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Expression of the p40 isoform of p63 has high specificity for cutaneous sarcomatoid squamous cell carcinoma

Cutaneous spindle cell malignancies such as sarcomatoid squamous cell carcinoma (SCC), leiomyosarcoma, desmoplastic melanoma (DM) and atypical fibroxanthoma (AFX) may be morphologically indistinguishable, yet accurate diagnosis is important for appropriate clinical management. The distinction among these entities relies on immunohistochemical evaluation for epidermal, muscle or melanocytic differentiation. Epidermal differentiation markers include cytokeratins and p63. p63 is expressed as two distinct isoforms, ΔNp63 (p40) and TAp63. p40 positivity is highly specific for pulmonary SCC and head and neck sarcomatoid SCC. We examined the utility of p40 vs. p63 immunostaining in the differentiation of a variety of cutaneous spindle cell malignancies, including sarcomatoid SCC (n = 27), AFX (n = 34) and DM (n = 10). p40 was less sensitive than p63 for detecting sarcomatoid SCC (56% and 81%, respectively). p63 and p40 were comparably specific for sarcomatoid SCC relative to AFX, with only rare weak staining of tumor cells for p63 and/or p40 in a minority of AFX cases, including one case with approximately 10% of cells staining weakly for p40. All cases of DM were negative for p40 and p63. Our results support continued use of p63 for diagnosis of cutaneous sarcomatoid SCC because of greater sensitivity relative to p40.

Keywords: atypical fibroxanthoma, deltaNp63, p40, p63, squamous cell carcinoma

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The classic differential diagnosis of malignant cutaneous spindle cell neoplasms includes spindle cell or sarcomatoid squamous cell carcinoma (SCC), atypical fibroxanthoma/superficial undifferentiated pleomorphic sarcoma (AFX), desmoplastic melanoma (DM) and leiomyosarcoma (LMS). The diagnosis is easier when the lesion displays a more well differentiated component or an *in situ* component such as keratinizing invasive SCC intermingling with

Table 1. Immunohistochemical expression of cytokeratin (CK), p63 and p40 in atypical fibroxanthoma (AFX) and sarcomatoid squamous cell carcinoma (S-SCC)

