J Cutan Pathol 2013: 40: 363–370
doi: 10.1111/cup.12085
John Wiley & Sons. Printed in Singapore

Journal of
Cutaneous Pathology

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The immunohistochemical differential diagnosis of microcystic adnexal carcinoma, desmoplastic trichoepithelioma and morpheaform basal cell carcinoma using BerEP4 and stem cell markers

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Background: Microcystic adnexal carcinoma (MAC), desmoplastic trichoepithelioma (DTE) and morpheaform basal cell carcinoma (BCC) frequently impose a considerable differential diagnostic challenge and immunohistochemistry is often used as a differentiating diagnostic adjunct.

Methods: Using standard immunohistochemical techniques, we examined 21 examples of DTE, 17 examples of morpheaform BCC and 10 examples of MAC for the expression of BerEP4, a marker of epithelial cells, and of three stem cell markers, pleckstrin homology-like domain, family A, member 1 (PHLDA1) [T cell death-associated gene 51 (TDAG51)], cytokeratin 15 (CK15) and cytokeratin (CK19).

Results: All but one MAC was negative for BerEP4 and all morpheaform BCC expressed BerEP4. Sixteen out of 21 DTE were immunoreactive for BerEP4. All 21 DTE were PHLDA1 positive and all 17 morpheaform BCC were PHLDA1 negative. MAC showed a mixed staining pattern for PHLDA1. CK15 was expressed in 20/21 DTE, whereas the majority of cases of MAC and morpheaform BCC were CK15 negative. CK19 stained more MAC than DTE and morpheaform BCC.

Conclusions: BerEP4 differentiates between MAC and morpheaform BCC but not between MAC and DTE whereas PHLDA1 differentiates between DTE and morpheaform BCC but shows variable staining in MAC. CK15 and CK19 are helpful adjuncts in the differential diagnosis of sclerosing adnexal neoplasms but are second in line to BerEP4 and PHLDA1. We propose an algorithm for the immunohistochemical work-up of sclerosing adnexal neoplasms.

Keywords: BerEP4, desmoplastic trichoepithelioma, microcystic adnexal carcinoma, morpheaform basal cell carcinoma, stem cell markers

Sellheyer K, Nelson P, Kutzner H, Patel RM. The immunohistochemical differential diagnosis of microcystic adnexal carcinoma, desmoplastic trichoepithelioma and morpheaform basal cell carcinoma using BerEP4 and stem cell markers.
J Cutan Pathol 2013; 40: 363–370. © 2013 John Wiley & Sons A/S. Published by Blackwell Publishing Ltd

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Accepted for publication November 19, 2012

Sclerosing adnexal neoplasms, most importantly microcystic adnexal carcinoma (MAC), desmoplastic trichoepithelioma (DTE) and morpheaform basal cell carcinoma (BCC), belong to a group of tumors in dermatopathology that frequently impose a considerable differential diagnostic challenge. A misdiagnosis can either lead to unnecessary extensive surgery or to insufficient treatment.

Immunohistochemistry is often used as a diagnostic adjunct to differentiate between these neoplasms. Among the most commonly employed markers are cytokeratin 7 (CK7), cytokeratin 15 (CK15), cytokeratin 19 (CK19), cytokeratin 20 (CK20), the androgen receptor and BerEP4.[1–7] Two other proteins were recently introduced into the literature which seem to differentiate between DTE and morpheaform BCC with a high degree of reliability, namely the fibroblast-activation protein[8] and the low-affinity p75 neurotrophin receptor (p75NTR).[9] In the latter two studies, MAC was not evaluated. The number of markers employed in the literature in an attempt to distinguish between DTE and morpheaform BCC increases exponentially if the conventional variants of these tumors are considered.[4]

The monoclonal antibody BerEP4 is an epithelial marker that recognizes two glycopolypeptides (34 and 39 kDa).[10] It differentiates with a high degree of reliability between BCC and cutaneous squamous cell carcinoma (SCC).[11–15] In a previous study, we showed that it also reliably differentiates between MAC and morpheaform BCC in that it is negative in the former and positive in the latter.[4] Since a recent publication[5] contested that finding, in this study, we repeated staining for BerEP4 on an additional 10 cases of MAC and 17 cases of morpheaform BCC and found an identical staining pattern, supporting our previous results. We also examined 21 cases of DTE.

