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ORIGINAL ARTICLE

Value of CD_{10} in Differentiating between Keratoacanthoma and Squamous cell carcinoma

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ABSTRACT
Keratoacanthoma (KA) is a common skin neoplasm characterized by rapid growth and histologic pattern similar to squamous cell carcinoma (SCC). SCC is the second most common skin cancer around the world that can provide metastases. According to different prognoses diagnosis of both disease requirements, there are not the clinical or histopathologic criteria for differentiating accurate between these two diseases. CD_{10} is a width membrane glycoprotein that is associated with cell growth rate. This expression increases in generating tissues and malignant tumors. This study was done to determine the expression of CD_{10} in the differential diagnosis between KA and SCC in tumoral and stromal cells. Study was done in 15 cases of KA and 15 cases of SCC. The CD_{10} immunohistochemical staining was performed with H&E, reviewed and those have definite pattern of KA or SCC were enrolled. The expression of this marker in tumoral and stromal cells of 15 SCC cases respectively was,12 (80%) and 1 (6.7%) cases had negative expression, 3 (20%) and 3 (20%) cases had low expression and 0 (0%) and 11 (73.3%) cases had a high expression, also this expression in 15 Keratoacanthoma cases respectively was, 7 (46.7%) and 8 (53.3%)cases a negative expression, 7 (46.7%) and 4 (26.7%) had a low expression and 1 (6.7%) and 3 (20%) cases, had high expression. These results suggests when the diagnosis of SCC cases from KA was not differentiated, the negative CD_{10} in tumoral cells and positive CD_{10} in stromal cells is an indicator of SCC.
Keywords: *Keratoacantoma, Squamous cell carcinoma, Immunohistochemistry, CD_{10}*

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INTRODUCTION

Invasive squamous cell carcinoma (SCC) is the second most common skin cancer after basal cell carcinoma and causes the majority of deaths among the non-melanoma skin malignancies [1]. SCC is amongst the top 3 common skin cancers [2]. It is a tumor that is locally invasive and which has the capacity to metastasize. Histopathologically, most cases of SCC are readily diagnosable. However, diagnostic challenges are occasionally encountered and contributed mainly by the myriad of histopathologic mimics of SCC and small biopsies that sample only part of the lesion [3]. For the simulators of SCC, on the one hand, there are benign squamous lesions that appear to be infiltrative histopathologically. Misdiagnosis of benign lesions as SCC would result in unnecessarily extensive surgery, while delayed diagnosis of SCC could lead to local tissue destruction by tumor, sometimes metastatic disease, and even death [4].

Keratoacanthomas (KAs) were first described in 1889 [5]. They have also been referred to by other terms such as molluscum sebaceum, molluscum pseudocarcinomatosum, self-healing primary squamous carcinoma and keratocarcinoma [6]. In its pathogenesis, chronic ultraviolet irradiation plays a major role, responsible for DNA mutations (usually in the p53 tumor suppressor gene) in transformed epidermal keratinocytes. However, recently new methods introduces such as CD_{10} for differentiate SCC from KA .

KAs can be difficult to distinguish histologically from conventional SCCs. This has prompted some to consider KAs and SCCs to be the same. Clinically, they are differentiated by their history of rapid growth and their volcano shape, yet histologically, there are too many features that overlap with SCC to allow reliable separation [6]. CALLA (CD_{10}) is expressed in a large percentage of cases of acute lymphoblastic leukemia, follicular lymphoma, Burkitt lymphoma, and some other hematopoietic tumors [7]. In addition, $CD_{10}$is also widely expressed in normal tissues, such as lymphoid precursor cells, the brush border of enterocytes, renal tubules and glomeruli, myoepithelial cells of the breast, hair follicles, eccrine glands, and sebaceous glands [8]. The function of CD_{10} is to reduce cellular response to peptide hormones by regulating local peptide hormone concentrations [9]. There are reports showing that the stromal expression of CD_{10} in cutaneous epithelial neoplasms may be an indicator of malignancy [10]. It is suggest CD_{10} as a useful adjunct marker in distinguishing cutaneous BCC and SCC.
Based on the literature, scarce information exists on role of CD_{10} in the differential diagnosis of the SCC and KA. So, the aim of the current study was to determine role of CD_{10} factor in differentiating between KA and SCC in patients.

