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Fibroblast-activation protein: a single marker that confidently differentiates morpheaform/infiltrative basal cell carcinoma from desmoplastic trichoepithelioma

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Microscopically, differentiating desmoplastic trichoepithelioma from morpheaform/infiltrative basal cell carcinoma can be difficult as both show 'islands and strands of basaloid cells embedded in a sclerotic stroma'. A superficial shave biopsy further compounds the diagnostic conundrum. Although a plethora of immunohistochemical markers have been touted as being of use as adjunct histologic tools, none thus far appears to be consistent and reliable in terms of specificity and/or sensitivity. Fibroblast-activation protein, a type II membrane-bound glycoprotein belonging to the serine protease family, is expressed in the granulation tissue of healing wounds. More recently, it has been identified as a marker of reactive tumor stromal fibroblasts, as it is reportedly selectively expressed in peritumoral stromal fibroblasts of multiple epithelial cancers including cutaneous malignancies such as basal cell carcinoma. Given this, we sought to ascertain the use of fibroblast-activation protein in distinguishing morpheaform/infiltrative basal cell carcinoma from desmoplastic trichoepithelioma. Immunohistochemical staining for fibroblast-activation protein was performed on desmoplastic trichoepithelioma ($n = 25$) and morpheaform/infiltrative basal cell carcinoma ($n = 25$), with the control group comprising scars from reexcision specimens ($n = 10$). As expected, fibroblast-activation protein expression was observed in stromal fibroblasts of all control cases (10 of 10, 100%). Of interest, fibroblast-activation protein expression was observed in peritumoral fibroblasts of all cases of morpheaform/infiltrative basal cell carcinoma (25 of 25, 100%) but not in any cases of desmoplastic trichoepithelioma (0 of 25, 0%). A gradient of fibroblast-activation protein expression was observed in morpheaform/infiltrative basal cell carcinoma with more intense expression noted in fibroblasts abutting the tumor cells, a less intense expression in the distal peritumoral stromal portion, and minimal to loss of expression in adjacent normal tissue. In summary, findings from this study underscore the use of fibroblast-activation protein as a histologic adjunct in confidently differentiating morpheaform/infiltrative basal cell carcinoma from desmoplastic trichoepithelioma.
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Morpheaform/infiltrative basal cell carcinoma is an aggressive distinct clinical and histologic variant of basal cell carcinoma that usually presents as a solitary, ill-defined, smooth, shiny, flat or slightly depressed, indurated plaque on the face of elderly patients.[1–3] Histopathology reveals infiltrating strands and islands of basophilic epithelioid cells, typically one or few cells thick, embedded in a dense sclerotic stroma.[1–3] Unlike other basal cell carcinoma variants, peripheral palisading, stromal mucin, and a clefting artifact are typically not observed.[1–3]

Desmoplastic trichoepithelioma is an uncommon benign neoplasm of follicular derivation that usually manifests as a sporadic asymptomatic small

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indurated annular lesion with a raised border and a depressed center over the face of adolescents and young adults.[3–6] Like morpheaform/infiltrative basal cell carcinoma, desmoplastic trichoepithelioma is characterized by infiltrating strands and islands of monomorphic, basaloid cells with scant cytoplasm and prominent oval nuclei embedded in a sclerotic and hypocellular stroma.[3–6] Features of use in distinguishing desmoplastic trichoepithelioma from morpheaform/infiltrative basal cell carcinoma include the additional presence of variably sized horn cysts and foreign-body granulomas in the former.[3–6]

Although desmoplastic trichoepithelioma is a benign tumor that can be managed by conservative treatment such as curettage or shave biopsy, morpheaform/infiltrative basal cell carcinoma is an aggressive malignant neoplasm that requires complete excision usually with Mohs micrographic surgery.[1–6] Based on the different biologic behaviors, the histopathologic distinction of desmoplastic trichoepithelioma from morpheaform/infiltrative basal cell carcinoma is not just semantics but crucial to patient management. This has thus driven an extensive effort to find an immunohistochemical marker of utility in differentiating the two. Immunohistochemical markers tested to date include CD34,[3,7–10] bcl-2,[3,9–12] CD10,[3,13] Ber-EP4,[10,14] androgen receptor (AR),[3,15,16] CK20,[3,16,17] stromelysin-3,[18] p53,[3,19,20] Ki-67,[3,19] p21,[19] transforming growth factor (TGF)-β,[21] lectins,[19,22] neurofilaments,[23] and p75 neurotrophin receptor.[24] None of these, to date, appears to be reliable in confidently differentiating desmoplastic trichoepithelioma from morpheaform/infiltrative basal cell carcinoma (Table 1).