One of the most exciting developments in contemporary dermatopathology is the use of stem cell markers, to elucidate the histogenesis of cutaneous neoplasms. As previously noted, CK15 and CK19 have already been employed in the differential diagnosis of sclerosing adnexal neoplasms and both are stem cell markers, with CK15 being more specific than CK19.[16] In this study on MAC, DTE and morpheaform BCC, we compared their staining patterns with that of one of the newest members of the ever increasing arsenal of stem cell markers, PHLDA1 (pleckstrin homology-like domain, family A, member 1), also known as TDAG51 (T cell death-associated gene 51). PHLDA1 has been found to be twice as much expressed in the human anagen bulge than CK15,[17] which is conventionally used as a marker for follicular stem cells.[18,19] PHLDA1 reliably discriminates between DTE and morpheaform BCC.[20] It is highly expressed in the former, but negative in the latter. It has also proven its usefulness in the evaluation of small biopsies of conventional trichoepithelioma (TE) and BCC[21] but has not been employed yet in

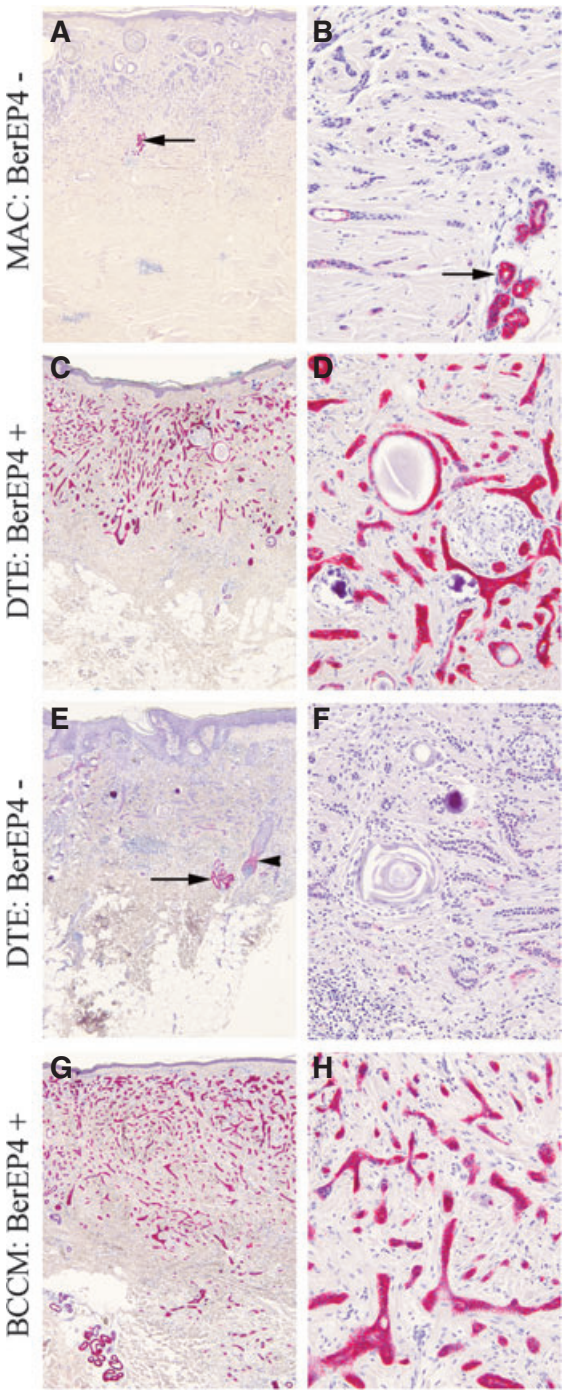

Fig. 1. Staining for BerEP4 in MAC, DTE and morpheaform BCC. Arrows in (A), (B) and (E) indicate positive internal control (eccrine glands). Arrowhead in (E) indicates positive internal control (secondary hair germ). Original magnifications: (A) ×25; (C), (E), (G) ×50; (B), (D), (F), (H) ×200.

