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ORIGINAL ARTICLE

Role of p53 factor in differentiating between Keratoacanthoma and squamous Cell carcinoma

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ABSTRACT
Squamous cell carcinoma (SCC) is the second most common skin cancer around the world and Keratoacanthoma (KA) known as a common skin neoplasm. However, because of lack of information, it is different prognoses diagnosis of both diseases. It is important to distinguish these neoplasms because they have different clinical behavior and different therapeutic planning. So, the main propose of the current study was to determine the expression of P53 in the differential diagnosis between Keratoacanthoma and SCC. This prospective study includes 15 cases of KA and 15 cases of SCC. Cases were collected randomly from archive of pathology department. Slides were stained with H&E and reviewed and those have definite pattern of KA or SCC, the P53 immunohistochemical staining was performed with P53 antibody. According to the results, 30% of cases were female (63.5±11.8 years) and 70% were male (61±23.1 years), respectively. A significant difference detected in expression of P53 was detected in 46.7% and in 93.3% of the KA and SCC cases, respectively (P<0.05). The results of this study suggest that extent of expression P53 in SCC cases was higher than KA cases. Therefore, in cases with difficulties in differentiation of these two diseases, p53 can help towards more precise differentiation.
Keywords: *Keratoacanthoma, Squamous cell carcinoma, Immunohistochemistry, p53*

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INTRODUCTION

Keratoacanthoma (KA) is a common cutaneous neoplasm that most often occurs on sun-exposed sites in light-skinned persons of middle age or older. Almost all KA arise from hair follicle [1]. Occasionally, it is seen on hairless areas such as nail beds or oral cavity. It is characterized by rapid growth with a histologic pattern often suggestive of squamous cell carcinoma [2]. Usually considered the prototype of cutaneous pseudo-malignancies for its histologic resemblance to squamous cell carcinoma (SCC), it has alternately been viewed as possibly pseudo-benign, or a cancer that resembles a benign neoplasm. Distinguishing between KA and SCC is not an uncommon histological diagnostic dilemma [3].

Several factors have been associated with increased aggressiveness of these tumors such as histopathological subtype, differentiation, depth of invasion and perineural invasion, among many others [4]. In addition, some authors have showed the relationship between some biological factors and cancer behavior [5]. Worldwide, SCC is the second most frequent skin cancer and occurs most frequently in the sun-exposed regions of the skin and in immunocompromised patients [6]. Clinically, rapid tumor growth may suggest a de novo cutaneous SCC, a relatively rare, aggressive tumor that produces regional or distant metastases [4]. Sometimes a well differentiated SCC can be difficult to distinguish from a KA without clinical history [7].

The P53, also known as TP53 is a gene that codes for a protein that regulates the cell cycle and hence functions as tumor suppression. It is very important for cells in multicellular organisms to suppress

cancer [7]. It is in the 53 kilodal-ton fraction of cell proteins. The tumor-suppressor gene p53, located on the short arm of chromosome 17, encodes for a nuclear protein which regulates cell proliferation by inhibiting cells entering S-phase. 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 [7]. The p53 mutations are alleged to be the commonest genetic abnormality in human cancer [7].

Based on the literature, scarce information exists on role of p53 in the differential diagnosis of the SCC and KA. So, the aim of the current study was to determine role of p53 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 (21 male and 9 female) were enrolled 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 p53 immunohistochemical staining [8]. Then, slides allocated into 60ºC oven for 60 minutes. After paraphenirezation and rehydration and inactivation of endo-peroxidase the antibody for p53 was done. The brownish cytoplasm or cell membrane was an indicator p53 [8]. Then slides studied for KA or SCC expression using 10HPF microscope. The mean expression for positive detection in tumoral (epithelial) or stromal (mesenchyme) cells were mentioned as described below:

1. Negative expression: <10%
2. Low expression: 10-50%
3. High expression: >50% [8].

Statistical analysis

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

RESULTS

The results for role of P53 factor in differentiating between KA and SCC is presented in tables 1 and 2. According to the data, a significant difference observed between sexes in SCC or KA patients. In this study, the frequency of the patients was 21 male and 9 female. In SCC patients, the 2 patients (13.3%) was male and 86.7 % (13 people) female. Also, in the KA patients, 7 (46.7%) was male while 53.3% (8 patients) of them were female. So, it seems female are more vulnerable to the SCC and KA (P<0.05).

