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# Expression of S100A6 protein in a broad spectrum of cutaneous tumors using tissue microarrays

**Background:** S100A6, a calcium-binding protein in the S100 family, has been observed in melanocytic nevi, neural tumors, fibrohistiocytic tumors and is overexpressed in melanoma. Previous studies reported S100A6 expression in atypical fibroxanthomas (AFX) but not in a small number of desmoplastic melanomas (DM). Limited data on S100A6 expression in cutaneous epithelial tumors exists in the literature. The goal of this study was to determine the specificity and sensitivity of S100A6 protein in a spectrum of cutaneous mesenchymal or epithelial tumors.
**Methods:** Tissue microarrays of cutaneous epithelial neoplasms, mesenchymal neoplasms, DM and malignant peripheral nerve sheath tumors (MPNST) were stained with S100A6 antibody.
**Results:** Eleven basal cell carcinomas (BCC) failed to express S100A6, whereas all 10 squamous cell carcinomas (SCC) expressed S100A6. Four of seven microcystic adnexal carcinomas (MAC) stained for S100A6. Tumors with duct differentiation variously expressed S100A6 protein, with two hidradenomas showing the strongest staining. Malignant spindle cell tumors, with the exception of 13 of 30 MPNST, had a high incidence of S100A6 positivity.
**Conclusions:** S100A6 expression may distinguish SCC from BCC, MAC from BCC and hidradenoma from other adnexal tumors. S100A6 expression favors DM over MPNST but overlap limits its diagnostic use.

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S100 proteins belong to a family of acidic, low molecular weight, calcium-binding proteins that regulate a variety of intracellular processes via interaction with different target molecules in a calcium-dependent manner.[1] These proteins share amino acid sequence homology and similar structure, in that they bind calcium through two EF-hand calcium-binding domains.[2–5] Once calcium is bound, these proteins undergo conformational change, interact with target proteins in signal transduction pathways, thereby exerting a pleiotropic effect on the cell.

S100A6 protein (calcyclin) was discovered in 1986 by Calabretta et al.[6] Subsequent studies have shown expression of S100A6 protein in a variety of normal cells and tissues, such as keratinocytes (weak expression), melanocytes, Langerhans' cells, Schwann cells, glandular epithelium of breast, endometrium, bile ducts, salivary glands and fibroblasts, including dermal dendrocytes (DD) of the papillary dermis.[7–9] S100A6 expression has been observed in some junctional and compound melanocytic nevi and blue nevi and is overexpressed in primary and metastatic

melanomas.[7,10–15] The pattern of S100A6 expression has been shown to differ significantly in Spitz nevi compared with melanomas and other melanocytic nevi and may be a useful marker in the differential diagnosis of diagnostically difficult lesions containing a junctional melanocytic component.[16] Interestingly, Ribé and McNutt included a small subset of desmoplastic melanomas (DM) and all three lesions were negative for S100A6. A variety of tumors derived from the Schwann cell and all types of neurothekeomas have been reported to express S100A6 protein.[17,18] The expression of S100A6 has also been shown in a spectrum of cutaneous fibrohistiocytic lesions, particularly those arising from DD, such as fibrous papules and dermatofibromas (DFs) and has been shown to be expressed in a small number of atypical fibroxanthomas (AFX) and malignant fibrous histiocytoma (MFH).[19–21]

The goal of this study, was to evaluate S100A6 protein expression in a broad spectrum of cutaneous lesions, with particular interest in the differential diagnosis of malignant spindle cell tumors and cutaneous epithelial tumors of the skin, to determine if this antibody has any diagnostic use in routine dermatopathology practice.

## Materials and methods

### Tissue samples and tissue microarrays

Following approval by the Institutional Review Board at the University of Michigan, tissue blocks were retrieved for a spectrum of infiltrative and neoplastic processes of the skin using a Systematized Nomenclature of Medicine (SNOMED) search of the laboratory database of the Department of Pathology. Separate Tissue microarrays (TMAs) were constructed to include a spectrum of cutaneous epithelial tumors, cutaneous mesenchymal tumors, cutaneous histiocytic infiltrates, DM and malignant peripheral nerve sheath tumors (MPNST). Three cores were obtained on each example of DM and MPNST included in their respective TMAs. As result of the smaller amount of lesional tissue in most of the cutaneous epithelial tumors, mesenchymal tumors and histiocytic infiltrates, a single core was obtained and included in their respective TMAs. A small percentage of these lesions lacked sufficient tissue in the TMA for evaluation following immunohistochemical staining. In addition to the study samples, each TMA contained normal control tissues and blue and yellow dyed cores for orientation. A database spreadsheet was developed for each TMA.

