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Original Article

Pathology Section

Immunohistochemical Expression of p53 and bcl-2 in Psoriasis

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ABSTRACT

Introduction: Apoptosis plays a major role in maintaining the balance between cellular proliferation and cell death in the skin. Blockage of apoptosis has been implicated as one of the contributing factors in the pathogenesis of psoriasis. P53 has a role in induction of cell cycle arrest, apoptosis as well as regulation of cell proliferation, bcl-2 is anti-apoptotic protein. Previous studies have reported controversial results relating to their expression in psoriatic skin.

Aim: To evaluate the immunohistochemical expression of p53 and bcl-2 in the epidermis, basal cells and lymphocytes of psoriatic skin and compare it with the adjacent perilesional skin.

Materials and Methods: This cross-sectional study was conducted in Hind Institute of Medical Sciences, Safedabad, Barabanki, Uttar Pradesh, India from June 2016 to December 2017. Fifty cases of psoriasis were included and punch skin biopsies including a small part of perilesional skin was taken. The sections were studied for the presence of immunohistochemical expression of p53 and bcl-2 using scoring systems. The perilesional part of the biopsy was used for comparing the histopathological and immunohistochemical expressions. The student t-test was used for comparison of groups using Statistical Package for the Social Sciences (SPSS) version 23.0 program and a p-value of <0.05 was taken as statistically significant.

Results: The age of the patients ranged from 15-68 years. Majority of the patients were males comprising 32 out of 50 cases (64%). The most common site was the extensor surfaces of limbs. The histopathological findings of psoriasis, such as acanthosis, spongiosis, suprapapillary thinning, dilated dermal vessels and dermal lymphocytic infiltrate was seen in all 50 cases of the lesional skin (100%). Dermal lymphocytic infiltrate was the most common finding in the perilesional skin and was observed in 21 cases (42%). Statistically significant immunohistochemical expression of p53 was seen chiefly in the epidermis, while bcl-2 expression was seen in the dermal lymphocytes of psoriatic (lesional) skin.

Conclusion: The immunohistochemical expression of p53 in the epidermal keratinocytes of the lesional skin in psoriasis is suggested to be of wild type in response to frequent DNA damage in the actively cycling cells of epidermis. The expression of bcl-2 in the dermal lymphocytes could point towards its role in promoting the chronic inflammatory and recurrent nature of psoriatic lesions.

Keywords: Acanthosis, Apoptosis, Erythema, Psoriasis vulgaris, Spongiosis

INTRODUCTION

Psoriasis is a chronic, relapsing, inflammatory and hyperproliferative skin disorder with a prolonged capacity to resist apoptosis in the epidermal keratinocytes [1]. The epidermal hyperplasia and the altered tissue architecture observed in psoriasis is postulated to be due to abnormal apoptotic pathways [2].

Apoptosis, also called the programmed cell death is required for various developmental and maintenance processes of the body including foetal development, immune system and balancing cell numbers in continuously renewing tissues [3]. This balance between cell death and cell proliferation maintains homeostasis of the epidermal keratinocytes of the skin, in which apoptosis plays a major role [4].

Increased epidermal expression of apoptosis related molecules causing suppression of apoptotic process has been postulated in the pathogenesis of epidermal hyperplasia [5]. The chronic and relapsing characteristics of this disease has also been proposed to be due to suppression of apoptosis in the T-lymphocytes and hence, their increased survival in the lesional skin [6].

Psoriatic keratinocytes are resistant to factors that induce programmed cell death. As a result of keratinocyte resistance to proapoptotic signals transmitted by TNF-a, a paradoxical increase in the concentration of this proinflammatory cytokine occurs. Inhibitors of apoptosis include the survivin protein belonging to the IAP (Inhibitors of Apoptosis Proteins) family that binds to caspases, virtually absent in the epidermis not affected by the disease process. However, the process of apoptosis, which is one of the main factors clearly affecting the pathomechanism of the disease, is not well understood [1]. Apoptosis is controlled by bcl-2 family of proteins which includes several pro-apoptotic (bax, bik, bad, bcl-xs) and anti-apoptotic proteins (bcl-2, bcl-xL, bcl-w, mcl-1) [7]. Bcl-2 is a proto-oncogene, and protects the cells from apoptosis [7]. P53 gene is a tumour suppressor gene, and plays a role in inducing cell cycle arrest or apoptosis as well as regulation of cell proliferation. The aberrant expression of p53 is seen in squamous epithelium of hyperproliferative skin diseases of inflammatory nature [8]. Several studies done in the past about the expression of p53 and bcl-2 have yielded controversial results [9,10]. The present study aimed to determine the role of p53 and bcl-2 in psoriasis by studying their immunohistochemical expression in the lesional and peri-lesional regions of the skin biopsy. The objectives were to study the histopathological features in the lesional and perilesional regions of psoriatic skin and to determine the immunohistochemical expression of apoptotic markers p53 and bcl-2 in them.

MATERIALS AND METHODS

This cross-sectional study was conducted in Hind Institute of Medical Sciences, Safedabad, Barabanki from June 2016 to December 2017. The study was conducted in the Department of Pathology to evaluate the apoptotic changes in the skin by immunohistochemical markers bcl-2 and p53. The study was started after approval from the Institutional scientific and Ethical Committee (HIMS/15-16/13) and is in accordance with the principles of Helsinki declaration. Fifty cases of psoriasis were included and punch skin biopsies including a small part of perilesional skin was taken.