Patient	Case	Sex	Age	Location	CK performed	CK result	p63	p40
1	AFX1	M	87	Right lower helix	MNF116	Negative	Rare (<5%)	Negative
2	AFX2	M	81	Left antihelix	MNF116, K903	Negative	Negative	Rare (<5%)
3	AFX3	M	65	Left scalp	MNF116, K903	Negative	Negative	Negative
3	AFX4	M	65	Left scalp	MNF116, K903	Negative	Negative	Rare (<5%)
4	AFX5	M	71	Upper scalp	MNF116, K903	Negative	Rare (<5%)	Negative
5	AFX6	F	47	Right chest	MNF116, AE1/AE3	Negative	Rare (<5%)	Negative
6	AFX7	F	86	Right cheek	MNF116, CK cocktail	Rare (<5%) (MNF116 only)	Rare (<5%)	Negative
7	AFX8	M	65	Left scalp	MNF116, K903	Negative	Negative	Negative
8	AFX9	M	76	Right tragus	AE1/3, CAM5.2	Negative	Negative	Negative
8	AFX10	M	74	Right forehead	K903, AE1/AE3	Negative	Negative	Negative
9	AFX12	M	91	Left frontal scalp	MNF116	Negative	Negative	Negative
10	AFX13	M	82	Vertex scalp	MNF116	Negative	Negative	Negative
11	AFX14	M	70	Left upper forehead	K903	Negative	Negative	Negative
12	AFX15	M	72	Left frontal scalp	MNF116, AE1/AE3	Negative	Negative	Negative
13	AFX16	M	70	Left cheek	MNF116, CK 5/6	Negative	Negative	Negative
14	AFX17	M	62	Right parietal scalp	MNF116, K903	Negative	Negative	Rare (<5%)
14	AFX18	M	61	Right lateral scalp	MNF116, K903	Negative	Negative	Negative
15	AFX19	F	28	Supra knee	K903	Negative	Negative	Negative
16	AFX20	M	92	Left parietal scalp	CK cocktail	Negative	Negative	Negative
16	AFX21	M	92	Left parietal scalp	K903	Negative	Negative	Negative
17	AFX22	M	74	Upper forehead	MNF116, K903	Negative	Negative	Negative
18	AFX23	M	91	Left concha	MNF116, K903	Negative	Negative	Negative
19	AFX24	M	72	Right temple	MNF116, CK cocktail	Negative	Negative	Negative
19	AFX25	M	72	Right temple	MNF116, CK cocktail	Negative	Rare (<5%)	Negative
20	AFX26	M	68	Left antihelix	MNF116, CK cocktail	Negative	Negative	Negative
21	AFX27	M	81	Left posterior scalp	MNF116, K903	Negative	Negative	Negative
22	AFX28	M	85	Left cheek	CK	Negative	Negative	Negative
23	AFX29	F	83	Left neck	MNF116, AE1/AE3	Negative	Negative	Negative
24	AFX30	M	83	Right vertex scalp	MNF116	Negative	Negative	Negative
25	AFX31	M	69	Posterior crown scalp	MNF116, K903	Negative	Negative	Negative
26	AFX32	M	68	Left conchal bowl	MNF116, AE1/AE3	Negative	Negative	Negative
27	AFX33	M	87	Vertex scalp	AE1/AE3, CAM5.2	Negative	Negative	Negative
28	AFX34	M	84	Right scalp vertex	CK cocktail, CK5/6	Negative	Negative	Negative
29	S-SCC1	M	72	Left preauricular	K903, AE1/AE3	Negative	Positive	Negative
30	S-SCC2	M	83	Left temple	MNF116, K903	Negative	Positive	Negative
30	S-SCC3	M	85	Left temple	K903, CK cocktail	Negative	Positive	Negative
31	S-SCC4	M	65	Left cheek	MNF116	Negative	Positive	Positive
32	S-SCC5	M	80	Vertex scalp	MNF116, CK5/6	Negative	Positive	Negative
32	S-SCC6	M	80	Vertex scalp	MNF116, CK5/6	Negative	Positive	Rare (<5%)
33	S-SCC7	M	64	Left lower lip	MNF116	Positive	Positive	Positive
34	S-SCC8	M	69	Left forehead	MNF116, K903	Positive	Positive	Positive
35	S-SCC9	M	75	Right face	CK5/6, K903	Positive	Positive	Positive
36	S-SCC10	M	91	Left ear	K903	Positive	Positive	Positive
37	S-SCC11	F	79	Back	CK	Positive	Positive	Positive
38	S-SCC12	M	80	Left forearm	K903	Positive	Positive	Positive
38	S-SCC13	M	81	L. epitrochlear node (metastasis)	Not performed (met from S-SCC12)	NA	Positive	Positive
39	S-SCC14	M	70	Left back	K903	Positive	Positive	Positive
40	S-SCC15	M	79	Scalp	MNF116	Positive	Positive	Positive
41	S-SCC16	F	50	Left eyelid	MNF116, AE1/AE3,CAM5.2	Positive	Positive	Positive
42	S-SCC17	M	76	Right ear	K903	Positive	Positive	Positive
43	S-SCC18	M	67	Right ear helix	MNF116, K903	Positive	Positive	Positive
44	S-SCC19	F	85	Right ear	Not performed (co-existing conventional component)	NA	Positive	Positive
45	S-SCC20	M	58	Left forehead	Not performed (SCC recurrence)	NA	Positive	Positive

Table 1. Continued

Patient	Case	Sex	Age	Location	CK performed	CK result	p63	p40
46	S-SCC21	F	84	Left frontal scalp/forehead	MNF116	Positive	Positive	Rare (<5%)
47	S-SCC22	F	61	Chin	MNF116, K903, CK cocktail	Negative	Positive	Negative
48	S-SCC23	M	81	Right temple	MNF116, K903, CK5/6	Positive (MNF116 only)	Rare (<5%)	Rare (<5%)
49	S-SCC24	M	64	Right preauricular	MNF116	Positive	Negative	Negative
50	S-SCC25	F	49	Chest	Not performed (co-existing conventional component)	NA	Negative	Negative
51	S-SCC26	M	92	Right posterior helix	MNF116, CK cocktail	Positive	Rare (<5%)	Negative
51	S-SCC27	M	92	Ear	MNF116, CK cocktail	Positive (MNF116 only)	Negative	Negative

a sarcomatoid SCC or melanoma *in situ* overlying a DM, respectively. More commonly, the distinction among these entities relies on the expression of immunohistochemical markers in support of a specific line of differentiation.