### Immunohistochemistry

Each TMA was stained with an antibody to S100A6 protein. Briefly, 4 μ thick TMA sections were deparaffinized and rehydrated. Following antigen retrieval in proteinase K for 5 min, a mouse monoclonal S100A6 protein (clone CACY-100, 1 : 250 dilution, Sigma-Aldrich, St. Louis, MO, USA) was applied to each TMA slides. Immunohistochemical staining was performed on a DAKO Autostainer (DAKO, Carpinteria, CA, USA) using DAKO LSAB+ and a 3,3′-diaminobenzidine chromogen. A negative control slide that lacked primary antibody was included. Individual cores of each TMA slide were evaluated for presence (+) or absence (−) of staining. The staining intensity was judged as weak (1+), moderate (2+) or strong (3+). For TMAs containing multiple cores, the strongest staining observed in any of the three samples was recorded for data analysis.

### Statistical analysis

Comparisons of frequency and intensity of staining between different diagnostic entities were made using the Chi-square test. A p-value $< 0.05$ was considered to be statistically significant.

## Results

The data for S100A6 expression in a spectrum of cutaneous epithelial tumors is presented in Table 1. The epithelial tumor cells in all 11 conventional basal cell carcinomas (BCC), which showed either infiltrative, including the morpheaform type, or circumscribed growth patterns, did not express S100A6 (Fig. 1A). The spindle cells in the stroma immediately adjacent to the BCC labeled with anti-S100A6 to a variable degree, with most cases showing a moderate expression. Interestingly, three of five fibroepithelioma of Pinkus (FEP) tumors showed weak expression of S100A6. All 10 squamous cell carcinomas (SCC), including 6 spindle cell (sarcomatoid) squamous cell carcinomas (SCSCC) and 6 of 8 (75%) keratoacanthomas showed at least focal S100A6 labeling; 6 of these 12 cases with positive staining had either moderate (4) or strong (2) intensity (Fig. 1B). The difference between BCC and SCC in frequency of positive cases and staining intensity of tumor cells was statistically significant ($p \leq 0.001$). With the exception of one case, which showed scattered weakly staining tumor cells, Merkel cell carcinomas were negative for S100A6.

Sebaceous tumors were generally negative for S100A6, with the exception of one case that showed very focal weak labeling. A variety of adnexal tumors showed variable expression of S100A6. No S100A6 expression was observed in any of the five poromas (Fig. 2A), whereas two of three porocarcinomas showed rare or focal positive staining. In contrast,

Table 1. Expression of S100A6 protein in a spectrum of cutaneous epithelial tumors

| Diagnosis | Number of cases | Staining results | | | | Number positive/ total number (%) |
|---|---|---|---|---|---|---|
| | | Negative | 1+ | 2+ | 3+ | |
| BCC | 11 | 11 | 0 | 0 | 0 | 0/11 (0) |
| FEP | 5 | 2 | 3 | 0 | 0 | 3/5 (60) |
| SCC | 4 | 0 | 2 | 1 | 1 | 4/4 (100) |
| SCSCC | 6 | 0 | 1 | 4 | 1 | 6/6 (100) |
| KA | 8 | 2 | 2 | 3 | 1 | 6/8 (75) |
| MCC | 4 | 3 | 1 | 0 | 0 | 1/4 (25) |
| SEBCA | 4 | 3 | 1 | 0 | 0 | 1/4 (25) |
| SEBAC | 2 | 2 | 0 | 0 | 0 | 0/2 (0) |
| SEBAD | 2 | 2 | 0 | 0 | 0 | 0/2 (0) |
| PORO | 5 | 5 | 0 | 0 | 0 | 0/5 (0) |
| POROCA | 3 | 1 | 1 | 1 | 0 | 2/3 (67) |
| HID | 2 | 0 | 0 | 0 | 2 | 2/2 (100) |
| HIDCA | 2 | 1 | 1 | 0 | 0 | 1/2 (50) |
| SPIR | 4 | 0 | 2 | 1 | 1 | 4/4 (100) |
| CYL | 3 | 0 | 1 | 2 | 0 | 3/3 (100) |
| HP | 3 | 0 | 0 | 1 | 2 | 3/3 (100) |
| APCA | 1 | 0 | 0 | 0 | 1 | 1/1 (100) |
| ECCA | 1 | 0 | 0 | 1 | 0 | 1/1 (100) |
| TE | 2 | 2 | 0 | 0 | 0 | 0/2 (0) |
| DTE | 2 | 1 | 0 | 1 | 0 | 1/2 (50) |
| MAC | 7 | 3 | 1 | 3 | 0 | 4/7 (57) |

