RESEARCH COMMUNICATION

Differential Diagnosis of Basal Cell Carcinoma and Benign Tumors of Cutaneous Appendages Originating from Hair Follicles by Using CD34

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Abstract

Background and Aims: Differential diagnosis of the group of benign trichoblastomas, trichofolliculomas, trichoadenomas and trichoepitheliomas, and basal cell carcinomas (BCCs) is troublesome for the clinician as well as the pathologist, especially when only small biopsy specimens are available. Here we investigated whether CD34 expression might be of assistance. Methods: Thirty benign tumors of cutaneous appendages originating from hair follicles (BTCOHF) and 30 BCCs were retrieved from our archives and immunohistochemically stained. CD 34 expression was graded from [0] to [2+] and compared among the groups and subgroups. Results: There was no significant difference between the degree of expression between [0] and [1+] and [0] and [2+] for each group. However, [1+] and [2+] immunopositivity of BTCOHFs was significantly stronger than in BCCs (p= 0.014). Conclusions: CD34 may contribute to differential diagnosis of skin lesions.

Keywords: Basal cell cancer - hair follicle lesions - CD 34 immunohistochemistry

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Introduction

Ackerman et al classified benign tumors of cutaneous appendages originating from hair follicle (BTCOHF)'s using eight textbooks of dermatopathology in 2001 as germ tumors of hair follicle and hamartomas, infindubular and isthmic tumors, tumors of external layer, tumors originating from matrix layer, and prominent perifollicular mesenchymal tumors (Ackerman et al., 2001; Weedon and Strutton, 2002). In the 2003 Classification of World Health Organization (WHO) division was into two main subgroups as, benign tumors including trichoblastoma (TB), pilomatrixoma, tricholemmoma (TL), multipl TL, trichofolliculoma (TF), and fibrofolliculoma/ trichodiscoma; malignant tumors consisting pilomatrix carcinoma and proliferated tricholemmal tumor (Cotton et al., 1991).

Nevus of hair follicles are rare hamartomas consisting of hypertrichosis localising on the head and neck region as small nodules and it may be confused with trichofolliculoma (TF) (Mehregan, 1985; Ackerman et al., 2001). The essential feature of TFs are rare tumors having numerous hair follicle structures around the infindubulum in the manner of "caput medusa" in the fibrotic stroma (Simpson, 1989; Ackerman, 2001). Trichoadenoma (TA) is a rare tumor, firstly determined by Nikolowski (1958) in 1958. TAs occur as a nodular lesion usually on the face and buttocks (Rahbari et al., 1977, Swaroop et al., 2008) and have a variant of verrucous TA mimicing seboreic keratosis.

Trichoepithelioma (TE) is a benign skin tumor with follicular differentiation determined in the classification of WHO as the synonym of TB (Cotton, 1991). TB can be differed from TE via size, localisation, and lacking of keratinized cysts. These lesions are also benign and the aggressive forms of it resembles a kind of basal cell carcinoma (BCC) (Headington 1976; Davis and Cohen, 1996; Abesamis-Cubillan et al., 2000). Besides, they potentially tend to metastasize (Schulz 2005; Schulz et al., 2005; Alsaad et al., 2007).

BCC was firstly determined by Jacob in 1827 as "ulcer localizing on the face and the eyelids" and the term of "ulcus rodens" was used in 1851. Krompecher detected that the lesion was originating from the cells of basal layers of the epidermis (Miller, 1995; Chan et al., 1999; Noguchi et al., 1999).

Skin cancers are the third frequent type of whole cancers in Turkey with an incidence of 18.9 per 100 thousand (Yilmaz et al., 2010). Moore et al designated that cancer and related lifestyle diseases are on the increase across Asia and already account for over half the disease-associated mortality in the vast majority of

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the included countries (Moore et al., 2010). However, BCC is the most common malignancy worldwide in white people (Miller, 1995) and accounts for 65-75 % of all skin tumors (Ionescu et al., 2006). It originates from epidermis and pluripotential primordial germ cells in basal layers of cutaneous appandages and morphologically mimics the structure of hair follicle (Chan et al., 1999; Noguchi et al., 1999). While having red or blond hair, green or blue eyes phenotypically and getting a suntan difficultly are some kinds of risks for BCC (Wong et al., 2003; Crowson, 2006); the most important exogen factor is being exposed to ultraviolet (UV) radiation (Gallagher et al., 1995; Lear et al., 1998; Maarten et al., 1998; Wong et al., 2003; Crowson, 2006; Roewert-Huber et al., 2007). It is thought that ultraviolet (UV) B radiation (290-320 nm, wavelength) is more effective than UVA radiation (320-400 nm, wavelength) (Roewert-Huber et al., 2007). Recently Ulrich et al reported that regular use of sunscreens, as part of a consequent UV-protection strategy, may prevent the development of further actinic keratoses, and invasive squamous cell carcinoma and, to a lesser degree, BCC in immune-compromised organ transplant recipients in their 24 months prospective case-control study (Ulrich et al., 2009).

