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Original Article

Value of CD10 Expression in Differentiating Cutaneous Basal from Squamous Cell Carcinomas and Basal Cell Carcinoma from Trichoepithelioma

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Abstract

Background: In addition to the well-defined histological criteria for squamous cell carcinoma (SCC) and basal cell carcinoma (BCC), immunohistochemical techniques can be used in difficult cases for their differentiation. As differential diagnosis between trichoepithelioma (TE) and BCC is sometimes difficult for the clinician and the pathologist, CD10 may be a useful marker for definite diagnosis. We aimed to evaluate the usefulness of this marker in the differentiation between SCC and BCC and also in the differentiation between BCC and TE.

Methods: Fifty-five BCC cases, 50 SCC cases, and 20 cases of benign adnexal tumor with follicular differentiation were retrieved from the archives of the pathology departments of hospitals affiliated with Shiraz University of Medical Sciences. Immunohistochemistry for CD10 was performed on the sections obtained from formalin-fixed, paraffin-embedded blocks. CD10 immunoreactivity in the stroma and/or tumor cells was determined as follows: negative (0); 1+(10-50% positive cells); and 2+(>50% positive cells).

Results: Comparison of CD10 expression between the BCC and SCC groups showed a significant difference ($P<0.001$) in each of the tumor and stromal cells. Comparison of CD10 expression between the BCC and TE groups demonstrated a significant difference in both the tumor and stromal cells ($P<0.001$). There was no significant difference in CD10 expression between the stromal and tumor cells of the BCC subtypes.

Conclusion: CD10 is a useful adjunct marker in distinguishing TE from BCC. CD10 is suggested to be one of the useful immunohistochemical markers to differentiate BCC from SCC.

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Keywords ● Squamous cell carcinoma ● Basal cell carcinoma ● Trichoepithelioma

Introduction

Basal cell carcinoma (BCC) is the most common cutaneous tumor, accounting for approximately 70% of all malignant diseases of the skin. It is locally aggressive and its metastasis is unusual. There is a considerable variability in the morphology of BCC, and a number of histopathological subtypes have been defined.[1] Immunohistochemical

studies support the notion that BCC originates from the basaloid epithelium of follicular bulges in the anagen hair bulbs and the follicular matrix cells.[2]

Cutaneous squamous cell carcinoma (SCC) is the second most frequent malignancy in humans.[3] Although SCC and BCC are biologically different, they have a similar clinical presentation. Moreover, both have common risk factors, but their histological interpretations are less confusing.[4,5] CD10 may help differentiate superficial BCC from SCC in the occasional cases of superficial, fragmented biopsies. These findings suggest that the positivity of CD10 may be due to the indolent nature of BCC, and the relatively lack of CD10 expression in SCC may be related to its aggressive patterns. It is suggested that CD10 immunostaining may be helpful in differentiating SCC from superficial BCC to increase the diagnostic accuracy in these occasionally histologically and clinically overlapping tumors.[5]

CD10 is a 100-kd transmembrane glycoprotein initially identified as the common acute lymphoblastic leukemia antigen, or CALLA.[6] CD10 expression exhibits a link with the growth rate of the cells. Its expression is increased in malignant tumors and regenerating tissues, but it is not lineage specific.[5] Furthermore, CD10 expression can be detected in the peritumoral fibroblast-like stromal cells within the invasive area of various cancers such as prostate, breast, colorectal, and lung carcinomas.[7]

Within normal adult skin, CD10 immunopositivity has been noted in the inner sheath of hair follicles, hair matrix, and perifollicular fibrous sheath.[8] In tumors of the skin, CD10 is expressed in dermatofibroma, dermatofibrosarcoma protuberans, and melanoma.[9] Differential diagnosis between trichoepithelioma (TE), trichoblastoma, trichofolliculoma, trichoadenoma, and BCC may be very difficult for the clinician and the pathologist. CD10 may be useful for the differential diagnosis between benign tumors of cutaneous appendages originating from the hair follicle and BCC as an immunohistochemical marker and it may solve a dilemma for the clinician and the pathologist, particularly in small and superficial biopsies.[10] Histologically, both are composed of nests of basaloid cells within the dermis. Although these differences are distinguishable in the majority of cases, there are cases in which distinction is difficult, not least in small and superficial biopsy specimens.[9]

The aim of this study was to compare the expression patterns of CD10 between BCC and SCC and between BCC and TE. Additionally, the usefulness of this marker in the differentiation between these tumors was assessed and CD10 expression was evaluated in different histological subtypes of BCC.