BCC, basal cell carcinoma; FEP, fibroepithelioma of Pinkus; SCC, squamous cell carcinoma; SCSCC, spindle cell squamous cell carcinoma; KA, keratoacanthoma; MCC, Merkel cell carcinoma; SEBCA, sebaceous carcinoma; SEBAC, sebaceoma; SEBAD, sebaceous adenoma; PORO, poroma; POROCA, porocarcinoma; HID, hidradenoma; HIDCA, hidradenocarcinoma; SPIR, spiradenoma; CYL, cylindroma; HP, hidradenomas papilliferum; APCA, apocrine carcinoma; ECCA, eccrine carcinoma; TE, trichoepithelioma; DTE, desmoplastic trichoepithelioma; MAC, microcystic adnexal carcinoma.

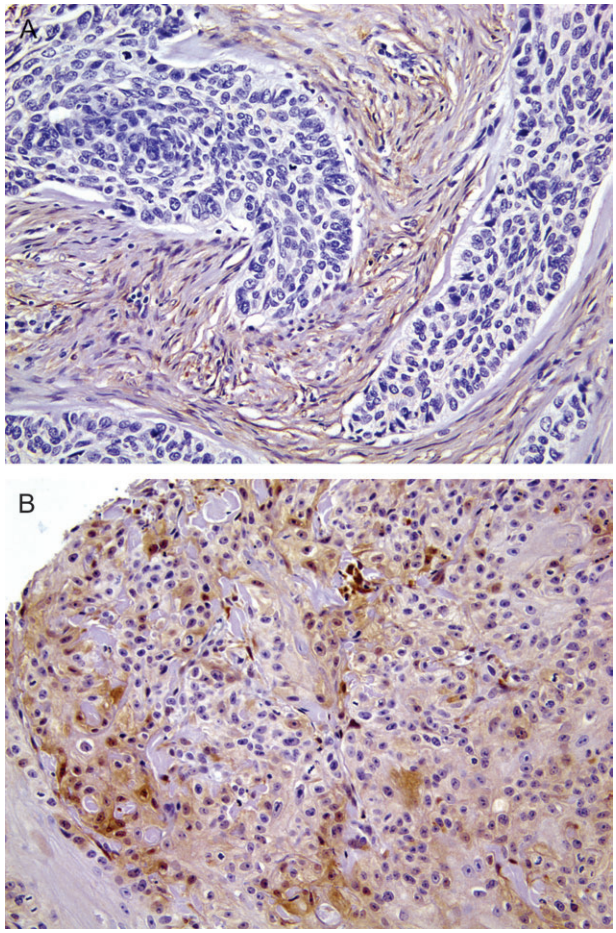


*Fig. 1.* S100A6 expression in basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). (A) Absence of S100A6 staining in tumor epithelium of BCC; note the strong staining in spindle cells in the peritumoral stroma. (B) Strong S100A6 staining of some tumor cells in a SCC.