MAC. Therefore, its differential diagnostic potential in MAC compared to morpheaform BCC and DTE is thus far unknown.

In this study, we evaluated the combined use of BerEP4, PHLDA1 (TDAG51), CK15 and CK19 in the differential diagnosis of MAC, DTE and morpheaform BCC.

Materials and methods

Specimens

We examined 21 cases of DTE, 17 morpheaform BCC and 10 MAC. The specimens were retrieved from the archives of Dermatopathologie, Friedrichshafen, Germany, the Department of Pathology, Medical Center of the University of Michigan, Ann Arbor, MI, USA and Nelson Dermatopathology Associates, Atlanta, GA, USA. The tissues were fixed in 10% neutral-buffered formalin and subjected to routine processing and paraffin embedding.

Immunohistochemical staining

Four-micron sections were placed on Colorfrost Plus® slides (Erie Scientific LLC, Portsmouth, NH, USA), deparaffinized in Bond® Dewax solution (Leica Microsystems Ltd, Newcastle Upon Tyne, UK) and dehydrated in decreasing concentrations of ethanol. Prior to incubation with the primary antibody, we used heat-induced epitope retrieval. The retrieval conditions depended on each of the four different antibodies employed. The antibodies were directed against BerEP4, PHLDA1, CK 15 and CK19. All incubation conditions, antibody specifications and positive controls are listed in Table 1. As negative control, we used a scalp sample from an excision of a trichilemmal cyst and omitted the primary antibody. Color products were developed using the Bond™ Polymer Refine Red Detection Kit (Alkaline Phosphatase/RED, Cat # DS9390, Leica Microsystems Ltd). The sections were counterstained with hematoxylin before dehydration and cover slipping. All procedures were done on the Leica Bond-III Automatic Stainer (Leica Microsystems Ltd).

Results

BerEP4 differentiates between MAC and morpheaform BCC but not between MAC and DTE

All but one of the MAC were negative for BerEP4 and the single positive case showed less than 26% immunoreactive cells (Table 2; Fig. 1A,B). In contrast, all morpheaform BCC were BerEP4