Differential diagnosis of BCC have a very wide spectrum due to it can improve differentiation on various directions. TE and TB are the tumors of cutaneous appandages which may confused with BCCs originating from abortive hair papilla formation which consist of basal cell islands with regular border in the dermis and pallisading on the periphery and having papillary mesenchymal corpuscle formation (Sloane, 1977). There are more mitoses and apoptotic cell necrosis in BCC than both TE and TB (Crowson, 2006).

CD34 is a 115 KD intercellular adhesion protein and cell surface glycoprotein expressing in the immature hematopoietic cells and endothelial cells. It is very useful in the differential diagnosis of such tumors of solitary fibrous tumor (CD34 [+]), desmoplastic mesothelioma (CD34 [-]), hemangiopericytoma (CD34 [+]), endometrial stromal sarcoma (CD34 [-]) and thymoma rich in differentiated lymphocyte (CD34 [+]). CD34 expressed in endothelial cells of the normal skin, perivascular interstitial dendritic cells of reticular dermis, around the hair follicle, and spindle cells in basal membrane zones of eccrine glands (Nickoloff, 1991; Kanitakis, 1999; Naeyaert et al., 2001).

Differential diagnosis of TA, TF, TE and TB from BCC may be troublesome for the clinician as well as the pathologist, particularly in the presence of small specimens. Thus, we purposed to compare the immunoreactivity patterns of BTCOHF and BCC by using the marker of CD 34 in this study is the first one regarding as a group of BTCOHF in literature to our kowledge.

Materials and Methods

Case Selection

The investigation conforms to the principles outlined in the appropriate version of 1964 Declaration of Helsinki and approval of the present study received by The Ethics Committee of Ankara Education and Research Hospital.

30 cases of BTCOHF (21 TE (Group 1a), 70%; 5 TB (Group 1b), 16.6%; 2 TA (Group 1c), 6.7%; 2 TF (Group 1d], 6.7%) and 30 cases of BCC were retrieved and analysed from the archives of Department of Pathology at our hospital where the cases of BTCOHF had been deposited between 2004 and 2008. The punch biopsies and incisional biopsies, not enclosing the neighboring epidermis and dermis were not included in the study.

BCCs were classified as 18 noduler (Group 2a, 60%), 4 superficial (Group 2b, 13.3%), 2 infiltrative (Group 2c, 6.7%), and 6 mixed (Group 2d, 20%) containing two or more types together. The immunoreactivities of CD34 are comparatively evaluated between both groups of BTCOHF and BCC totally and between all each subgroups belong to same group.

Immunohistochemistry

Formalin (10% solution; PH 7.0-7.6) fixed, parafin-embedded tumoral tissues are prepared for the immunohistochemical evaluation. Afterwards, a pair of 4 μm sections of placed on slides is covered by poly-L lysine fo each case. The original H&E stained slides were detained for comparision with immunostained sections. The tissue sections were dried for 12 hours in a 37°C oven and then deparaffinized with xylene and rehydrated through graded alcohols. Antigen retrieval was performed by heating them under pressure for 9 min under pressure in citrate buffer (Scy Tek Laboratories, Logan, Utah, USA). The sections placed in aforementioned solutions for 20 min at room temperature were then taken into phosphate - buffered saline (PBS) solution. Endogenous peroxidase was inhibited by incubation with 1% H_2O_2 for 15 minutes. After washing of samples in PBS, they were incubated with sUltra V Block (Scy Tek Laboratories, Logan, Utah, USA) to hinder non-specific binding. Each pair of the sections were incubated for 1 hour with mouse monoclonal antibody of anti CD34 (Ab-1 clone QBE and / 10 Neomarkers Fremont, CAS, USA) as primary antibodies at room temperature. Additional washing with PBS by four times performed and followed by biotinylated ultratech - anti - polyvalent antibody (Scyteck) for 20 min as a seconder antibody. They were washed again in PBS and were added them DAB (Scy Tek Laboratories, Logan, Utah, USA) chromogene / substrate KIT for 5 min. The sections were counterstained with H&E, then dehydrated in alcohols and cleared in xylene, and lastly balsam performed onto them and coverslip was mounted. Sections of the tonsil for CD34 were used for positive controls (i6000 automatical staining system Biogenex) were performed for each case.