both hidradenomas, which were characterized by large polygonal cells with abundant eosinophilic cytoplasm and smaller polygonal cells with clear cytoplasm, showed strong and diffuse labeling for S100A6 (Fig. 2B,C). Four spiradenomas and three cylindromas had S100A6 staining localized primarily to the lining cells of duct lumens in all lesions (Fig. 2D). One apocrine carcinoma had strong S100A6 labeling of duct epithelium lining the glandular neoplasm. All three hidradenoma papilliferum lesions had focal strong staining in the apocrine epithelium (Fig. 2E). Microcystic adnexal carcinoma (MAC) and conventional and desmoplastic variants of trichoepithelioma (TE) showed more variable staining. Four of seven MACs had weak to moderate staining for S100A6, with focal staining localized primarily within the lining epithelium of small ducts (Fig. 3). The staining in MAC was statistically significant when compared with BCC, excluding FEP tumors ($p \leq 0.025$). Two conventional TEs failed to stain for S100A6, while one of two desmoplastic trichoepitheliomas (DTE) had focal moderate S100A6 labeling.

A spectrum of spindled and epithelioid mesenchymal tumors was evaluated for S100A6 expression and the staining results are presented in Table 2. Several morphologic variants of DF or fibrous histiocytoma were included in this study and all 28 lesions showed expression of S100A6 to a variable degree. The epithelioid cell histiocytoma and hemosiderotic variants were more probable to show strong S100A6 staining when compared with the other variants that had more spindled fibroblastic cells within the individual tumors. Five of five (100%) dermatomyofibromas and two of two (100%) superficial acral fibromyxomas were labeled with antibodies to S100A6. In addition to the aforementioned benign fibrohistiocytic tumors, low-grade and high-grade malignant fibrohistiocytic tumors also expressed S100A6. Specifically, 9 of 10 (90%) of dermatofibrosarcoma protuberans (DFSP) tumors, 9 of 9 (100%) AFX and 8 of 9 (89%) MFHs were positive for S100A6. The higher-grade tumors tended to show more intense staining than the weak to moderate staining observed in DFSP lesions, but this difference did not reach statistical significance ($p \leq 0.10$). Cutaneous mesenchymal tumors of neural differentiation, such as neurofibromas and