Materials and Methods

Fifty-five cases of BCC, 50 cases of SCC, and 20 cases of benign adnexal tumor with follicular differentiation, including 13 cases of trichoepithelioma and 7 other benign adnexal tumors with follicular differentiation comprising trichoblastoma, trichoadenoma, sebaceoma, pilomatricoma, and pilar tumor were retrieved from the archives of the pathology departments of hospitals affiliated with Shiraz University of Medical Sciences.

The specimens consisted of punch biopsy with adequate tumor tissue and excisional resection. Very tiny punch biopsies and poorly fixed specimens were excluded. H&E sections were reviewed by a dermatopathologist and were determined to be diagnostic cases of SCC, BCC, or other adnexal tumors. We classified 55 BCCs into 5 groups of superficial (1 case), nodular (macro and micro) (38 cases), sclerosing/morpheic (3 cases), keratotic (4 cases), and basosquamous (9 cases).

Immunohistochemistry was performed for all the specimens (125 cases). However, in this study, trichoepithelioma was compared with BCC, which comprised the largest group of adnexal tumors of a follicular origin. This tumor has many overlapping histological features with BCC. Immunohistochemical staining was done on 5-µm sections obtained from formalin-fixed, paraffin-embedded blocks using the avidin-biotin peroxidase complex method. The primary antibody was mouse monoclonal antibody CD10 (Novocastra) (RTU-CD10-2), and the secondary antibody was Envision (K4061, Dako, Denmark).

A judgment by the consensus of two independent observers was made as to the pattern of CD10 expression in all the cases. For each case, 10 fields were examined at high magnification (×400).

Localization of anti-CD10 to the stroma and/or tumor cells was determined in the cases with immunoreactivity as follows: negative (0-<10% positive cells); 1+, regionally positive (10-50% positive cells); and 2+, diffusely positive (>50% positive cells).[8] Reactivity of the tumor cells was analyzed for central and/or peripheral staining. CD10 expression was compared with the positive control (perifollicular or peri-sebaceous gland area).

Statistical Analysis

The data were collected, tabulated, and statistically analyzed, using Statistical Package for the Social Sciences (SPSS). The Fisher

exact and Chi-square tests were employed for comparison between the nominal variables, and the Mann-Whitney U test was used to compare the ordinal variables. A p value less than 0.05 was considered significant for all the tests.

Results

The patients with BCC were comprised of 20 females and 35 males, ranging in age from 34 to 81 years (mean±SD=59±10.98). Most of the BCC cases (53 of 55) were localized in the head region, and 2 of them were in the trunk. The BCC cases were classified into 5 groups. The patients with SCC included 12 females and 38 males, ranging in age from 45 to 85 years (mean±SD=62.02±9.00). Forty out of the 50 cases of SCC were localized in the head and neck and 8 cases were in the extremities; the site of the lesion was not specified in the remaining 2 cases. The patients with TE consisted of 10 females and 3 males, ranging in age from 18 to 70 years (mean±SD=38.38±15.48). Eleven cases of TE were localized in the face, one in the forearm, and one in the knee

Stromal and tumor cell (peripheral and/or central) expression of CD10 in all the cases was graded from [0] to [2+]. A comparison of CD10 expression between the BCC and SCC groups is displayed in table 1 and that between the BCC and TE groups is depicted in table 2. The patterns of CD10 expression in BCC and TE are demonstrated in figures 1 and 2, respectively. Of note, 100% of the SCC and 60% of BCC cases had stromal CD10 reactivity, with strong reactivity in 70% and 18.2% of the SCC and BCC cases, respectively.