One of the most reliable markers for sarcomatoid SCC is p63,[1–3] a member of the *TP53* gene family. p63 is essential for the development of limbs, craniofacial structures and squamous epithelia including associated adnexal structures.[4,5] p63 expression is highly specific for squamous epithelium,[6–10] but p63 is also expressed in normal basal cells, myoepithelial cells, trophoblasts, thymic epithelium[11] and urothelium. Some non-squamous neoplasms also express p63, including some lymphomas[12]; a small number of sarcomas[13]; and adenocarcinomas from the lung,[10,14–17] gastrointestinal and gynecologic tract.

The p63 gene product consists of two primary isoforms, TAp63 and ΔNp63, which differ only in their N-terminal domain.[18] Interestingly, these two isoforms have opposing functions. TAp63 acts as a tumor suppressor in a manner similar to p53, while ΔNp63 antagonizes both TAp63 and p53 in a manner analogous to an oncogene.[18] ΔNp63 is preferentially expressed in the basal cells of stratified epithelium, where it is believed to confer 'stem cell' properties.[19–21]

The most routinely used anti-p63 antibody, 4A4, does not distinguish between the different p63 isoforms; whereas the anti-p40 antibody specifically recognizes the ΔNp63 isoform. Anti-p40 has gained diagnostic application in the past several years, most notably in the setting of lung carcinoma where it is used to distinguish pulmonary SCC from pulmonary adenocarcinoma.[22] Anti-p40 is also used to differentiate head and neck sarcomatoid SCC from mesenchymal neoplasms.[22,23]

Because ΔNp63 is highly expressed in SCC and knowledge of differences between p63 and p40 expression in different cutaneous spindle cell tumors is largely unknown, this study was undertaken to assess the utility of p40 vs. p63 in diagnosing cutaneous sarcomatoid SCC relative to AFX, DM and other frequently encountered cutaneous spindle cell neoplasms.

Methods

Case selection and tissue microarray construction

The study was approved by the Institutional Review Board at the University of Michigan

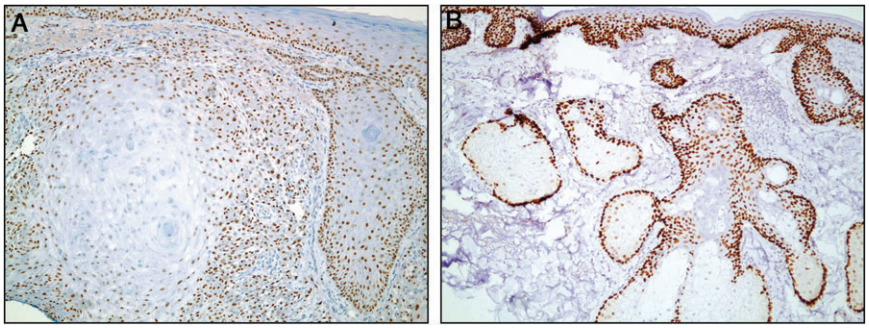

Fig. 1. p40 expression in conventional squamous cell carcinoma (A) and normal skin (B) (hematoxylin and eosin, ×100 magnification).

Table 2. Expression of p40 and p63 in dermal spindle cell neoplasms and reactive mimics