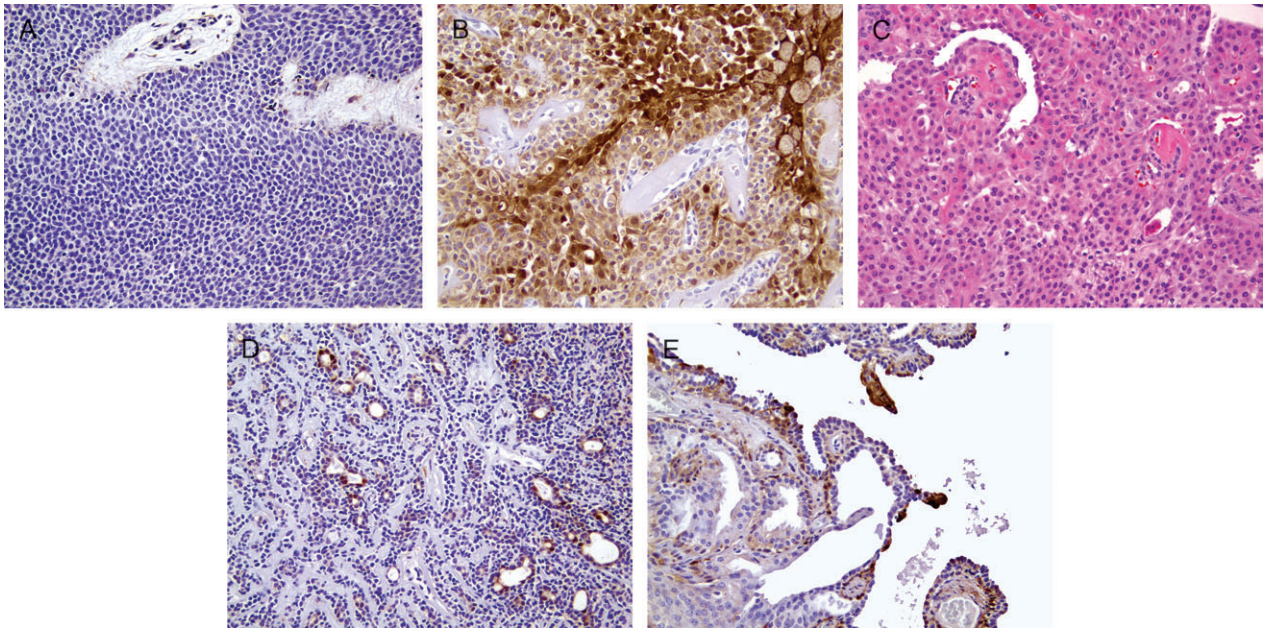


*Fig. 2.* Adnexal tumors with duct differentiation. (A) Poroma lacks S100A6 staining in tumor epithelium. (B) Hidradenoma with diffuse S100A6 staining of tumor cells. (C) Hidradenoma in (B) is composed of large polygonal cells with abundant eosinophilic cytoplasm and smaller polygonal cells with clear cytoplasm (hematoxylin and eosin). (D) Spiradenoma with preferential staining of duct lining epithelium. (E) Hidradenoma papilliferum showing focal staining of apocrine lining epithelium.

cellular neurothekeomas and smooth muscle differentiation, such as leiomyomas and leiomyosarcomas (LMS), also showed positive staining for S100A6 in a high percentage of cases.

A small number of histiocytic lesions, namely three xanthomas (XA), two reticulohistiocytomas (RH), six juvenile xanthogranulomas (JXG), three Langerhans' cell histiocytoses (LCH) (3) and one Rosai-Dorfman disease (RDD), were included in this study and were positive for S100A6.

The S100A6 expression data for DM and MPNST are provided in Table 3. S100A6 staining of spindled tumor cells was detected in 32 of 33 (97%) lesions of DM (Fig. 4A). Several examples of DM had moderate or strong staining in at least one of the three cores included on the TMA slide. The soft tissue MPNSTs were more often negative or weaker in intensity when compared with DMs. In fact, slightly less than half (13 of 30; 43%) of the MPNST lesions failed to show S100A6 staining in any of the three tissue cores (Fig. 4B). Of the 17 MPNST lesions that had S100A6 expression, only 7 (41%) had moderate or strong staining. Strong S100A6 staining was identified in only one MPNST lesion and it was very focal, because it was evident in only one of three tissue cores.

Various malignant spindle cell tumors that involve the skin or soft tissues were evaluated for S100A6 staining and their results are presented in Table 4. Briefly, SCSCC, DFSP, AFX, MFH, LMS, DM and MPNST all showed at least 50% of lesions staining for S100A6 protein, although MPNST had a lower percentage of cases staining compared with the other tumors. The difference in number of positive cases and staining intensity of tumor cells between MPNST and DM was statistically significant ($p \leq 0.001$). LMS and DFSP were more probable to show weak intensity staining for S100A6 compared with the other malignant spindle cell tumors.

## Discussion

S100A6 protein was expressed in a limited number of epithelial tumors. Consistent with the observation of Cross et al., we did not identify S100A6 staining in conventional types of BCC.[22] The absence of S100A6 expression in BCCs is not surprising, because Shrestha et al. failed to show S100A6 expression in normal basal cells of the epidermis.[23] We found that SCCs, including the spindle cell variant, were characteristically positive for S100A6, in contrast to the negative staining results for BCC. While BCC could be distinguished from SCC based on the absence or presence of S100A6 expression in all of our samples, we did not include any BCCs with squamous differentiation, keratotic BCCs, or metatypical BCCs, which pose a greater diagnostic challenge in differentiation from SCCs, in our study.

Tumors of the skin derived from either eccrine or apocrine duct epithelium were frequently positive for S100A6. These results are comparable with the staining pattern reported by Huang et al. in a subset