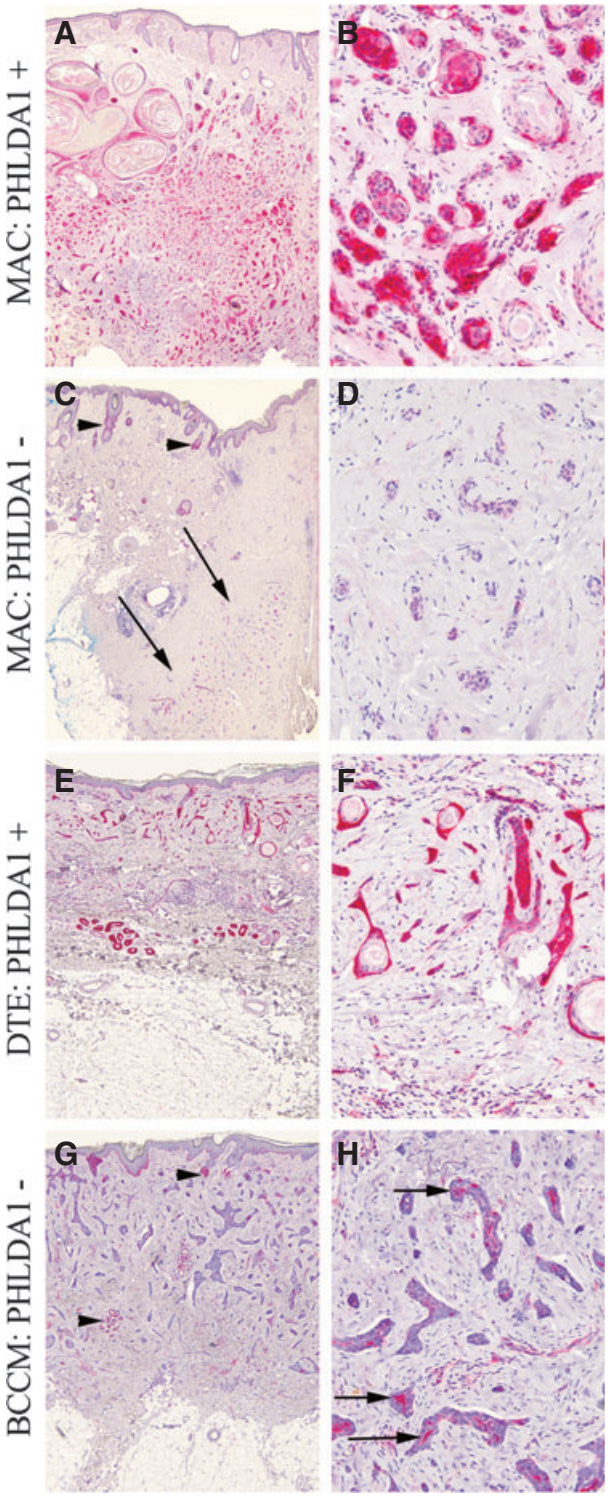

Fig. 2. Staining for pleckstrin homology-like domain, family A, member 1 (PHLDA1) in microcystic adnexal carcinoma (MAC), desmoplastic trichoepithelioma and morpheaform basal cell carcinoma. Arrows in (C) indicate the location of tumor cells of MAC. Arrowheads in (C) and (G) indicate positive internal control [vellus hairs in (C) and (G) and also eccrine gland in (G)]. Arrows in (H) indicate scattered positive cells representing PHLDA1-positive melanocytes. Original magnifications: (A) ×25; (C), (E), (G) ×50; (B), (D), (F), (H) ×200.

Table 1. Monoclonal antibodies utilized

Antibody	Clone	Dilution	Manufacturer	Epitope retrieval	Positive control
BerEP4	VU-1D9	RTU	Leica Microsystems Ltd (PW31) Newcastle Upon Tyne, UK	Citrate buffer* pH 6.0; 10 min	Internal (secondary hair germ, eccrine glands)
PHLDA1	RN-6E2	1 : 50	Santa Cruz Biotechnology (sc-23866) Santa Cruz, CA, USA	EDTA buffer† pH 9.0; 20 min	Internal (melanocytes and eccrine glands)
CK15	LHK15	1 : 200	Santa Cruz Biotechnology (sc-23866) Santa Cruz, CA, USA	Citrate buffer* pH 6.0; 20 min	Internal
CK19	A53-B/A2	1 : 400	Santa Cruz Biotechnology (sc-23866) Santa Cruz, CA, USA	Citrate buffer* pH 6.0; 20 min	Internal

CK105, cytokeratin 15; CK19, cytokeratin 19; PHLDA1, pleckstrin homology-like domain, family A, member 1; RTU, ready-to-use primary antibody solution.
*Bond Epitope Retrieval Solution 1 (AR9961; Leica Microsystems Ltd).
†Bond Epitope Retrieval Solution 2 (AR9640; Leica Microsystems Ltd).

positive, with 16 cases revealing immunoreactivity in over 75% and one case in over 25% of cells (Table 2; Fig. 1G,H). In 16 cases of DTE staining for BerEP4, the number of positive cells varied between one and over 75%; five DTE were immunonegative (Table 2; Fig. 1C–F).

PHLDA1 differentiates between DTE and morpheaform BCC but shows variable staining in MAC

All 21 DTE were PHLDA1 positive and all 17 morpheaform BCC were PHLDA1 negative (Table 2; Fig. 2E–H). Six of the MAC were PHLDA1 positive and three were PHLDA1 negative (Table 2; Fig. 2A–D). The number of positive cells varied between less than 26% and over 75% in MAC.