MATERIAL AND METHODS

Sampling
This prospective study includes 15 cases of KA and 15 cases of SCC. Cases were collected randomly from archive of pathology department of Imam Khomeini hospital, Ahwaz University of Medical Sciences, Ahwaz, Iran in a one year period from 2015 to 2016.
Staining
Tissue slide sampling was done using H&E staining from all patients (n=15 in each group). Then all slides studied for expression of KA or SCC pattern. Then a 3µm thickness of each sample was put on the poly-L-lysine covered slide for CD_{10} immunohistochemical staining [11]. Then, slides allocated into 60 ºC oven for 60 minutes. After paraphenirezation and rehydration and inactivation of endo-peroxidase the antibody for CD_{10} was done. The brownish cytoplasm or cell membrane was an indicator CD_{10} [11]. Then slides studied for KA or SCC expression using 10HPF microscope. The mean expression for positive detection in tumoral cell (epithelial) or stromal (mesenchyme) was mentioned as described below:
I. <10%: Negative expression
II. 10-50%: Low expression
III. >50%: High expression [11].

Statistical analysis

Data was processed in excel and analyzed using SPSS ver. 21.

RESULTS

The results of value of CD_{10} in differentiating between KA and SCC are presented in figures 1-4 and tables 1 and 2. The distribution of patients based on tumoral expression is presented in figure 1. According to the data (figure 1), the negative tumoral expression was much more frequent among patients. As seen, the negative expression was 27.78 and 33.33% in women and men, respectively. The expression of the low tumoral was 16.67 in both genders. Also, the high expression only detected in women (5.556%).

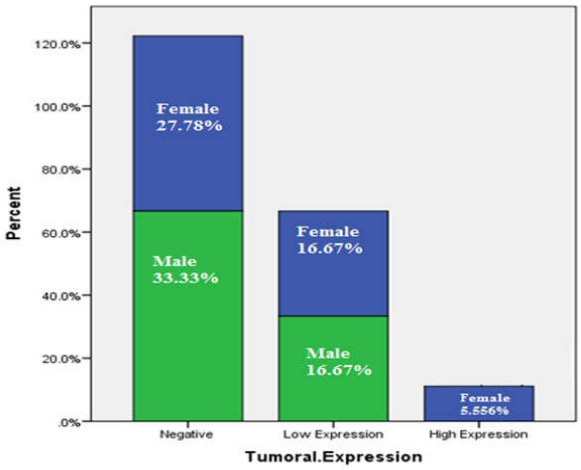

Figure 1. The distribution of patients based on tumoral expression.

As seen in figure 2, the negative expression of SCC was higher in men (56.6%) compared to the women (26.42%) and the low SCC expression was only detected in men (16.98%). Furthermore, the expression of the negative and low KA was 28.77 and 16.44% in women and men, respectively. The high KA expression was detected only in women (9.589%).

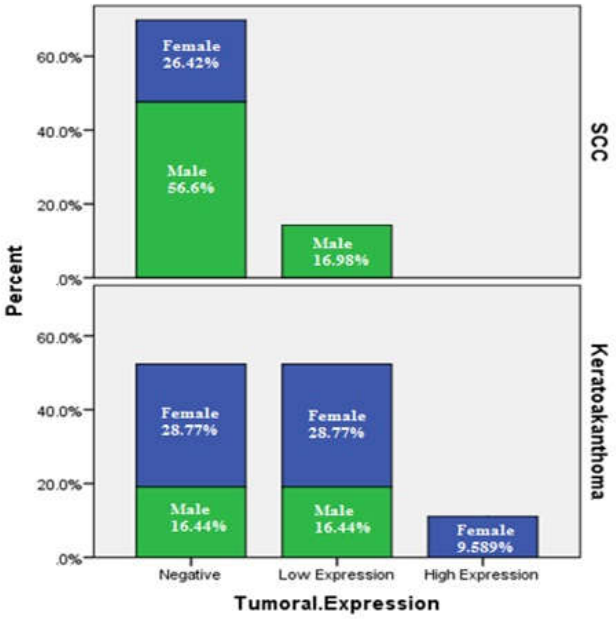

Figure 2. The distribution of patients based on tumoral expression based on the level of expression.