Fibroblast-activation protein (FAP) is a type II membrane-bound glycoprotein that belongs to the serine protease family as it has both a dipeptidyl peptidase and a collagenolytic activity.[25,26] It has recently been identified as a marker of reactive tumor stromal fibroblasts, as it is selectively expressed in peritumoral stromal fibroblasts of multiple epithelial cancers including breast, colorectal, pancreatic and lung carcinomas, and in the granulation tissue of healing wounds.[25–29] Similarly, FAP expression has also been shown to be upregulated in the stromal fibroblasts of cutaneous epithelial malignancies such as basal and squamous cell carcinomas as well as benign and malignant melanocytic lesions.[30,31]

In this study, we sought to ascertain the use of expression of FAP in differentiating morpheaform/infiltrative basal cell carcinomas from desmoplastic trichoepithelioma.

Materials and methods

The study was approved by the institutional review board of Boston Medical Center (H-29370). Archival materials with a diagnosis of desmoplastic trichoepithelioma and morpheaform/infiltrative basal cell carcinoma were retrieved from the database of the Skin Pathology Laboratory, Boston University School of Medicine, Boston, MA. A total of 25 cases of desmoplastic trichoepithelioma and 25 cases of morpheaform/infiltrative basal cell carcinoma fit criteria for inclusion in the study. The histologic sections of all cases were re-reviewed and the diagnoses were confirmed by the dermatopathologist (MM). Of the 25 cases of desmoplastic trichoepithelioma, 9 were sampled using shave biopsy technique, 14 using punch biopsy, and 2 using excisional biopsy. Of the 25 cases of morpheaform/infiltrative basal cell carcinoma, 7 were sampled using shave biopsy technique, 13 using punch biopsy, and 5 using excisional biopsy. Only cases with a straightforward histopathologic diagnosis of desmoplastic trichoepithelioma and morpheaform/infiltrative basal cell carcinoma were included in the study. Clinical information was extracted from the medical records. All patient data were deidentified. Ten scars (ranging from 2 to 12 weeks in age) from re-excision specimens served as controls.

Criteria for diagnosis of desmoplastic trichoepithelioma included a symmetric proliferation of basaloid strands and islands of cells with minimal cytologic atypia, and/or horn cysts. Pertinent negatives were the absence of a connection of the tumoral cells with the epidermis and clefting artifact.

Criteria for diagnosis of morpheaform/infiltrative basal cell carcinoma included an asymmetric proliferation of basaloid strands and islands of cells with cytologic atypia, frequent connection to the overlying epidermis and presence of clefting artifact. Pertinent negatives were the absence of horn cysts and foci of dystrophic calcification.

Immunohistochemical Analysis

Sections (5-μm thick) were obtained for immunohistochemical studies, which were performed on formalin-fixed, paraffin-embedded tissue. The avidin–biotin complex immunoperoxidase method for FAP was carried out as previously described.[27–29] In brief, clone D8 (FAP/seprase antibody, 1:200; SUNY, Stony Brook, NY, USA) was applied to sections pretreated with microwave (10 min) in 0.01 M Tris-EDTA buffer (pH 9.0). After incubation with the primary antibody, endogenous peroxidase activity was blocked by treating the sections for 5 min with 3% hydrogen peroxide in Tris-buffered saline. As the secondary antibody, we used a biotinylated horse anti-rat IgG (1:200; Vector Laboratories, Burlingame, CA, USA). Chromogen 3,30-diaminobencidine was used for the visualization of the final reaction product. Sections were counterstained with Harris' hematoxylin. Appropriate positive and negative controls were included. All stained slides were initially reviewed and scored by the first author (OA) and re-reviewed by the dermatopathologist

Table 1 Historic overview of different immunohistochemical markers used in differentiating TE from BCC