Evaluation and Statistical Analysis

All specimens were examined under a light microscope and the amount of immunupositive tumor cells and stromal cells were evaluated by using a scale of [0] to [2+] as follows: [0], negative (<10 % positive cells); [1+], regionally positive (10 - 50 % positive cells); [2+], diffusely positive (> 50 % positive cells). For the statistical analysis SPSS - 13.0 is a statistical programme is based on computer. All the datas were expressed as means

± standard errors of means (SEM). In the analysis of numerical variants Student T test, for comparing rational datas Pearson chi-square and Fisher's Exact tests were used at suitable areas. Pearson correlation analysis was used for the relationship between the numerical datas and p - value less than 0.05 was considered significant for all the tests.

Results

The expression of CD34 in both tumors was graded from [0] to [2+] for each case. While stromal expression of CD34 in BTCOHF was observed adjacent to external surface of tumoral islands; in BCC it was not (Figures 1, 2). 9 of 30 cases (30%) of BCC and 5 of 30 cases of BTCOHF (16.7%) had [0] immunoreactivity with CD34, so 21 of 30 cases F were stained with CD34. Besides, 10 of 30 cases (33.3%) of BCC and 3 of 30 cases of BTCOHF (10 %) had [1+] immunoreactivity of CD34. 22 of 30 cases (73.3%) of BTCOHF (36.7%) and 11 of 30 cases of BCC had [2+] immunoreactivity of CD34 (Figure 3). There was no significant difference between the degree of expression between [0] & [1+] and [0] & [2+] for each group. However, the degree of expression between [1+] & [2+] for BTCOHF was significant.

Patients with BTCOHF (14 females and 16 males) were ranged in age from 26 to 74 years (Median, 61.4±14.4) and patients with BCC (12 females and 18 males) were ranged in age from 34 to 85 years (Median, 64.6±10.9). Though both tumor groups localised on the area of head; BTCOHFs were frequently staged on the nasal area and BCCs on eye circumference.

CD34 immunopositivity of BTCOHF was significantly stronger than BCC regarding as both the numerical and the degree of expression (p= 0.014). CD34 expression of subgroups of both groups are summarized in Table 1 and 2 and there was no significant diference between them.

Discussion

Differentiating BCC which can metastasize (even very rare (0.0028%-0.55%)), exhibit local aggressiveness or recurrences (5% for 5-year survival), account for accounts for 65-75% of all skin tumors and is the most common malignancy worldwide in white people from BTCOHF which is seen more seldomly have been being very difficult to date (Miller, 1955; Brenn and Mc Kee, 2005; Ionescu et al., 2006; Tiftikçioğlu et al., 2006).

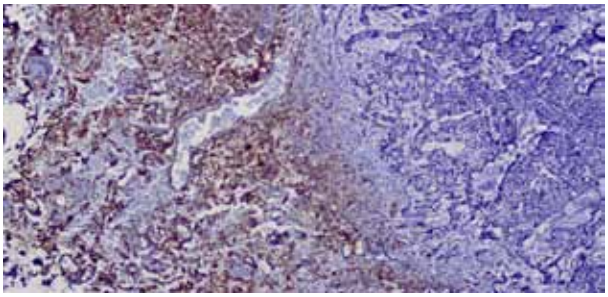

Figure 1. Stromal Expression [2+] of CD34 for BCC

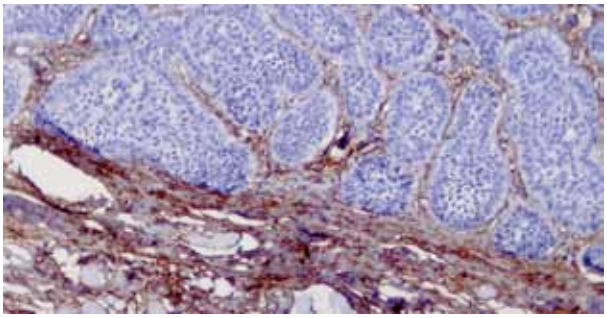

Figure 2. Stromal Expression [2+] of CD34 for TE

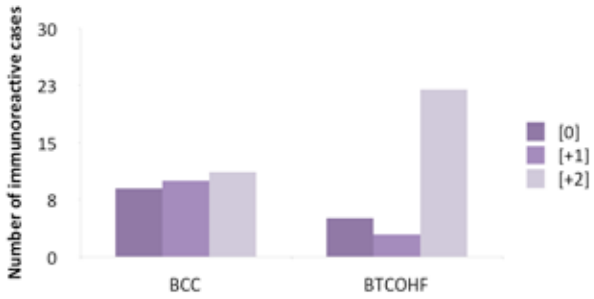

Figure 3. Comparison of the CD34 Staining Patterns of BTCOHFs and BCCs

Kirchmann et al stained 19 cases of BCC including 10 nodular, 6 superficial and 3 desmoplastic; and 16 cases of TE comprising 15 soliter, 1 desmoplastic with CD34 in their study. They observed that while the spindle-shaped cells surrounding the islands of trichoepithelioma cells were focally strongly positive for CD34; surrounding the nests of tumor cells were negative in all basal cell carcinomas. So they suggested that, CD34 staining pattern differentiates between trichoepithelioma and basal cell carcinoma and it may be helpful in discerning between these two tumors particularly on small punch