Table 1: Comparison of CD10 expression pattern between BCC and SCC groups

Components	Stromal cells			Tumor Cells		
Intensity	**2+**	**1+**	**0**	**2+**	**1+**	**0**
BCC	10 (18.2%)	23 (41.8%)	22 (40%)	19 (34.5%)	23 (41.8%)	13 (23.6%)
SCC	35 (70%)	15 (30%)	0 (0%)	0 (0%)	0 (0%)	50 (100%)

Table 2: Comparison of CD10 expression pattern between BCC and TE groups

Components	Stromal cells			Tumor cells		
Intensity	**2+**	**1+**	**0**	**2+**	**1+**	**0**
BCC	10 (18.2%)	23 (41.8%)	22 (40%)	19 (34.5%)	23 (41.8%)	13 (23.6%)
TE	12 (92.2%)	1 (7.8%)	0 (0%)	0 (0%)	0 (0%)	13 (100%)

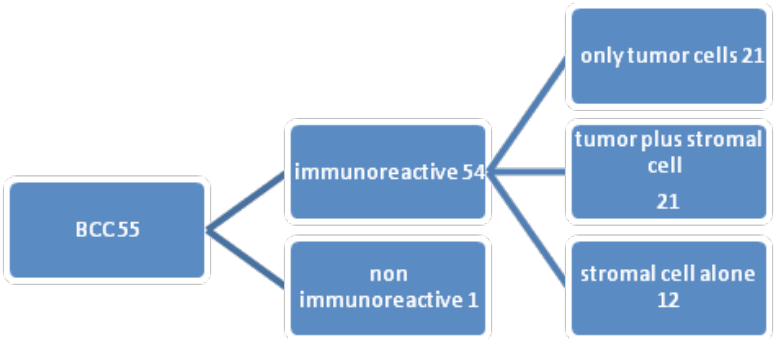

Figure 1: CD10 staining patterns of 55 cases of basal cell carcinoma (BCC).

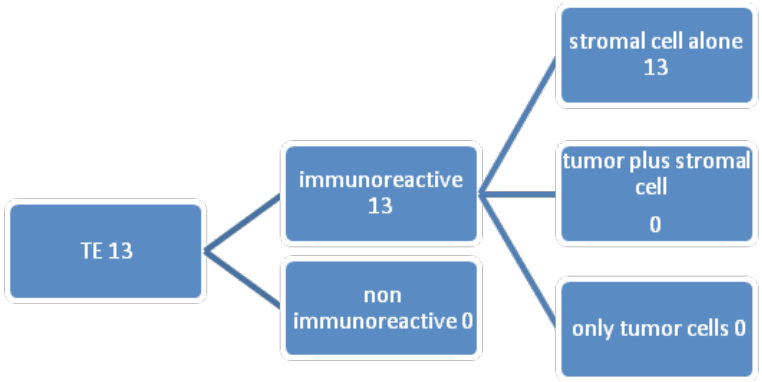

Figure 2: CD10 staining patterns of 13 cases of trichoepithelioma.

Stromal reactivity of the SCC cases is presented in figure 3. In 5 (10%) of these cases, immunoreactivity was detected in the tumor cells at the center of the epithelial nests. The reaction was focal in less than 10% of the tumor cells and was, thus, considered negative. All (100%) of the TE cases had stromal reactivity (figure 4). The patterns of CD10 expression in the epithelial component of 31 (56%) BCC cases were peripheral (figure 5), 3 (5.4%) central, and 8 (14.5%) diffuse. The patterns of CD10 staining in the epithelial component of the various subtypes of BCC are presented in table 3. The dominant pattern of staining was peripheral in keratotic (80.0%) and nodular (macro and/or micro) (60.5%). However, there was no significant difference in CD10 expression between the various subtypes of BCC. A comparison of CD10 expression between the BCC and SCC groups revealed a significant difference (P<0.001) in both tumor and stromal cells. There were two cases diagnosed in H&E as trichoblastoma; nonetheless, CD10 staining showed only epithelial staining in the outermost basaloid cells, similar to the other typical cases of BCC.

None of the TE cases had tumor cell expression of CD10. There was a significant difference in CD10 expression between the TE and BCC groups in the tumor (P<0.001) and stromal cells (P<0.001).