Marker	*Localization*	*References*	*Entities (number)*	*Results*
CD34	Peritumoral stroma	7	16 TE, 19 BCC (10 BCCN, 6 BCCS, 3 BCC desmoplastic)	TE, 100% positive; BCC, 0%
		8	10 dTE, 10 mBCC	dTE, 80% positive; mBCCs, 30%
		9	10 TEs, 15 BCCs (2 early, 2 BCCN, 7 ulcerative, 3 morpheic, 1 BCCI)	TE, 20% positive; BCC, 7% positive
		10	TE (36, including 7 dTEs), BCC (43, including 7 miBCCs)	TE, 56% positive; BCC, 14% positive
		3	dTE (19), mBCC (18)	dTE, 0% positive; mBCC, 0% positive
bcl-2	Lesional cells	11	TE (10), BCC (10)[a]	TE, 100% positive (peripheral tumoral staining only); BCC, 100% positive (diffuse tumoral staining)
		12	TE (10), BCC (nodular) (20)	TE, 100% positive (peripheral tumoral staining only); BCC, 95% positive (diffuse tumoral staining)
		9	10 TEs, 15 BCCs (2 early, 2 BCCN, 7 ulcerative, 3 morpheic, 1 BCCI)	TE, 50% positive (20% peripheral tumoral staining, 30% diffuse tumoral staining); BCC, 47% positive (40% diffuse tumoral staining, 7% peripheral tumoral staining)
		10	TE (36, including 7 dTEs), BCC (43, including 7 miBCCs)	TE, 27% positive (diffuse tumoral staining); BCC, 9% positive (peripheral tumoral staining)
		3	19 dTE (19), mBCC (18)	dTE, 100% positive; mBCC, 100% positive
CD10	Lesional cells and peritumoral stroma	13	TE (13), nodular BCC (23)	TE, 92% positive (peritumoral stroma and tumor cells in 2 and only stroma in 10); BCC, 87% positive (only tumor cell positivity in 17, tumor cells and stroma in 3)
		3	19 dTE (19), mBCC (18)	dTE, inconsistent stromal positivity mBCC, 44% (stroma in 8 and tumor aggregates in 7)
Ber-EP4	Lesional cells	10	TE (36 including 7 dTEs), BCC (43 including 7 miBCCs)	TE, 81% positive (including 71% of dTEs); BCC, 100% positive
		14	dTE (16), miBCC (28)	dTE, 75% positive; BCC, 100% positive
Androgen receptor	Nuclei of lesional cells	15	TE (6), miBCC[a] (32)	TE, 0% positive; BCC, 78% positive
		3	19 dTE (19), mBCC (18)	dTE, 0% positive; mBCC, 100%
		16	dTE (15), mBCC (31)	dTE, 13% positive; mBCC, 65% positive
CK20	Merkel cells in the epithelial strands	16	dTE (15), mBCC (31)	dTE, 100% positive; mBCC, 3% positive
		3	dTE (19), mBCC (18)	dTE, 100% positive; mBCC, 0%
		17	dTE (14), mBCC (11)	dTE, 100% positive; mBCC, 9% positive
Stromelysin	Peritumoral stroma	18	dTE (12), mBCC (50)	dTE, 0% positive; mBCC, 68% positive
p53	Lesional cells	19	TE (16), BCC[a] (20)	Overexpression in BCC compared to TE
		20	20 TEs, 20 BCCs (16 solid type, 3 with adenoid features, 1 BCCS)	No statistically significant differences between cell indices (% of positive cases not specified)
		3	dTE (19), mBCC (18)	Both entities—Positive in at least few cells in all cases, a thirds of mBCCs showed no difference in expression compared to dTE
Ki-67	Lesional cells	19	TE (16), BCC[a] (20)s	BCC, qualitatively greater proliferative fraction than TE
		3	dTE (19), mBCC (18)	Both entities—Positive in at least few cells in all cases, a thirds of mBCCs showed no difference in expression compared to dTE
p21	Lesional cells	19	TE (16), BCC[a] (20)	BCC, 10% scattered nuclear positivity; TE, negative
TGF-β	Lesional cells	21	TE (5), BCC ?subtype(5)	TE, 100% positive; BCC, 20% positive