Table 1. The Comparision of the Staining Patterns of Subgroups of BTCOHF with CD34

Staining with CD34	TE	TB	TA	TF	p
	n:21	n:5	n:2	n:2	
0	3 (14.3%)	2 (40%)	-	-	
1	3 (14.3%)	-	-	-	0.653
2	15 (71.4%)	3 (60%)	2 (100%)	2 (100%)	

Table 2. Comparision of Staining Patterns of the Subgroups of BCC with CD34

Staining with CD34	Nodular	Superficial	Infiltrative	Mixed	p
	n:18	n:4	n:2	n:6	
0	4 (22.2%)	2 (50%)	1 (50%)	2 (33.3%)	
1	8 (44.4%)	1 (25%)	1 (50%)	-	0.368
2	6 (33.4%)	1 (25%)	-	4 (66.7%)	

biopsies or in difficult diagnostic cases (Kirchmann et al., 1994). Illueca et al strengthened the results of that first study about CD34 expression as the differentiating agent (Pham, 2006). Naeyaert et al compared the CD34 staining patterns of TE with Pincus tumor (fibroepithelioma) and nodular BCC are the variants of BCC. They also did not detect the peritumoral stromal expression of CD34 in that variants of BCC (Naeyaert et al., 2001). However; Verhaegh et al deteced the CD34 expression adjacent to the 2 of 5 tumoral islands of BCC (Verhaegh et al., 1997) and Basarab et al., 1998 observed the immunoreactivity in peritumoral stroma for 20 % of TE and 7 % of BCC (Basarab et al., 1998). Then, Swanson et al detected the stromal immunopositivity of CD34 in 20 of 36 cases of TE and 6 of 43 cases of BCC (Swanson et al., 1998).

Papillary mesenchymal bodies may be stained with CD34, p27kip1, bcl - 2 and S100 in variable ratios (Wallance and Smoller et al., 1997; Cesinaro et al., 2002). While CD34 stains stroma in TE and TB, it stains surface of external layer of tumoral islands in BCC in plenty of studies (Kirchmann et al., 1994; Bryant and Penneys, 1995; Swanson et al., 1998; McNiff et al., 1999; Poniecka and Alexis, 1999). TE demonstrated CK5, 6, 7, 14, 17, 15 expression, but BCC not (Sloane, 1977). Besides, bcl - 2 stains peripherally pallisading cells in TE, but diffusely staining is seen in BCC (Yamamoto and Asahi, 1999, Abdelsayed et al., 2000; Corrêa Mde et al., 2009). Recently androgen receptors are used for differential diagnosis. While androgen receptors and BerEP4 stains all types of BCC, not nonbasaloid squamous cell carcinoma (Carr and Sanders, 2007; Fan et al., 2007). Besides, Yu et al reported that BerEP4 labeling is not reliable in superficial biopsies of BCC with squamoid features (Yu et al., 2009).

In the present study, we determined stromal expression of CD34 for 25 (83.3 %) of 30 cases in BTCOHF and 9 (30 %) of 21 (70 %) in BCC. While stromal expression of CD34 for BTCOHF was observing just the adjacent to the tumoral islands; it was not like that for BCC. There was CD34 expressions in the surrounding stromas of BCCs with the adjacent zones which were not stained with CD34. The significant difference was detected between two groups concerning both the numerical and degree of staining; but not between subgroups. Stromal differences of BTCOHF such grooving dissimilarities, fibronectin, musin production of glucoseaminoglycan, and mesenchymal bodies may cause that different staining pattern with BCC. Although there are incompatible results in some investigations; CD34 is one of the essential markers for differential diagnosis is based on immunhistochemical technique

In conclusion we can suggest that, CD34 may be useful for the differential diagnosis between BTCOHF and BCC as an immunuhistochemical marker. So, CD34 may contribute to go beyond the dilemma for pathologists and also for the other clinicians especially in the small and superficial biopsies. So, especially in small specimens, one may only differ BCC from BTCOHF via using CD34, while histopathology is almost same. According to our point of view, searching to immunoreactivity of CD34 may even be a life-saving method for the selected cases. In the current study, limited number of the cases was the handycap. Notwithstanding; varied immunological markers, different research techniques, and the larger series are necessary for the accurate diagnoses.

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