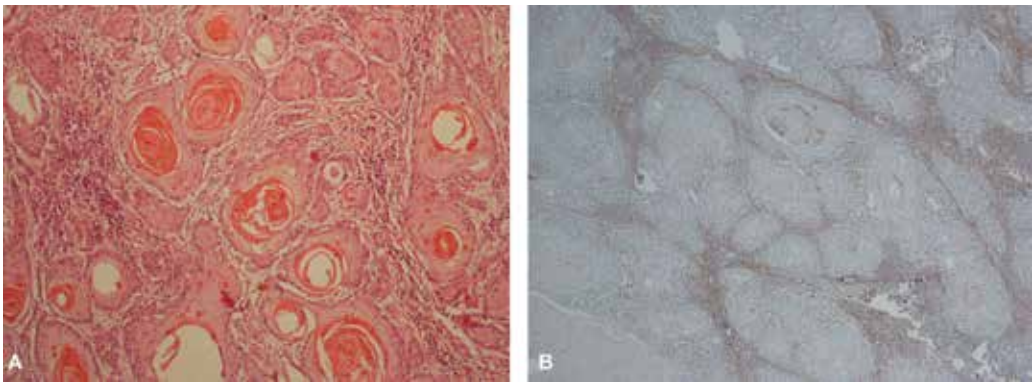

Figure 3: (A) Well-differentiated squamous cell carcinoma (H&E, ×100), (B) 2+stromal CD10 immunoreactivity and non-specific positivity in some of keratin pearls (×100).

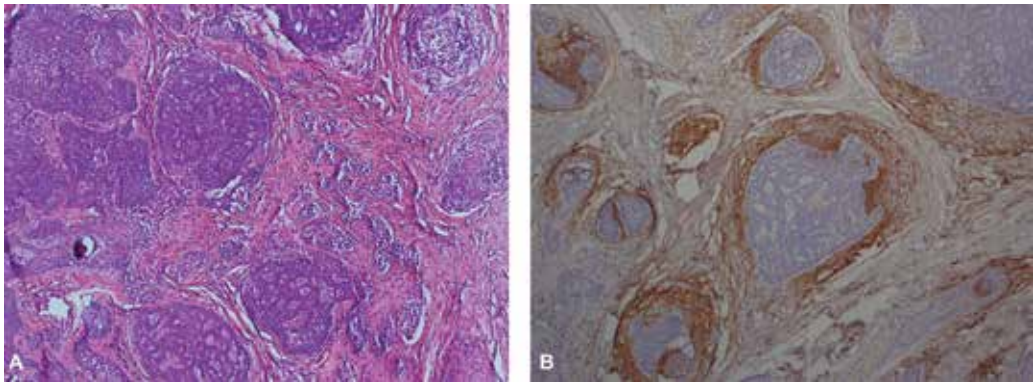

Figure 4: (A) Trichoepithelioma (H&E, ×100) and (B) 2+stromal immunoreactivity for CD10 at the periphery of tumor nests in trichoepithelioma (×100).

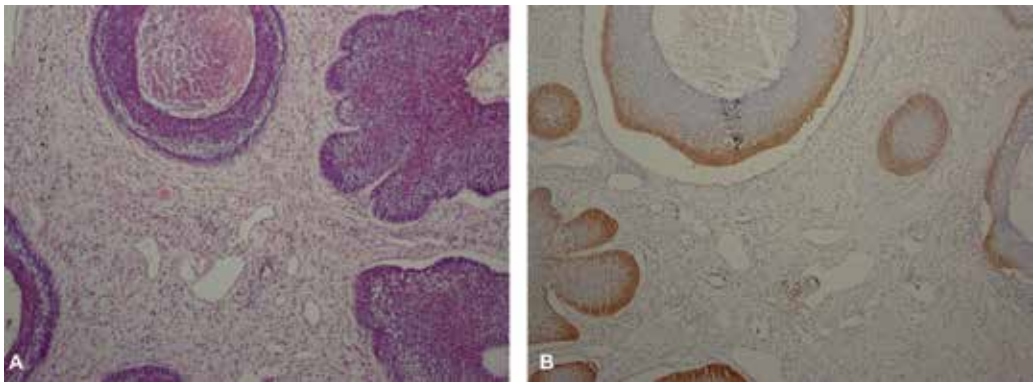

Figure 5: (A) Basal cell carcinoma, nodular type (H&E, ×100) and (B) 2+peripheral expression of CD10 in BCC (×100).