Table 1 Continued

Marker	*Localization*	*References*	*Entities (number)*	*Results*
Lectins	Peritumoral stroma	[22]	103 BCCs (55 nonulcerated, 48 ulcerated)	96%, bandlike peritumorous staining
		[9]	10 TEs, 15 BCCs (2 early, 2 BCCN, 7 Ulcerative, 3 morpheic, 1 BCCI)	TE, 90% positive (10% positive continuous bandlike peritumorous staining, 80% discontinuous bandlike); BCC, 60% positive (40% positive continuous bandlike peritumorous staining, 20% discontinuous bandlike)
Neuro-filaments	Perifollicular nerve plexus	[23]	5 TEs, 10 BCCs (7 solid, 2 infiltrative, 1 morpheaform)	TE, 100% positive; BCC, 100% positive
p75NTR	Lesional cells	[24]	16 dTE (16), mBCC (14)	dTE, 100% positive in 100%; BCC, 14% positive
FAP	Stroma	This study	dTE (25), miBCC (25)	dTE, 0%; miBCC, 100% (gradient observed)

BCC, basal cell carcinoma; CK20, cytokeratin 20; dTE, desmoplastic trichoepithelioma; miBCC, morpheaform or infiltrative basal cell carcinoma; mBCC, morpheaform basal cell carcinoma; p75NTR, p75 neurotrophin receptor; TE, trichoepithelioma; TGF-β, transforming growth factor-β; FAP, fibroblast-activation protein.
[a]Subtype of BCC not specified.

(MM) in a masked manner to ensure consistency of interpretation. Stained sections were scored as positive or negative.

Statistical Analysis

The statistical association of FAP expression was analyzed using the Fisher's exact test to determine whether there were differences of significance in expression between the two entities. A two-tailed P-value of <0.05 was considered to be statistically significant.

Results

The clinical features of this series of desmoplastic trichoepithelioma and morpheaform/infiltrative basal cell carcinoma are outlined in Table 2. Positive FAP staining was noted by ascertaining cytoplasmic expression of stromal fibroblasts. Any nuclear staining was considered background artifact. All control cases of scar showed positive expression of FAP within fibroblasts (Figure 1). Positive staining of mature sebocytes within sebaceous glands was also noted in a few cases.

Desmoplastic Trichoepithelioma

Patients with desmoplastic trichoepithelioma (19 females and 6 males) ranged in age from 14 to 77 years (mean of 45 years). All lesions were located on the face except for one case on the back.

All 25 cases of desmoplastic trichoepithelioma showed negative expression of FAP (Figure 2).

Table 2 Demographic data of patients in study

	dTE	*miBCC*
Mean age (years, range)	45 (14–77)	72 (42–85)
Sex (male/female ratio)	6/19	15/10
Location (%)	Face (96)	Head (60)
	Back (4)	Trunk (20)
		Extremities (20)

DTE, desmoplastic trichoepithelioma; miBCC, morpheaform/infiltrative basal cell carcinoma.

Morpheaform/Infiltrative Basal Cell Carcinoma

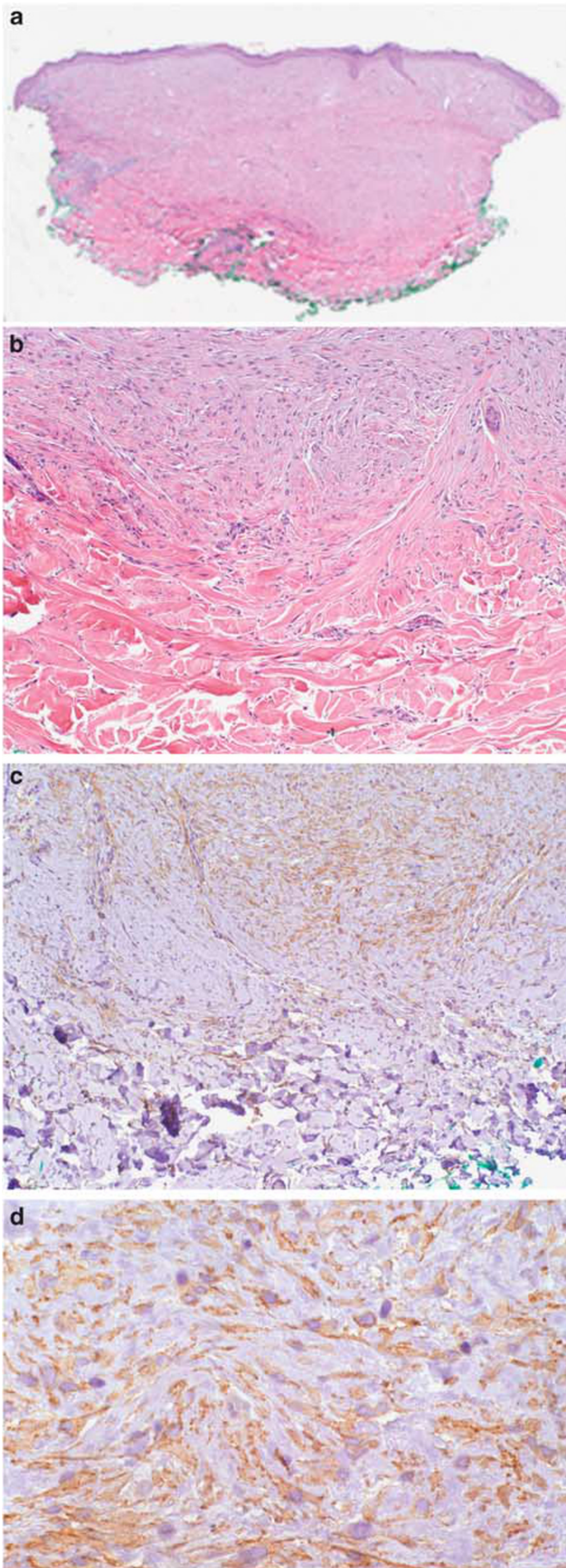
Patients were with morpheaform/infiltrative basal cell carcinoma (15 men, 10 women) aged from 42 to 85 years (mean, 72 years). Lesions were located on the head in 15 (60%) cases, trunk in 5 (20%) cases, and extremities in 5 (20%).