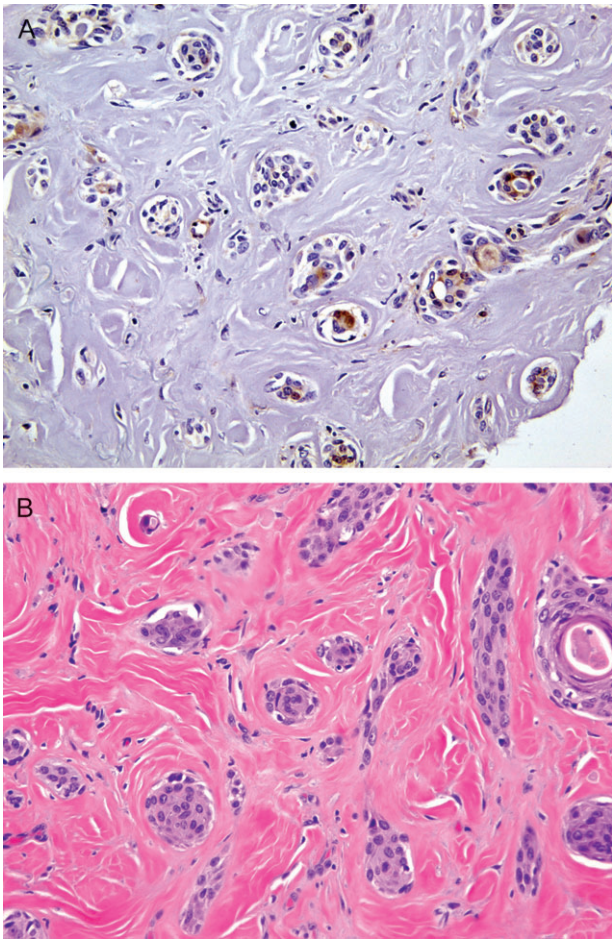


*Fig. 3.* Microcystic adnexal carcinoma. (A) Moderate staining intensity of tumor nests with foci of duct differentiation showing accentuation of staining in the lining epithelium. (B) Tumor nests with duct differentiation infiltrate the dermis in association with sclerotic collagen (hematoxylin and eosin).

of salivary gland tumors.[24] These results differ, however, from those of Shrestha et al. who reported the absence of S100A6 localization in a small subset of putative eccrine tumors of the skin.[23] Our small group of apocrine tumors showed even stronger staining intensity compared with our eccrine tumors and tended to be focal, with staining primarily limited to the secretory portion of the ducts. One notable exception to this staining pattern was our two hidradenomas, which were characterized by a mixture of large polygonal cells with abundant eosinophilic cytoplasm and smaller polygonal cells often with clear cytoplasm. Both hidradenomas showed strong and relatively diffuse staining for S100A6, with the strongest staining seen in the larger polygonal cells. Considering these results, it would be interesting to stain a larger number and broader spectrum of hidradenomas to see if there are different patterns of S100A6 expression depending on whether the tumor shows histologic evidence

Table 2. Expression of S100A6 in mesenchymal tumors of the skin and soft tissues

| Diagnosis | Number of cases | Staining results | | | | Number positive/total number (%) |
|---|---|---|---|---|---|---|
| | | Negative | 1+ | 2+ | 3+ | |
| DF | 17 | 0 | 6 | 11 | 0 | 17/17 (100) |
| ECH | 9 | 0 | 2 | 3 | 4 | 9/9 (100) |
| HFH | 2 | 0 | 0 | 1 | 1 | 2/2 (100) |
| DMF | 5 | 0 | 3 | 2 | 0 | 5/5 (100) |
| SAF | 2 | 0 | 0 | 1 | 1 | 2/2 (100) |
| DFSP | 10 | 1 | 6 | 3 | 0 | 9/10 (90) |
| AFX | 9 | 0 | 1 | 6 | 2 | 9/9 (100) |
| MFH | 9 | 1 | 3 | 3 | 2 | 8/9 (89) |
| LM | 9 | 1 | 6 | 1 | 1 | 8/9 (89) |
| LMS | 4 | 1 | 3 | 0 | 0 | 3/4 (75) |
| NF | 10 | 0 | 0 | 10 | 0 | 10/10 (100) |
| CNT | 2 | 0 | 0 | 2 | 0 | 2/3 (67) |

DF, dermatofibroma; ECH, epithelioid cell histiocytoma; HFH, hemosiderotic fibrous histiocytoma; DMF, dermatomyofibroma; SAF, superficial acral fibromyxoma; DFSP, dermatofibrosarcoma protuberans; AFX, atypical fibroxanthoma; MFH, malignant fibrous histiocytoma; LM, leiomyoma, LMS, leiomyosarcoma; NF, neurofibromas; CNT, cellular neurothekeoma.

of apocrine or eccrine differentiation or whether a significant myoepithelial component is present.