Diagnosis	n	p40		p63	
		Negative (<5%)	Positive	Negative (<5%)	Positive
Spindle cell malignancies					
Sarcomatoid squamous cell carcinoma	27	12 (44%)	15 (56%)	5 (19%)	22 (81%)
Atypical fibroxanthoma	34	34 (100%)	0 (0%)	34 (100%)	0 (0%)
Undifferentiated pleomorphic sarcoma	9	6 (67%)	3 (33%)	9 (100%)	0 (0%)
Desmoplastic melanoma	10	10 (100%)	0 (0%)	10 (100%)	0 (0%)
Leiomyosarcoma	4	4 (100%)	0 (0%)	4 (100%)	0 (0%)
Dermatofibrosarcoma protuberans	10	10 (100%)	0 (0%)	10 (100%)	0 (0%)
Benign mesenchymal lesions					
Dermatofibroma, conventional	6	6 (100%)	0 (0%)	6 (100%)	0 (0%)
Dermatofibroma, lipidized	1	1 (100%)	0 (0%)	1 (100%)	0 (0%)
Dermatofibroma, hemosiderotic	2	2 (100%)	0 (0%)	2 (100%)	0 (0%)
Dermatofibroma, cellular	4	4 (100%)	0 (0%)	4 (100%)	0 (0%)
Epithelioid fibrous histiocytoma	7	7 (100%)	0 (0%)	7 (100%)	0 (0%)
Dermatomyofibroma	5	5 (100%)	0 (0%)	5 (100%)	0 (0%)
Superficial acral fibromyxoma	2	2 (100%)	0 (0%)	2 (100%)	0 (0%)
Cellular neurothekeoma	1	1 (100%)	0 (0%)	1 (100%)	0 (0%)
Leiomyoma	9	9 (100%)	0 (0%)	9 (100%)	0 (0%)
Neurofibroma	10	10 (100%)	0 (0%)	10 (100%)	0 (0%)
Histiocytic lesions					
Xanthoma	3	3 (100%)	0 (0%)	3 (100%)	0 (0%)
Juvenile xanthogranuloma	5	5 (100%)	0 (0%)	5 (100%)	0 (0%)
Reticulohistiocytoma	2	2 (100%)	0 (0%)	2 (100%)	0 (0%)
Rosai-Dorfman	1	1 (100%)	0 (0%)	1 (100%)	0 (0%)
Langerhans cell histiocytosis	1	1 (100%)	0 (0%)	1 (100%)	0 (0%)

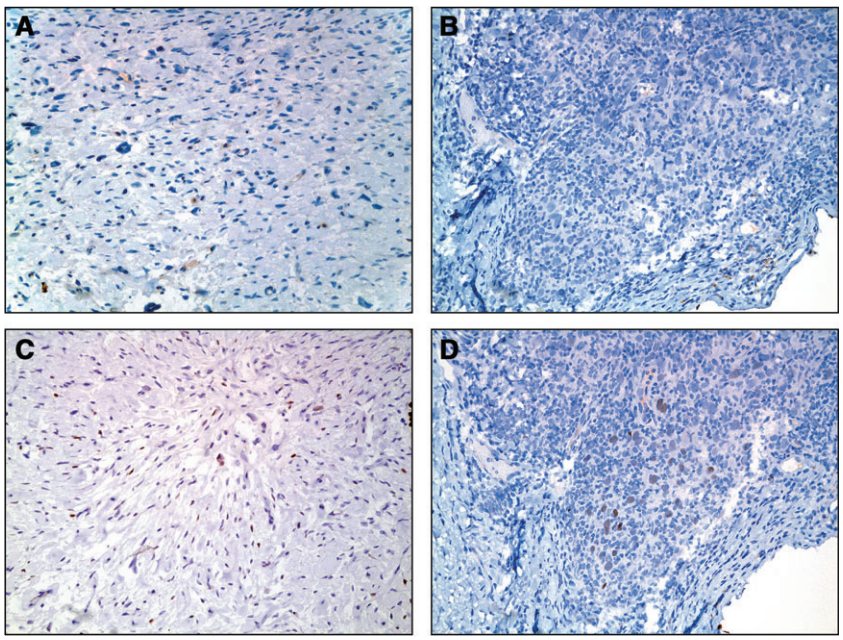

Fig. 2. Immunohistochemical expression of p40 and p63 in atypical fibroxanthoma (AFX). All AFX in this study lacked significant expression of p40 (A), although a minority of cases displayed faint cytoplasmic 'blush' (B). The same AFX cases displayed weak-moderate staining with p63 (C and D) (×200 magnification).

Health System and was carried out in accordance with the guidelines for human subject research.

The study includes previously constructed tissue microarrays (TMAs) representing a spectrum of primary cutaneous epithelial neoplasms, cutaneous spindle cell tumors, histiocytic/fibrohistiocytic lesions and their microscopic mimics.[24] In addition to TMAs, whole tissue sections of sarcomatoid SCC, DM and additional AFX cases were identified by a retrospective search of the pathology archives at the University of Michigan, Department of

Pathology from 2004 to 2013. Hematoxylin and eosin-stained sections and a subset of previously performed immunohistochemical stains were reviewed for diagnosis confirmation by two pathologists (P.W.H. and T.T.H.L.).