Fibroblast-activating protein was expressed in peritumoral stromal fibroblasts of all 25 cases of morpheaform/infiltrative basal cell carcinoma (100%) (Figure 2). An inverse gradient was observed in FAP expression with more intense expression noted in fibroblasts abutting tumor cells with the intensity of staining of stromal fibroblasts decreasing with increasing distance from the tumor.

The difference in FAP expression between morpheaform/infiltrative basal cell carcinoma and desmoplastic trichoepithelioma was statistically significant ($P=0.000003$).

Discussion

Although mutations in oncogenes or tumor suppressor genes contribute to the mechanisms initiating



cancer development, progression of cancer is the result of complex reciprocal interactions between neoplastic cells and their microenvironment.[32–35] The stroma appears to be important at different steps of tumor progression impacting proliferation, migration, and vascularization of tumor cells as well as degradation of the extracellular matrix (ECM).[36,37] One stromal component in particular, ie, the activated stromal fibroblast, a fibroblastic cell with a myofibroblastic phenotype, seems to be pivotal to formation of the stroma of cancerous cells.[32,36–38] Recent studies on a variety of human tumors such as skin, lung, breast, and colon cancers have shown that one of the major functions of these myofibroblasts, similar to that of neoplastic cells, is degradation of the ECM by the production of ECM-degrading enzymes.[32,36–38] In addition to their expression of α-smooth muscle actin, these myofibroblasts also express FAP.[25–30,38,39] In skin, FAP expression has been shown in stromal fibroblasts of both benign and malignant melanocytic tumors as well as epithelial cancers such as squamous and basal cell carcinomas.[30,31] The expression pattern in the latter category was noted as a gradient.[30] Findings from this study corroborate this in that all cases (100%) of morpheaform/infiltrative basal cell carcinomas showed strong FAP staining of peritumoral stromal fibroblasts. Like Huber *et al*,[30] we observed a gradient in the pattern of FAP staining with prominent expression noted in fibroblasts directly surrounding the tumor cells, a more diffuse pattern in the distal part of the peritumoral stroma and with minimal or absent expression in adjacent normal tissue.

