-1 in lung and CDX2 in colon can be of additional assistance. However, as the name suggests, TTF-1 is also present in thyroid cancer and SCC of the lung is often TTF-1 negative. Expression of GCDFP, ER, PR, and mammaglobin favor breast metastasis over a primary cutaneous tumor but it should not be surprising given the similar origin, that primary cutaneous apocrine carcinomas can rarely express these markers. GATA3 expression is quite common in sebaceous and apocrine neoplasms of the skin and thus should not be considered pathognomonic of breast metastasis. GATA3 is also expressed in urothelial carcinoma. Other less common cutaneous metastases and associated immunohistochemical markers include PAX8 in ovary, thyroid, and renal tumors, PSA (prostate specific antigen) in prostate carcinoma, and renal cell carcinoma marker in its namesake.

References: [23, 31, 66, 278, 279, 385, 386, 398–402].

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