According to the results, the negative expression of the stromal was higher in women (27.78%) compared to the men (9.524%). Also the low expression was 16.67% in women compared to the men (9.524%). Furthermore, the high tumoral expression was detected in men than women, 30.95 vs. 5.556%, respectively (figure 3).

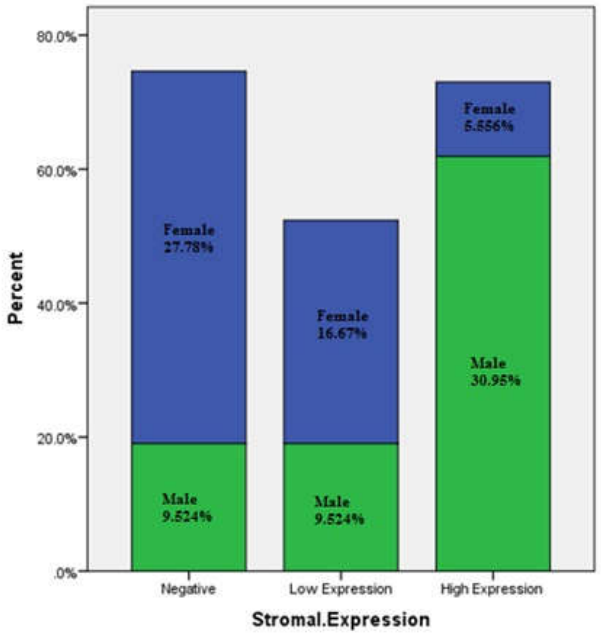

Figure 3. The distribution of patients based on stromal expression

The stromal expression among patients with KA and SCC is shown in figure 4. As seen, the negative SCC was just detected in men (5.66%). The low SCC expression was detected in men (11.32) and women (13.21%). The high SCC expression for man and women were 56.6 and 13.21%, respectively. Furthermore, the negative KA expression was 47.95 and 12.33% for female and male, respectively. Additionally, the low KA expression for male and female were 8.21 and 19.18%, respectively. Also, high KA expression was only detected in men (12.33%).

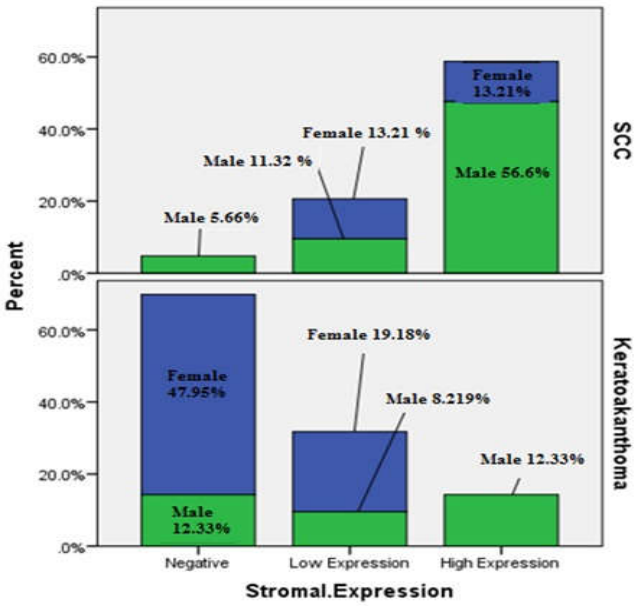

Figure 4. The stromal expression among patients with KA and SCC.
Keratoacanthoma: KA, squamous cell carcinoma: SCC.

The mean of age and age among patients with KA or SCC is provided in table 1. According to the results, the age variation among the patients was approximately uniform in both KA and SCC patients.

Table 1. The mean of age among patients with KA or SCC.