None of the cases of desmoplastic trichoepithelioma showed FAP expression in stromal fibroblasts, making this a specific and sensitive immunohistochemical marker and more importantly one that reliably distinguishes morpheaform/infiltrative basal cell carcinoma from desmoplastic trichoepithelioma. Immunohistochemical markers putatively useful in reliably differentiating trichoepithelioma (and/or trichoblastoma) and basal cell carcinoma in general and desmoplastic trichoepithelioma and morpheaform/infiltrative basal cell carcinoma in particular include CD34, Bcl-2, CK20, and AR.[3,7–12,15–17] Positive peritumoral staining of trichoepithelioma and desmoplastic trichoepithelioma by CD34, shown by Kirchmann *et al*, in 100% of cases of both with negative staining in all cases of basal cell carcinoma was contradicted by subsequent studies that showed

Figure 1 Representative example of scar from study. (**a** and **b**) H&E: (**a**) original magnification, ×2); (**b**) original magnification, ×10 (scar tissue in upper half and normal connective tissue in lower half). (**c** and **d**) Immunohistochemical staining for FAP: (**c**) (original magnification, ×10); positive FAP expression in stromal fibroblasts in scar tissue and lack of expression in normal connective tissue; (**d**) original magnification, ×20.

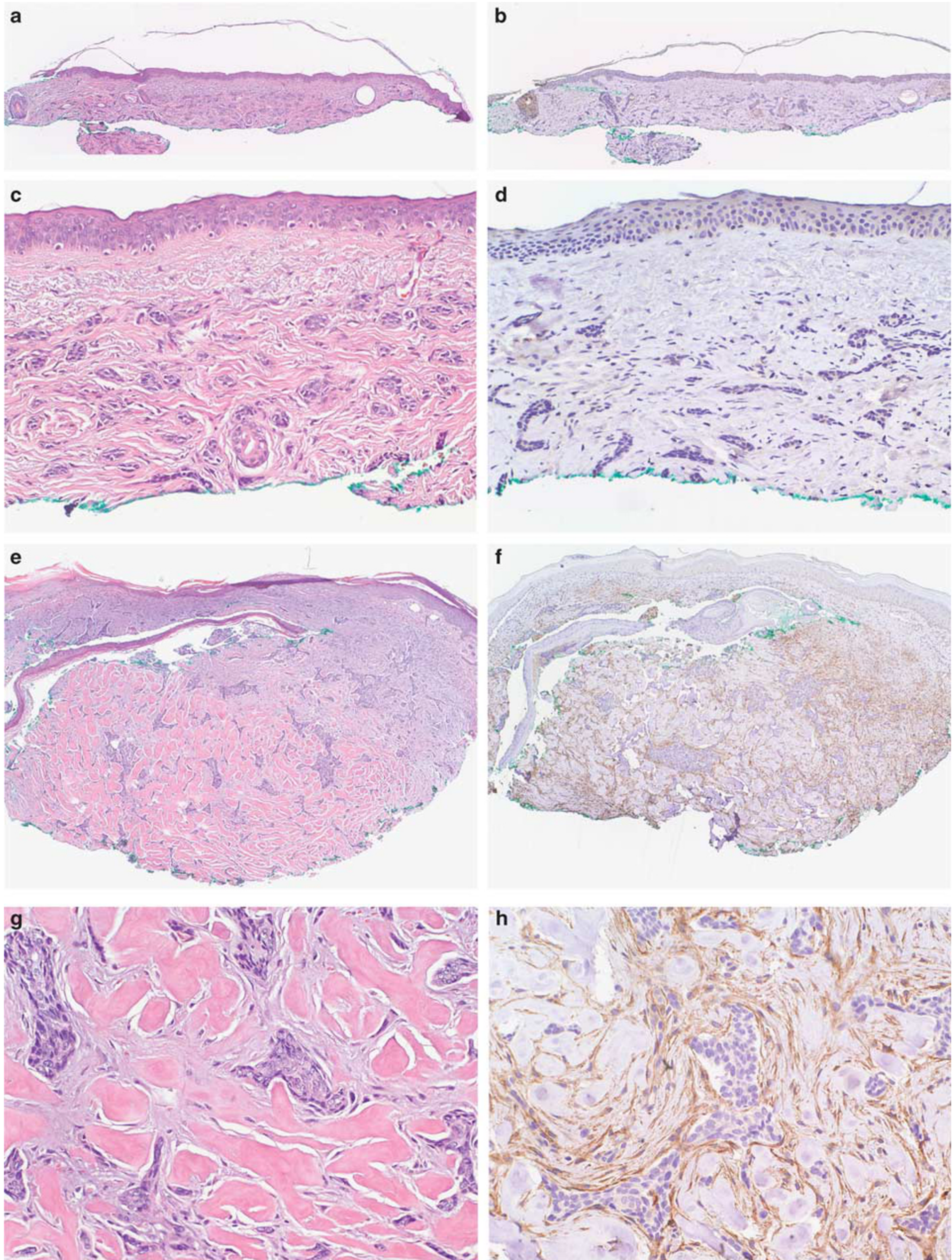


Figure 2 Representative examples of desmoplastic trichoepithelioma and morpheaform/infiltrative basal cell carcinoma from study. (**a–d**) Desmoplastic trichoepithelioma; (**e–h**) BCC, morpheaform, keloidal type; H&E: (**a**, **e**) original magnification, ×4; (**c**, **g**) original magnification, ×20; FAP: (**b**, **f**) original magnification, ×4; (**d**, **h**) original magnification, ×20.