More DTE than MAC and morpheaform BCC are positive for cytokeratin 15

CK15 is expressed in 20 of the 21 DTE examined (Table 2; Fig. 3C,D). Nineteen of the 20 CK15-positive cases showed immunoreactivity in over 75% of the neoplastic cells and one case in over 25% of cells. Nine of the 17 morpheaform BCC were CK15 negative (Table 2; Fig. 3E,F) and in two more less than 25% of cells were CK15 positive. Only 6/17 cases of morpheaform BCC showed immunoreactivity for CK15 in more than 75% of cells. MAC also did not expressed CK15 in the majority of cases. Five cases were CK15 negative and in three cases less than 25% cells were immunoreactive (Table 2; Fig. 3A,B).

High expression of cytokeratin 19 favors MAC over DTE and morpheaform BCC

All MAC were CK19 positive with seven showing immunoreactivity in more than 75% of cases (Table 2; Fig. 4A,B). Out of the 21 cases of DTE, nine were completely CK19 negative and 10 showed immunopositivity in less than 25% of the cells (Table 2; Fig. 4C,D). In morpheaform BCC, 10 cases were CK19 negative and 5/17 were CK19 positive in over 75% of the tumor cells (Table 2; Fig. 4E,F).

Discussion

MAC, DTE and morpheaform BCC display overlapping histopathologic features in hematoxylin- and eosin-stained sections. Thus, immunohistochemistry has evolved as an adjunct in the often difficult differential diagnosis of these three sclerosing neoplasms. Not a single marker, however, is able to differentiate all three of them and a battery of antibodies is frequently employed. In this study, we used a marker of epithelial cells (BerEP4) as well as three follicular stem cell markers (PHLDA1, CK15 and CK19).

BerEP4 is known for its intense labeling of BCC and the lack thereof in SCC.[11–15] In a previous study on 13 cases of MAC, not a single neoplasm was immunoreactive for BerEP4 whereas all 28 morpheaform BCC stained for BerEP4.[4] The results of this study on an additional 10 cases of MAC corroborate these previous findings although 1 of 10 MAC was BerEP4 positive, albeit in less than 25% of the tumor cells. Therefore, combining both

Table 2. Percentage of cells stained in microcystic adnexal carcinoma, desmoplastic trichilemmoma and morpheaform basal cell carcinoma

Tumor	PHLDA1				CK15				CK19				BerEP4			
	0	1–25	26–75	>75	0	1–25	26–75	>75	0	1–25	26–75	>75	0	1–25	26–75	>75
Microcystic adnexal carcinoma (10)*	3	2	1	3	5	3	1	0	0	1	1	7	9	1	0	0
Desmoplastic trichilem-moma (21)	0	0	0	21	1	0	1	19	9	10	1	1	5	4	5	7
Morpheaform basal cell carcinoma (17)	16	1	0	0	9	2	0	6	10	1	1	5	0	0	1	16

CK15, cytokeratin 15; CK19, cytokeratin 19; PHLDA1, pleckstrin homology-like domain, family A, member 1.

*For BerEp4, all 10 cases were evaluated. The sections for one of the case stained for three stem cell markers fall off the slide and the block was exhausted, not allowing for a repeat of the staining on that case.