Immunohistochemistry

Unstained slides from the TMAs and conventional paraffin blocks were stained with p40 and p63 antibody. Briefly, 4-uM-thick unstained sections were pretreated with Ventana CC1 Solution (pH 8.0) for antigen retrieval and were incubated with mouse monoclonal anti p63 antibody (clone 4A4, predilute; Ventana Medical Systems, Tucson, AZ, USA), and rabbit polyclonal anti p40 antibody (clone 5-17, 1:8000 dilution; Calbiochem, Darmstadt, Germany) using a Ventana Benchmark XT system (Ventana Medical Systems). The UltraVision System and a 3,3′-diaminobenzidine chromogen were used for detection. Staining conditions for p40 were validated on pulmonary SCC (n = 2) and normal epidermis with pulmonary adenocarcinoma (n = 2) as negative controls. Nuclear staining in at least 5% of lesional cells was considered positive for p63 and p40. The distribution of positivity (restricted to the basal layer or diffuse) was also noted.

Results

Our study cohort included a total of 34 cases of AFX (from 28 patients), 27 cases of sarcomatoid SCC (from 23 patients) and 10 cases of DM (from 10 patients). These included two cases of AFX which were re-classified as sarcomatoid SCC upon review of immunohistochemical profiles. DM cases included seven pure desmoplastic melanomas, two melanomas with predominantly desmoplastic features and a co-existing component of spindled melanoma and one desmoplastic melanoma with a focal area with sarcomatoid appearance. Clinical features and immunohistochemical profiles of AFX and sarcomatoid SCC cases are presented in Table 1.

p40 antibody was validated in direct comparison with p63. Positive controls included pulmonary SCC (n = 2), cutaneous SCC (n = 8) and hypertrophic lichen planus (n = 4). Negative controls were pulmonary adenocarcinoma (n = 2). p40 was positive with moderate staining intensity in 100% of pulmonary SCC and conventional cutaneous SCC and negative in both cases of pulmonary adenocarcinoma. p40 showed the same distribution of positivity although weaker nuclear intensity compared to p63. Cutaneous SCCs displayed basal layer staining in well-differentiated tumors (Fig. 1A)

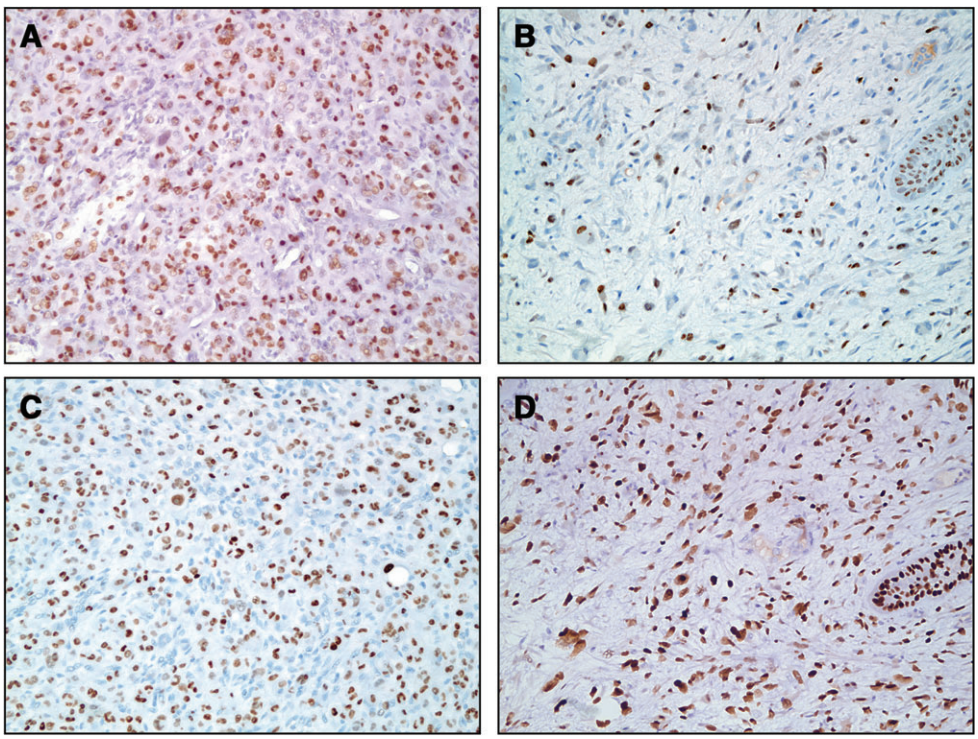

Fig. 3. Immunohistochemical expression of p40 and p63 in cutaneous sarcomatoid squamous cell carcinoma (sarcomatoid SCC). A) Sarcomatoid SCC with diffuse strong p40. B) Sarcomatoid SCC with moderate p40 expression. C and D) Strong p63 expression in both tumors (×200 magnification).

or diffuse staining in less-differentiated tumors. We also evaluated normal skin and found similar expression patterns of p40 and p63 with basal staining of the epidermis and adnexal epithelium (Fig. 1B).