	Sex	Mean	Std.	Min.	Max.
SCC	female	61.5	2.1	60	6
	male	63.4	24.2	13	86
	total	63.2	22.4	13	86
KA	Female	64.1	13.5	50	90
	Male	57	22.1	11	84
	Total	60.3	18.3	11	90
Total	Female	63.5	11.8	50	90
	Male	61	23.1	11	86
	Total	61.7	20.2	11	90

KA: Keratoacanthoma, SCC: squamous cell carcinoma.

In table 2 and 3, the age and sex of the patients for CD_{10} marker in SCC and KA in tumoral and Stromal expression is presented.

Table 2. The mean of the age and sex of the patients for CD10 marker in SCC and KA in Tumoral Expression

	Tumoral Expression	Sex	Mean	Std.	Min.	Max.
	Negative	Female	61.5	2.1	60	63
		Male	67.9	22	13	86
		Total	66.8	20.1	13	86
SCC	Low Expression	Female	48.6	30	14	67
		Total	48.6	30	14	67
	total	Female	61.5	2.1	60	63
		Male	63.4	24.2	13	86
		Total	63.2	22.4	13	86

	Negative	Female	67.3	20.5	50	90
		Male	48	27.6	11	78
		Total	56.2	25	11	90
KA	Low Expression	Female	60.6	9.7	50	69
		Male	66	12.6	55	84
		Total	63.7	10.9	50	84
	High Expression total	Female	65	.	65	65
		Total	65	.	65	65
	Total	Female	64.1	13.5	50	90
		Male	57	22.1	11	84
		Total	60.3	18.3	11	90
Total	Negative	female	65	14.8	50	90
		Male	62.2	24.5	11	86
		Total	62.9	22	11	90
	Low Expression	female	60.6	9.7	50	69
		Male	58.5	21.6	14	84
		Total	59.2	18.2	14	84
	High Expression	female	65	.	65	65
		Male	65	.	65	65
	total	Total	63.5	11.8	50	90
		male	61	23.1	11	86
		total	61.7	20.2	11	90

Table 3. The mean of the age and sex of the patients for CD10 marker in SCC and KA in Stromal Expression

	Stromal Expression	Sex	Mean	Std.	Min.	Max.
SCC	Negative	Male	14	.	14	14
		Total	14	.	14	14
	Low Expression	Female	60	.	60	60
		Male	78	7.7	73	84
		Total	72.3	12	60	84
	High Expression	Female	63	.	63	63
		Male	65.4	21.2	13	86
		Total	65.1	20.1	13	86
	Total	Female	61.5	2.1	60	63
		Male	63.4	24.2	13	86
		Total	63.2	22.4	13	86
KA	Negative	Female	67.2	14.5	50	90
		Male	66.3	15.5	55	84
		Total	66.8	13.7	50	90
	Low Expression	Female	56.5	9.1	50	63
		Male	58	9.8	51	65
		Total	57.2	7.8	50	65
	High Expression	Male	47	33.7	11	78
		Total	47	33.7	11	78
	Total	Female	64.1	13.5	50	90
		Male	57	22.1	11	84
		Total	60	18.3	11	90
Total	Negative	Female	67.2	14.5	50	90
		Male	53.2	29	14	84
		Total	61	21.8	14	90
	Low Expression	Female	57.6	6.8	50	63
		Male	68.2	13.8	51	84
		Total	63.7	11.9	50	84
	High Expression	Female	63	.	63	63
		Male	61.1	24.3	11	86
		Total	61.2	23.4	11	86
	Total	Female	63.5	11.8	50	90
		Male	61	23.1	11	86
		Total	61.7	20.2	11	90