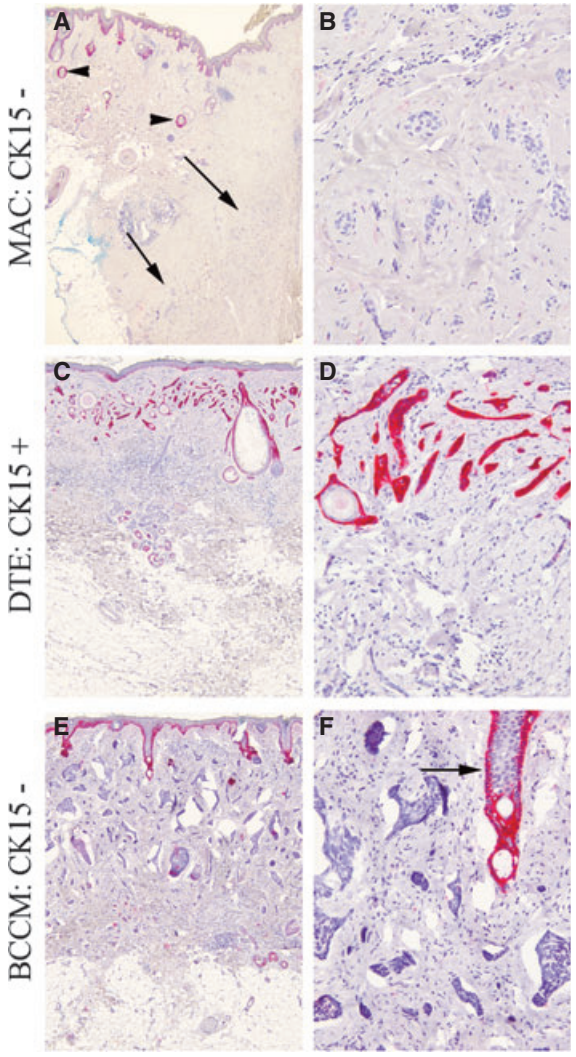

Fig. 3. Staining for cytokeratin 15 in microcystic adnexal carcinoma (MAC), desmoplastic trichoepithelioma and morpheaform basal cell carcinoma. Arrows in (A) indicate the location of tumor cells of MAC. Arrowheads in (A) indicate positive internal control (transversely cut bulge of hair follicles). Arrow in (F) indicate positive internal control (hair follicle). Original magnifications: (A) ×25; (C, E) ×50; (B, D, F) ×200.

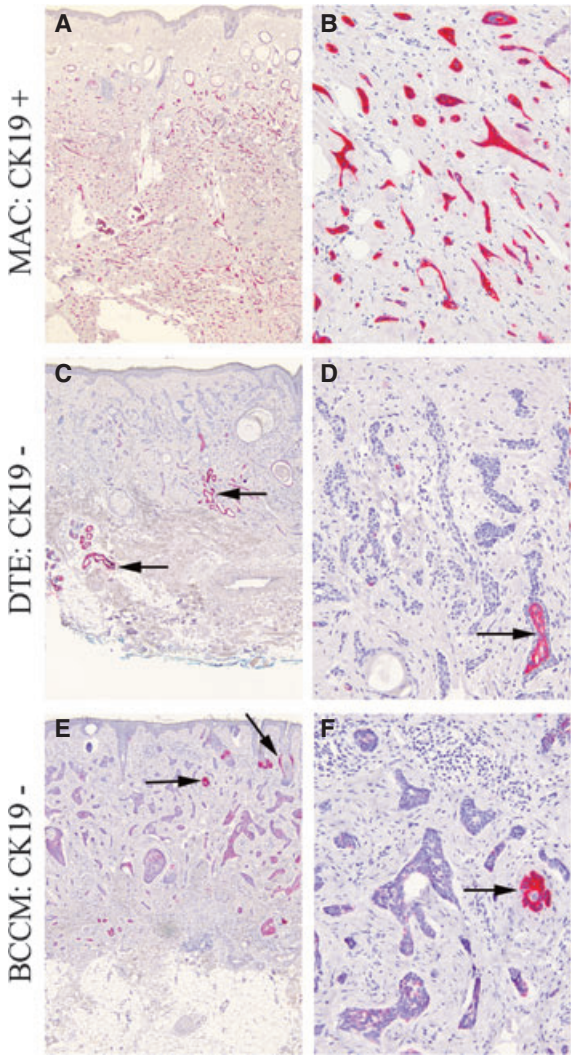

Fig. 4. Staining for cytokeratin 19 in MAC, DTE and morpheaform BCC. Arrows in (C) indicate positive internal control (eccrine glands). Arrow in (D) indicate positive internal control (intradermal duct of eccrine gland). Arrows in (E, F) indicate positive internal control (hair follicles). Original magnifications: (A) ×25; (C, E) ×50; (B, D, F) ×200.