The majority of studies to date show absent or only focal p63 and CK expression in AFX.[1,25–27] Thus, we set the threshold for significant p63 and CK expression as weak to strong immunolabeling in ≥5% of lesional cells. p63 and p40 immunolabeling was performed in parallel. All AFX cases lacked significant p40 and p63 expression (Tables 1 and 2, Fig. 2). A few of the cases scored as negative showed rare cells (<5%) immunoreacting to p40 (n = 3) and p63 (n = 4) (Fig. 2B).

Significant p40 expression was seen in 55.6% of sarcomatoid SCC (n = 15) whereas 81.5% of sarcomatoid SCC (n = 22) were positive for p63 (Tables 1 and 2, Fig. 3). An additional two cases (7.5%) showed moderate p40 labeling in <5% of lesional cells, which did not reach this study's threshold for positivity. For sarcomatoid SCC, p40 and p63 labeling were concordant in 74% of cases. Fifteen cases showed dual positivity while five cases showed dual negativity. The remaining seven cases (26%) showed significant staining for p63 but not p40. Interestingly, in six of these seven cases, CK stains were also negative. In the remaining $p63^{+}/p40^{-}$ sarcomatoid SCC case, CK was positive and p40 weakly stained rare cells (below the threshold considered positive). Notably, the lesion was not highly cellular and this discrepancy could be a result of intratumoral heterogeneity. CK and p40 showed concordant results in 73% of cases.

We further compared p40 and p63 expression in additional benign and malignant cutaneous spindle cell lesions (Table 2). These included nine cases of cutaneous undifferentiated pleomorphic sarcoma (also known as pleomorphic dermal sarcoma), defined as spindle cell malignancies that lack expression of lineage markers such as cytokeratin, and that are not classified as AFX because of the presence of necrosis, lymphovascular invasion, perineural invasion, large size or significant subcutaneous extension. Three of nine (33%) cases of undifferentiated pleomorphic sarcoma displayed nuclear expression of p40 in 5–10% of tumor cells. Interestingly, these lesions did not show significant staining with p63. p40 and p63 were negative in all of the remaining dermal spindle cell neoplasms and histopathologic mimics, including all cases of DM (n = 10) (Table 2, Fig. 4).