A subset of MAC lesions expressed S100A6 in tumor nests and epithelial cells lining duct lumens. This finding suggests that S100A6 may be useful in distinguishing a MAC from an infiltrative or morpheaform BCC, because the latter tumor failed to express S100A6. Interestingly, a subset of FEP tumors had weak staining for S100A6, but this tumor would not present diagnostic difficulty in distinguishing it from a MAC. Moreover, recent evidence suggests that the FEP may be better classified as a variant of trichoblastoma than a BCC.[25] Unfortunately, only two DTEs were available for evaluation in our series and one was focally positive for S100A6. The small tumor size of DTEs in this study created a technical problem. Two samples were excluded from our analysis because of inadequate tissue in the core of the TMA block. Thus, we did not have a sufficient sample size of DTEs for comparison with MACs or BCCs. However, preliminary results suggest that a positive result for S100A6 can reasonably exclude BCC from the differential diagnosis of sclerosing and infiltrative basaloid epithelial tumors. An additional study that evaluates S100A6 expression in full tissue sections

Table 3. Expression of S100A6 in primary cutaneous melanomas and MPNST

| Diagnosis | Number of cases | Staining results | | | | Number positive/total number (%) |
|---|---|---|---|---|---|---|
| | | Negative | 1+ | 2+ | 3+ | |
| DM | 33 | 1 | 11 | 16 | 5 | 32/33 (97) |
| MPNST | 30 | 13 | 10 | 6 | 1 | 17/30 (57) |

DM, desmoplastic melanoma; MPNST, malignant peripheral nerve sheath tumor.

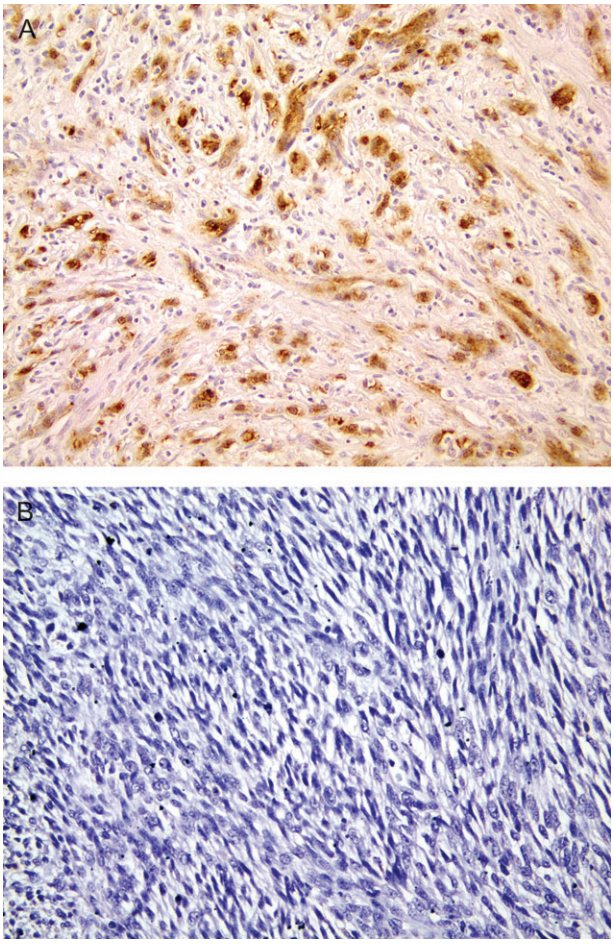


*Fig. 4.* A) Desmoplastic melanoma with strong expression of S100A6. B) Malignant peripheral nerve sheath tumor with no evidence of S100A6 staining in the tumor cells.

obtained from paraffin blocks of MAC, DTE, BCC and syringoma may prove more informative with regard to the utility of S100A6 in distinguishing among entities in the differential diagnosis of sclerosing epithelial tumors.