studies revealed immunoreactivity for BerEP4 in 22/23 cases of MAC. Our results contradict a recent study on 13 cases of MAC that found five tumors to be BerEP4 positive and the remaining eight showing no immunoreactivity.[5] Intriguingly, the authors also reported 3/8 SCCs staining for BerEP4.[5] The latter result is in disagreement with the literature. Five other studies found all 23,[13] 22,[22] 21,[11] 6,[23] and 3[24] cases of SCC (combined 75 cases) to be BerEP4 negative. Not a single case of SCC was positive for BerEP4. Therefore, it is likely that technical differences in the study by Hoang et al.[5] lead to BerEP4 immunoreactivity not only in SCCs but also in MAC, rendering a portion of them falsely BerEP4 positive. On the basis of our current and previous[4] study, we consider BerEP4 as a reliable differential diagnostic tool to differentiate between MAC and DTE. However, it does not allow differentiating between MAC and DTE. Five out of 21 cases of DTE were also BerEP4 negative. Previously, we reported a similar number (4/16 DTE BerEP4 negative).[4]

PHLDA1 (TDAG51), a recently described follicular stem cell marker discovered with DNA microarrays,[17] has been shown to reliably differentiate not only TE and BCC in small biopsy specimens[21] but also DTE from morpheaform BCC.[20] In addition, its staining pattern confirmed the nature of fibroepithelioma of Pinkus as a BCC with a tumor-specific type of epidermal hyperplasia[25]

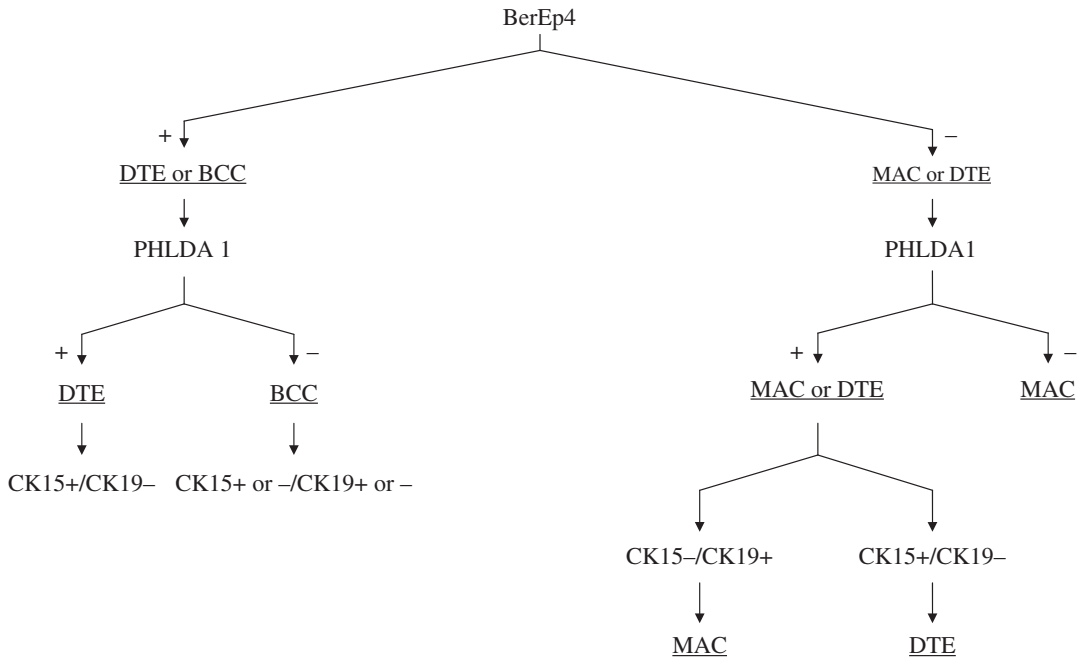

Fig. 5. Algorithm for the immunohistochemical differential diagnosis of microcystic adnexal carcinoma, desmoplastic trichoepithelioma and morpheaform basal cell carcinoma utilizing BerEP4 and stem cell markers pleckstrin homology-like domain, family A, member 1, cytokeratin 15 and cytokeratin 19.

as opposed to a fenestrated trichoblastoma.[26] In this study, PHLDA1 was confirmed as a powerful tool to differentiate between DTE and morpheaform BCC. All DTE were PHLDA1 positive and all morpheaform BCC were PHLDA1 negative (with the exception of one case in which less than 26% of morpheaform BCC tumor cells were immunoreactive). However, PHLDA1 showed an inconsistent staining pattern in MAC. Three tumors were PHLDA1 negative and six were positive. The PHLDA1-positive MAC showed variable numbers of immunoreactive tumor cells and a consistent pattern between tumor islands in the upper and lower portion of the dermis with their frequently different histological differentiation was not seen. Therefore, PHLDA1 does not seem to be a suitable marker in the diagnosis of MAC.