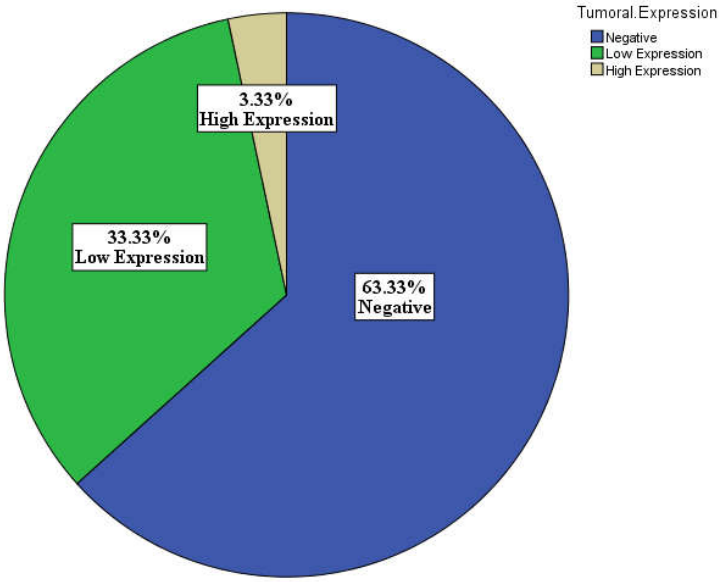

Figure 5. The stromal expression among patients with KA and SCC

DISCUSSION

According to the results, the negative expression of CD_{10} in tumoral and stromal cells of SCC cases were 12 (80%) and 1 (6.7%), Also, low expression 3 (20%) and 3 (20%) and high expression 0 (0%) and 11 (73.3%). The negative expression of CD_{10} in KA group was 7 (46.7%) and 8 (53.3%) negative expression, 7 (46.7%) and 4 (26.7%) cases with low expression and 1 (6.7%) and 3 (20%) cases had high expression, respectively. These results suggests when the diagnosis of SCC cases from KA was not differentiated, the negative CD_{10} in tumoral cells and positive CD_{10} in stromal cells is an indicator of SCC.

CD_{10} is a 90-110-kDa cell surface zinc dependent metalloprotease that has been called neutral endopeptidase, enkephalinase, neprilysin and common acute lymphoblastic leukemia antigen [11]. It can be detected in the per-tumoral fibroblast-like stromal cells within the invasive area of various cancers such as prostate, breast, colorectal and lung carcinomas [12]. Once a carcinogenetic process takes place, breast cancer cells may gradually induce the CD_{10} stromal cells as a coordinated invasive and metastatic partner. This notion may be in accordance with the recent report by Iwaya *et al*. [12] that showed that the stromal CD_{10} expression was a significant predictor of clinical outcome in invasive breast carcinomas. CD_{10} may be induced by the cancer cells through soluble factors similar to other metalloproteinase family members.

Nowadays, Immunohistochemistry has become an important diagnostic tool in dermatopathology. With regard to CD_{10} expression, some authors suggest that CD_{10} may be an indicator of tumor invasiveness if expressed in stromal cells, while it may be a marker of follicular differentiation if it is expressed in the epithelium of tumors [14]. It is supported the utility of CD_{10} as a marker for early BCC, especially when SCC could not be excluded clinically or by conventional stains [13]. Similarly, concluded that CD_{10} might be a useful immunohistochemical marker to differentiate between BCC and SCC; At least, if tumor cells were CD_{10} positive, this would favor BCC over SCC [14].

The stromal CD_{10} expression is associated with malignant transformation of keratinocytes together with infiltration of dermal macrophages and loss of Langerhans cells in skin tumors.

The mechanism of generation and function of CD_{10} stromal cells remained unclear [11]. In a study, Gouda *et al*. [15] reported CD_{10} immunopositivity were in 16.7% of KA and 100% SCC biopsies. The CD_{10} labeled tumor stroma in 100% of SCC cases. CD_{10} staining was present in peripheral tumoral cells in 11.1 % of SCC cases, but negative in central tumoral cells. Our results support CD_{10} as a useful adjunct marker in distinguishing between KA and SCC tumors. To date no reported criteria are sensitive enough to discriminate reliably between KA and SCC, and consequently there is a clinical need for discriminating markers. Our results suggest in KA and SCC cases with difficulties in differentiation, CD_{10} can help towards more precise differentiation. The authors imply however there are controversial reports, this results can use as baseline information for further researches.

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