Table 3: Patterns of CD10 staining in the epithelial component of various subtypes of BCC

Subtypes \ Pattern	Peripheral	Central	Diffuse	Negative	Total
Nodular	23 (60.5%)	2 (5.3%)	6 (15.8%)	7 (18.4%)	38
Superficial	1 (100%)	0	0	0	1
Sclerosing/morpheic	0	1 (33.3%)	0	2 (66.7%)	3
Keratotic	4 (100.0%)	0	0 (0.0%)	0	4
Basosquamous	3 (33.3%)	0	2 (22.2%)	4 (44.5%)	9
Total	31	3	8	13	55

Discussion

CD10 is deemed a useful immunohistochemical marker in the differentiation between BCC and SCC. In cases of positive CD10 in tumor cells, the diagnosis tends to be most likely BCC rather than SCC; this is clinically important because BCC is not as aggressive as SCC.[4] In our study, CD10 was expressed diffusely in the stromal cells around the tumor nests of all the SCC cases.

Our study has an advantage over previous studies insofar as it investigated a large number of BCC and SCC cases and also included basosquamous cases. Furthermore, it is the only study of its kind to present the expression patterns of CD10 not only in BCC by comparison with SCC but also in BCC in comparison to TE. The comparison of the CD10 expressions between our SCC and BCC groups showed a significant difference between the CD10 expressions in the tumor cells ($P<0.001$) as well as stromal cells ($P<0.001$).

One previously conducted study, performed on 16 SCC cases and 17 solid, 2 morphoeic, and 2 adenoid types of BCC, concluded that the absence of CD10 expression in the tumor cells of SCC and infiltrating BCC and overexpression in the stromal cells might be due to the invasive properties of these tumors.[4] In the present study, there was no significant difference in CD10 expression between the stromal and tumor cells of the BCC subtypes, which may be due to the small number of the subtypes in this study.

Although CD10 has been implicated in the pathogenesis of various lung and lymphoid neoplasms, further studies aiming at defining the exact role of CD10 in the pathogenesis of BCC and SCC as well as a study of an expanded number of these tumors are needed prior to adopting its application in the routine evaluation of these occasionally difficult cases.[6]

In another study, strong CD10 expression in the tumor cells of superficial BCC was mentioned to be probably in consequence of the indolent nature of these tumors, while lower levels of CD10 expression in the tumor cells were found in aggressive variants of BCC.[5] One case of superficial BCC in our study exhibited strong CD10 expression of the tumor cells at the periphery of the tumor nests. One study reported the usefulness of CD10 for differential diagnosis between benign tumors of cutaneous appendages originating from the hair follicle and BCC as an immunohistochemical marker, especially in the small and superficial biopsies. Condensation of CD10-positive stromal cells was shown around basaloid nests, which was statistically significant in differentiating TE from BCC. Conversely, CD10-positive basaloid cells were seen predominantly in BCC. No BCC cases demonstrated stromal expression alone in that study, including only the nodular type. The expression of CD10 by peritumoral stroma alone favored a diagnosis of TE, whereas staining of basaloid cells supported a diagnosis of BCC.[10]

The results of the present study also showed a significant difference in CD10 expression between the TE and BCC groups in the tumor cells and stromal cells, while stromal expression alone occurred in 12 BCC cases. The results of a similar study showed that Bcl-2 failed to differentiate between trichoblastoma and BCC with follicular differentiation. In contrast, CD10 proved very useful for the detection of areas of basocellular proliferation with follicular differentiation, which could be misinterpreted as trichoblastoma. Consequently, it could help the pathologist to identify lesions of different malignancy in patients who are likely to benefit from a more suitable treatment.[11] Elsewhere in the literature, one study retrieved 30 cases of benign tumors of cutaneous appendages originating from the hair follicle and 30 cases of BCC. The stromal CD10 immunopositivity of the benign tumors of the cutaneous appendages originating from the hair follicle was stronger than that of the BCC cases ($P=0.003$) with respect to both the numerical and the degree of expression. However, the peripheral CD10 of the BCC cases was stronger than that of the benign tumors.[10]