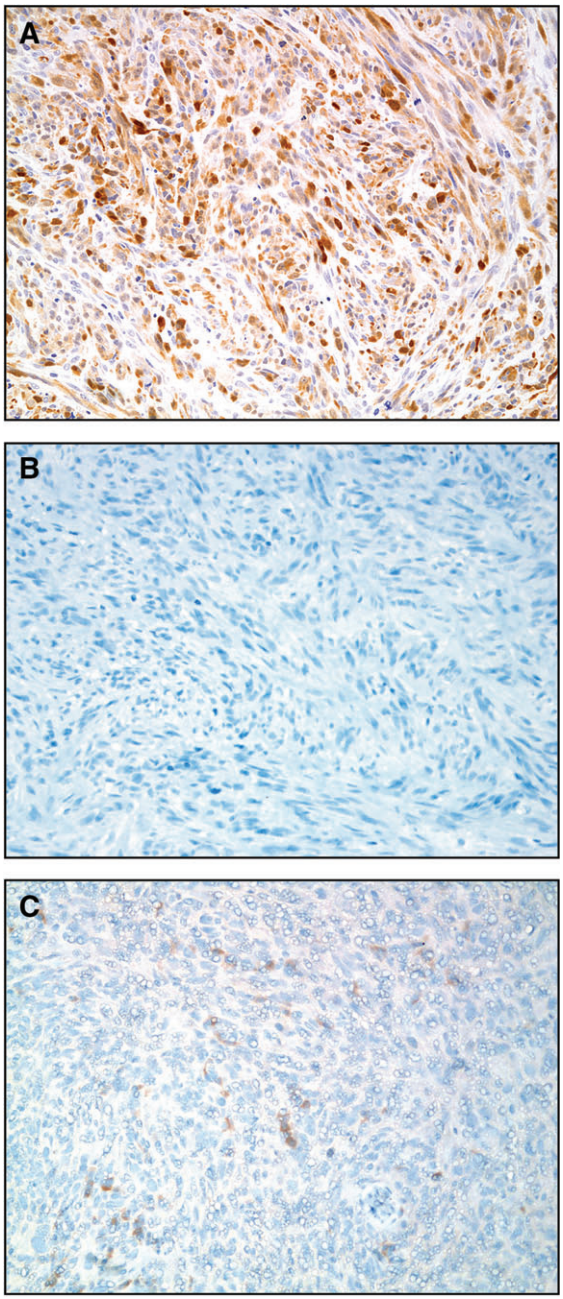

Fig. 4. Immunohistochemical expression of S100 and p40 in desmoplastic melanoma. A) S100 is strongly and diffusely positive. B) Absence of p63 expression. C) The same case lacks p40 expression (×200 magnification).

We also examined p40 and p63 expression in a small number of cutaneous histiocytic lesions. As expected, both p40 and p63 were negative in all cases (Table 2).

Discussion

Poorly differentiated cutaneous spindle cell neoplasms, including desmoplastic melanoma, sarcomatoid SCC and AFX, vary greatly in

clinical outcome but may be impossible to reliably distinguish on morphologic grounds. Therefore, immunohistochemical stains play an important role in the differential diagnosis of these poorly differentiated neoplasms. In addition to cytokeratin, p63 is frequently used to identify or confirm squamous cell differentiation. The most commonly used antibody to p63 recognizes both the ΔNp63 and TAp63 isoforms of the p63 gene product. The polyclonal anti-p40 antibody used in this study is specific for the ΔNp63 isoform, which possesses oncogene-like properties. This antibody has been shown to have superior specificity for pulmonary SCC relative to the commonly used p63 antibody. However, the expression of p40 in primary cutaneous neoplasms is not well understood and the utility of the anti-p40 antibody in recognizing cutaneous sarcomatoid SCC has not been established.

This study shows that p40 expression is similar to p63 in normal skin structures and cutaneous spindle cell tumors. Specifically, p40 is consistently expressed in non-neoplastic skin including normal epidermis, adnexal structures and reactive epidermal conditions including hypertrophic lichen planus. In addition to AFX, p40 is also consistently negative in other tumors of fibrohistiocytic, fibroblastic or smooth muscle differentiation, with the exception of positive cells in some cases of undifferentiated pleomorphic sarcoma. As observed in this study and noted in other studies with regards to p63, a small subset of AFX cases displayed rare tumor cells (<5%) with weak nuclear expression for p40 and/or p63 not reaching the study's threshold for significance (Table 1). In these cases of rare focal staining, p40 and p63 were sometimes but not consistently co-expressed, possibly reflecting intratumoral heterogeneity. By our criteria for significant expression, p40 was relatively specific for sarcomatoid SCC relative to AFX and undifferentiated pleomorphic sarcoma (93.0%).

Although highly specific, p40 displayed limited sensitivity for sarcomatoid SCC (55.6%) (Table 2). The expression of p40 mirrors closely that of CKs. Specifically, five of six sarcomatoid SCC that lacked significant cytokeratin expression also lacked p40 expression, despite significant p63 expression (Table 1). Cytokeratin-negative/p63-positive cutaneous spindle cell tumors are poorly described in the literature. However, sarcomatoid SCC arising in mucosal sites may lose cytokeratin expression yet retain p63 expression[28] and a similar phenomenon is likely to occur in cutaneous sarcomatoid SCC. To our knowledge, loss of p40 isoform expression with retained p63 expression (presumably TAp63 isoform) has not been extensively described. Further investigation is needed to determine whether cutaneous cytokeratin-negative/p40-negative/p63-positive tumors display differences in biology or clinical behavior relative to other sarcomatoid SCC.

In conclusion, p40 is a highly specific but less sensitive marker for sarcomatoid SCC compared to p63. This result suggests that p40 is useful, however not interchangeable with p63 in a diagnostic immunohistochemical stain panel for cutaneous spindle cell malignancies.

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