As seen, the average age on the patients in this study was 61.7±20.2 years (range 11-90 years).

Table 1. Frequency of the samples for P53

	Positive (%)	Negative (%)
SCC	14 (93.3%)	1 (6.7%)
KA	7 (46.7%)	8 (53.3%)
Total	21 (70%)	9 (30%)

SCC: Squamous cell carcinoma, KA: Keratoacanthoma

Frequency of the expression for positive detection in tumoral or stromal cells for p53 is presented in table 2. According to the data, the 70% of the patients had SCC or KA. Also, 93.3 % (14) of them was SCC and the 46.7% of them with positive p53. Also, a significant difference detected in biopsy samples and p53 detection (P<0.05). In this study 8 (53.3%) of the KA patients was Negative (>10%) and in 1 (6.7%) the SCC detected (P<0.05). Also, no significant difference detected for KA and SCC among the patients (P>0.05). In high expression (>50%) of the p53, the 9 (60%) of them was SCC and the 3 (20%) observed as KA (P<0.05).

Table 2. Frequency of the expression for positive detection in tumoral or stromal cells for P53

	Negative (>10%)	**Low Expression (10-50%)**	**High Expression (>50%)**
SCC	1 (6.7%)	5 (33.3%)	9 (60%)
KA	8 (53.3%)	4 (26.7%)	3 (20%)
Total	9 (30%)	9 (30%)	12 (40%)

SCC: Squamous cell carcinoma, KA: Keratoacanthoma

DISCUSSION

According to the data, the expression P53 in SCC cases was higher than KA cases. Therefore, in cases with difficulties in differentiation of these two diseases, P53 can help towards more precise differentiation. Approaches to treatment of cancer based on the immune system have focused on cytologic effector cells [9]. The KA and SSC are epithelial skin tumors exhibiting distinctive clinical and histological features. However, the differential diagnosis between them in individual cases may be difficult or even impossible [1]. SCC harbors significant risk of metastasis that can eventually lead to death. However, KA usually undergoes spontaneous regression as part of its natural history [10].

In the KA, positive cells were usually located in the basal layers at the periphery of the lesion. The SCC displayed positive cells in a diffuse pattern. The P53 tumor-suppressor gene is the classic example of these genes, as it is found mutated in human malignant tumors including skin cancers [3]. In our study, 30% of cases were female (63.5±11.8 years) and 70% were male (61±23.1 years), respectively. A significant difference detected in expression of p53 was detected in 46.7% and in 93.3% of the KA and SCC cases, respectively. In a study it is report, 88.9% of SCC cases were positive to p53 expression in a diffuse pattern and also in dysplastic epidermis adjoining lesional nests. Furthermore, 66.7% of KA cases showed positive nuclear expression of p53. Positive cells were located in the basal layers at the periphery. This pattern of P53 expression was in SCC and KA (Gouda et al. 2014). On the other hand, Cain *et al*., [11] found that the p53 staining showed basal, patchy, or diffuse patterns. These patterns were present in all cases of KA, well differentiated SCC, and there were no statistical differences among the examined groups. Also, Batinac *et al.,* [12] found that P53 immunostaining of KA, and SCC was detected in 66.7% and 86.7% of cases, respectively.

Khodaeiani *et al.,* [13] reported that the expression rate of P53 was 50.20% for the SCCs, and null for the KAs which our results was similar to their observation. P53 protein was expressed in the cells at the periphery of both KA and SCC. The keratoa-canthomas intense P53 expression was detected; however in SCC, it was heterogeneously expressed. Kerschmann *et al*., [14] found 80% of the KAs showed nuclear staining with anti-p53 antibody, distributed along the outermost layers of the aggregates of neoplastic cells, while 60% of the SCCs were p53 positive. This overlapping expression patterns of p53 in KA and SCC supports the hypothesis that these tumors represent a possible biologic spectrum.

The mechanisms involved in the involution of KA have not been completely elucidated. The frequent presence of inflammatory cell infiltrates associated with KAs suggests a role for an immunologic host response in confining local growth, preventing distant metastasis, and inducing regression. Supporting this supposition are numerous studies demonstrating an increase of activated intratumoral CD4- positive T cells, fewer numbers of eosinophils and increased Langerhans' cells in KA compared with SCC and a high incidence of KA in patients who experience immunosuppression [15]. 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, P53 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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