CK15 is one of the most specific follicular bulge markers available.[16] In this study, it highlighted 20/21 DTE and therefore approached the number of DTE positive for PHLDA1 (21/21). This is not surprising since PHLDA1 represents an equally specific follicular bulge marker.[17] The positive staining pattern of DTE for CK15 and PHLDA1 highlights the follicular nature of this adnexal neoplasm at the immunohistochemical level. Whereas PHLDA1 was preferentially expressed in DTE as opposed to MAC and morpheaform BCC, CK15 does not reach the discriminatory power that PHLDA1 has in the differential diagnosis of DTE vs. morpheaform BCC. In 6/17 morpheaform BCC, over 75% of the cells were CK15 positive and in an additional two cases at least less than 26% of tumor cells in morpheaform BCC were CK15 positive. In 4/9 MAC, the tumor cells were CK15 positive, although at a lower percentage. While similar for DTE, our staining results for CK15 is different from the one reported by Hoang et al.[5] in respect to MAC and morpheaform BCC. The authors found the majority of their 13 cases of MAC to be CK15 positive and all of their infiltrative morpheaform BCC were CK15 negative. While on a scale of 3+, 2+ and negative, 10/13 MAC scored at 2+ and further two cases at 3+, only one MAC was CK15 negative.[5] Differences in antibody manufacturer, dilution and retrieval may account for these different results between this study and the one published by Hoang et al.[5] Our antibody was from Santa Cruz Biotechnology, Santa Cruz, CA, USA, and was used at a dilution of 1 : 200 whereas Hoang et al.[5] employed an antibody from NeoMarkers, Fremont, CA, USA, at a dilution of 1 : 80. We used standardized heat-induced epitope retrieval in a citrate buffer at pH 6.0 performed directly on the Leica Bond-III Automatic Stainer (Leica Microsystems Ltd). Hoang et al.[5] employed heat-induced epitope retrieval via microwave and in a buffer not further specified. Antigen retrieval via microwave is more prone to variable results than standardized retrieval on an automatic stainer.

CK19 demarcates follicular bulge stem cells but is not as specific as cytokeratin 15 as it also labels

transient amplifying cells migrating down the outer root sheath.[6] Thus, it was logically intuitive that its staining pattern in the three sclerosing neoplasms studied allowed one to favor one tumor over the other but did not have the discriminatory power that some of the other staining results had. Positive reaction for CK19 favored MAC over DTE and morpheaform BCC. This is in agreement with this study that reported a higher percentage of CK19-positive tumor cells in MAC vs. DTE (morpheaform BCC was not included in that study).[7] In view of the dual staining of stem cells and their descendent transient amplifying cells by CK19, we speculate that the immunoreactivity for CK19 in MAC reflects its complex nature as opposed to DTE and morpheaform BCC that show a lower percentage of staining for CK19.

We conclude that CK15 and CK19 are helpful adjuncts in the differential diagnosis of sclerosing adnexal neoplasms but are second in line to BerEP4 and PHLDA1 and propose the algorithm shown in Fig. 5 for the immunohistochemical work-up of sclerosing adnexal neoplasms. Not a single marker is sufficient to differentiate between all of them but a combination of several antibodies in conjunction with the clinical presentation and the features observed on routine histological sections should enable pathologists to make a definitive diagnosis when faced with one of these challenging tumors. The panel of the markers studied represents a useful adjunct for arriving at the correct diagnosis.

Acknowledgements

We thank Ms. Tomekia Trimble, BS, HT (ASCP), HTL (FL), for her outstanding technical assistance in immunohistochemistry and Ms. Teresa Lucas, BS, MBA, HT (ASCP), for the preparation of superb histological sections. There is no funding source.

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