A previous study on S100A6 expression in fibrohistiocytic lesions showed a high percentage of DFs and AFXs were positive but DFSPs were consistently negative.[19] Our data confirms the prior results for DFs and AFXs; however, a high percentage of DFSPs in the current study showed expression of S100A6. It is probable that the discrepancy between the DFSP results is because of an enhanced sensitivity of the current method compared with the previous immunohistochemical protocol. As a result of the high frequency of AFX lesions and the moderate to strong intensity of staining of tumor cells, the possibility that S100A6 could discriminate between some types of malignant spindle cell tumors that occur in the skin was entertained. In addition, a previous study had shown absence of S100A6 in a limited number of DM[16], which further suggested that S100A6 might distinguish between AFX and DM. In contrast to the findings of Ribé and McNutt, we found a very high percentage of DM lesions with S100A6 labeling. The reason for this may again be because of differences in the method of immunochemical staining with heightened sensitivity in the current study. A significant proportion of LMS lesions and, as mentioned above, SCSCC lesions were also positive in our study. Thus, our results clearly show that S100A6 has a broad expression profile in mesenchymal tumors and cannot discriminate between AFX, SCSCC, DM or LMS.

Table 4. Expression of S100A6 in malignant spindle cell tumors of the skin and soft tissue

| Diagnosis | Number cases | Staining Results | | | | Number positive/total number (%) |
|---|---|---|---|---|---|---|
| | | Negative | 1+ | 2+ | 3+ | |
| SCSCC | 6 | 0 | 1 | 4 | 1 | 6/6 (100) |
| DFSP | 10 | 1 | 6 | 3 | 0 | 9/10 (90) |
| AFX | 9 | 0 | 1 | 6 | 2 | 9/9 (100) |
| MFH | 9 | 1 | 3 | 3 | 2 | 8/9 (89) |
| LMS | 4 | 1 | 3 | 0 | 0 | 3/4 (75) |
| DM | 33 | 1 | 11 | 16 | 5 | 32/33 (97) |
| MPNST | 30 | 13 | 10 | 6 | 1 | 17/30 (57) |

SCSCC, spindle cell squamous cell carcinoma; DFSP, dermatofibrosarcoma protuberans; AFX, atypical fibroxanthoma; MFH, malignant fibrous histiocytoma; LMS, leiomyosarcoma; DM, desmoplastic melanoma; MPNST, malignant peripheral nerve sheath tumor.

Since S100A6 has been previously reported to be expressed in Langerhans' cells, we evaluated a small cohort of histiocytic infiltrates in the skin.[7] S100A6 expression was found in both Langerhan's cell histiocytoses (LCH) and a small series of non-LCH lesions, such as XA, RH, JXG and RDD.

Our data showed a statistically significant difference in frequency of S100A6-positive lesions and intensity of staining of tumor cells between DM and MPNST. A significant percentage of MPNST lesions failed to express S100A6. Those MPNST lesions that expressed S100A6 usually had weak intensity staining. In contrast, almost all DM lesions were positive and generally had stronger staining intensity. Thus, a negative S100A6 staining result, in conjunction with appropriate immunostained controls, would favor a MPNST over a DM.

In summary, S100A6 protein is widely expressed in mesenchymal tumors that arise in the skin. Although there was a statistically significant difference between MPNST and other malignant spindle cell tumors included in this study, significant overlap in their staining results limits the diagnostic use of S100A6 in this differential diagnosis. The distribution of S100A6 was more restricted in our series of cutaneous epithelial tumors and could reliably discriminate between BCC and SCC lesions in this study. This protein is preferentially expressed in duct lining epithelium of apocrine and eccrine tumors of

the skin, with the exception of hidradenomas, which both showed strong and diffuse S100A6 staining. An additional study analyzing a larger series of hidradenomas is necessary to see if these results are reproducible and whether hidradenomas can be distinguished from other cutaneous adnexal tumors, as well as metastatic renal carcinomas involving the skin. Within this limited study group, the presence of S100A6 staining could differentiate a small subset of MAC from BCC; however, a larger series of cases, which includes syringomas and more examples of DTE is necessary to determine if S100A6 has even broader use in the differential diagnosis of sclerosing basaloid epithelial tumors.

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