In the current study, we found that all TE cases demonstrated strong CD10 staining of the stromal cells with accentuation around the tumoral nests, but no TE tumor cell staining. In another study,

the CD10 expression pattern was analyzed in 23 cases of nodular type BCC and 13 cases of TE. CD10 expression by peritumoral stroma alone favored a diagnosis of TE, whereas staining of basaloid cells supported a diagnosis of BCC.[9] In our BCC group, expression of CD10 by tumor cells was observed in 42 out of 55 cases (76%) with mostly peripheral staining (61%). Diffuse stromal only staining for CD10 was witnessed in 12 cases of the 55 BCCs (21%), 4 of them being basosquamous cell carcinoma. This finding does not chime in with the Pham et al. study,[9] in which no "stromal cell alone" staining was seen in a total of 23 BCC cases. Their study contained a smaller number of cases and did not include basosquamous cell carcinoma. In our study, two cases were diagnosed as trichoblastoma, a tumor commonly mistaken for nodular BCC. CD10 staining of these two tumors showed only epithelial staining in the outermost basaloid cells, similar to the typical cases of BCC. In one study, there was a large number of trichoblastoma diagnosed with hematoxylin and eosin, which were reclassified as BCC and BCC-FD with CD10 immunostaining.[11] The authors stated that this pattern might reflect the differences in stromal expression between the two lesions, which may be a result of the different regulation of tumor growth or host response.[11]

Eighteen cases of morphoeic basal cell carcinoma and 19 cases of desmoplastic trichoepithelioma were studied by Costache et al.[12] who concluded that the expression of CD10 was a reliable indicator for the diagnosis of morphoeic basal cell carcinoma only when the expression was present in the aggregations of cells, whereas stromal reactivity was not a useful marker for differentiation. We did not have a desmoplastic type of TE. Be that as it may, one out of three cases of morphoeic basal cell carcinoma showed epithelial staining. Our study also showed that stromal reactivity may not be a useful marker for differentiation.

CD10 is also regarded as a myoepithelial-specific marker; and in some studies, it is described as involving benign eccrine tumors. Bahrami,[13] showed that CD10 was beneficial in distinguishing metastatic cutaneous renal cell carcinoma from skin tumors with eccrine and apocrine differentiation, but not tumors with sebaceous differentiation. Recently, the expression of CD10 has been reported in a variety of epithelial and mesenchymal neoplasms. CD10-positive epithelial neoplasms include renal cell carcinoma, hepatocellular carcinoma, urothelial carcinoma, and prostatic carcinoma.[8,14]

CD10 has been allied to tumor progression and metastasis in different tumors. For example, a significant positive relationship has been found between CD10 expression and Breslow thickness, Clark level, and ulceration in malignant melanoma.[15]

In the oral cavity SCC, CD10 stromal positivity is correlated with the presence of metastasis, local recurrence, and high tumor grade.[16] In one study, CD10 expression was investigated in 20 cases of cutaneous SCC of different grades (well, moderately, and poorly differentiated), and the authors concluded that 1) stromal expression of CD10 is not lost in deeply invasive SCC, as previous literature suggested; and 2) lack of cytoplasmic expression of CD10 by cutaneous SCC can be considered as an additional prognosis factor to investigate in the future.[17] In another study, CD10 was expressed in the stromal cells of a total of 9 SCC cases.[8] In the current study, immunoreactivity was detected in the stromal cells of all the 50 SCC cases. Nevertheless, in the tumor cells at the center of the epithelial nests, immunoreactivity was detected in 5 cases (10%), which were placed focally in less than 10% of the tumor cells.

In future studies, we aim to investigate CD10 expression in SCC groups of low and high risk according to the degree of differentiation, size, and depth of invasion (perineurial and lymphovascular invasion).[18] CD10 expression will be compared between these groups.

Conclusion

The present study showed a statistically significant difference in the CD10 staining pattern between TE and BCC. Condensation of CD10-positive stromal cells around basaloid nests favors TE over BCC. Thus, CD10 is a useful adjunct marker in distinguishing these tumors. We would suggest that CD10 may be a useful marker to differentiate between BCC and SCC in difficult cases. CD10-positive tumor cells would favor BCC over SCC.

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