positive peritumoral staining in some cases of basal cell carcinoma and absence of the same in cases of trichoepithelioma.[7–10] The diffuse staining of bcl-2 in tumor nests of basal cell carcinoma and peripheral staining of tumor nests in cases of trichoepithelioma reported in some studies was refuted by others claiming that the differential expression pattern at the periphery compared with the center of lesional aggregates cannot be assessed reliably, as the epithelial strands are usually thin in the desmoplastic variants of both neoplasms.[3,9–12] Use of expression of the AR, initially shown by Izikson *et al*, were later reproduced by Costache *et al*.[3] Both groups showed AR expression in >75% of basal cell carcinomas tested and lack of the same in both trichoepithelioma and desmoplastic trichoepithelioma.[15] Undermining these results were those obtained by Katona *et al* who found AR expression in only 65% of basal cell carcinomas tested and also showed AR positivity in 13% of desmoplastic trichoepitheliomas in their series.[16] Several studies have shown that cytokeratin 20-positive cells, labeling Merkel cells, are present in only trichoepitheliomas, including desmoplastic trichoepithelioma, but not in basal cell carcinomas, including morpheaform basal cell carcinoma.[3,17] Conflicting this is evidence showing the presence of CK20-positive cells in a few cases of morpheaform basal cell carcinoma.[17] In addition, small and superficial biopsy specimens resulting in falsely negative results question the discriminatory values of this marker.

Desmoplasia, a paucicellular host response characterized by a hyalinized or sclerotic stroma, has classically been associated with the malignant phenotype of neoplasias of noncutaneous origins including breast, prostate, oral squamous cell, pancreatic, and thyroid carcinomas, among others.[40–44] In contrast, in the skin, the desmoplastic stromal response may be observed in malignant and benign tumors.[3,4,45–52] Given this, the obvious question is whether desmoplasia associated with a benign neoplasm is any different from that associated with malignant tumors. Findings from this study indicate that there does appear to be a difference in mechanisms underlying the desmoplastic reaction pattern in a malignant cutaneous epithelial neoplasm compared with one that is benign. Does the stromal response actually contribute to the biologic behavior of the neoplasm or is it a mere epiphenomenon? That desmoplasia in cutaneous malignancies such as squamous cell, sebaceous, and sweat gland carcinomas is associated with a poorer prognosis with a higher risk of tumor recurrence, metastasis, and/or tumor-related death, argues in favor of the former hypothesis.[50,51] A scientific explanation for this might be that collagen production is induced by tumor cells that cause activation of fibroblasts and subsequent proliferation.[30,39,44,51]

Expression of FAP has also been previously noted in the granulation tissue of healing wounds.[53–55] Our findings confirm this in that all scars in this study expressed FAP. The retention of FAP expression in scars provides support for the long-standing hypothesis that cancers may essentially represent nonhealing wounds,[53–55] as all the scars in our study showed positive staining of stromal fibroblasts similar to morpheaform/infiltrative basal cell carcinoma cases. Multiple cellular and molecular studies have verified this hypothesis by showing that tumors, especially carcinomas, activate the latent wound-healing host program in a prolonged and exaggerated manner.[53–55] In addition, most of the genes that control the wound-healing process are also important regulators of cancer growth and progression.[53–55]

In conclusion, this study supports the use of FAP as a sole immunohistochemical marker to differentiate morpheaform/infiltrative basal cell carcinoma from desmoplastic trichoepithelioma. Expression of FAP by peritumoral stromal fibroblasts establishes a diagnosis of morpheaform/infiltrative basal cell carcinoma whereas lack of FAP staining supports a diagnosis of desmoplastic trichoepithelioma.

Disclosure/conflict of interest

The authors declare no conflict of interest.

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