Inclusion and Exclusion criteria: All the clinically diagnosed and histopathologically confirmed cases of psoriasis were included in the study. The patients suffering from any co-existing dermatological or systemic illness (known to affect the skin) were excluded from the study.

Sample size calculation: The sample size was calculated taking α (type I) error as 5%, the confidence interval of 95% and the power of the study as 80%.

Study Procedure

The clinical and demographic parameters of the patients were noted and a 6 mm punch biopsy including a small part of perilesional skin was performed. The skin biopsies were immediately fixed in 10% buffered formaldehyde solution and subjected to routine histopathological processing and haematoxylin and eosin staining. The histopathological characteristics of the lesional and perilesional part of the biopsy were studied. Serial 5 micrometer thick sections from the paraffin embedded biopsies were mounted on poly-L-lysine coated slides. The sections were immersed in xylene for 5 minutes and hydrated using a gradient series of alcohol. Antigen retrieval was performed by immersing the sections in citric acid buffer (pH 6.0) in a microwave oven for 15 minutes. Endogenous peroxidase activity was blocked with 3% hydrogen peroxide for 10 minutes and then incubated with a primary antibody in a humidified chamber overnight at 40°C. Monoclonal p53 antibody and monoclonal mouse antibody bcl-2 (Dako) were used as primary antibody at 1:200 dilution. About 500 cells were counted at 400X microscopic magnification under light microscope and an average was taken. The immunostaining results were analysed semi-quantitatively as a percentage of positive cells.

Localisation of immunohistochemical staining was observed, grouped and classified as epidermal cells, epidermal basal layer cells and dermal lymphocyte staining. Nuclear expression of p53 and nuclear as well as cytoplasmic expression of bcl-2 were taken as positive. Tumour cells of serous adenocarcinoma of the fallopian tube were taken as positive control for p53. The T and B-lymphocytes from mantle zone of reactive follicles of tonsillar tissue were taken as positive controls for bcl-2. The level of p53 and bcl-2 expression in keratinocytes was evaluated by a scoring system as devised by Liang S et al., in which a sum of two scores is taken as representative of the level of expression [8]. The scoring system has a score ranging from 0-3 for both the degree of positivity (0 denotes <1%, 1 denotes 1-10%, 2 denotes 10-50%, 3 denotes >50% of positively stained keratinocytes) and the intensity of staining (relative colour intensity of positively stained cells from faint-brown for score 1 to deep brown for score 3), which were then added up. In the dermal lymphocytes, the immunohistochemical expression of p53 and bcl-2 was scored in a range from 1-4 in which score of 0 means no staining, 1:<25%, 2: 26-50%, 3:51-75% and 4: >75% staining of the lymphocytes in accordance with that used by Yildiz L et al., [6].

STATISTICAL ANALYSIS

The results were statistically analysed using SPSS 23.0 version program. The data were expressed as mean and standard deviation. The student's t-test was used to compare the groups and a p-value of <0.05 was considered statistically significant.

RESULTS

Among the 50 patients included, the age of the patients included ranged from 15-68 years. Majority of the patients were males, comprising 32 out of 50 cases (64%). With regard to the site, extensor surface involvement was the most common, seen in 27 cases (54%) followed by flexor 9 (18%), back 8 (16%) and erythrodermic and scalp psoriasis 3 cases (6%) each.

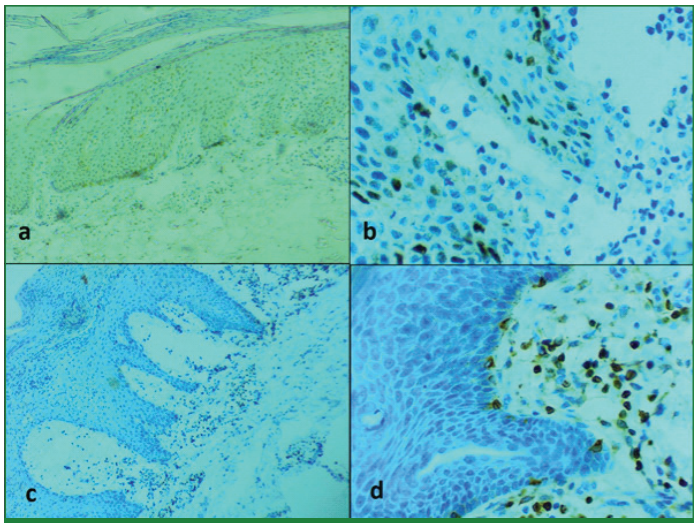
The duration of the disease was <6 months and >24 months in 16 patients (32%) each respectively. The patients with the duration of disease 12-24 months and 6-11 months were 11 (22%) and 7 (14%), respectively. Clinically plaque like lesions was seen in 47 (94%) cases. Grattage sign was positive in 32 (64%) patients. The auspitz sign and silvery white scaling could be seen in 40 (80%) patients each respectively.

On histopathology of the lesional tissue, features such as acanthosis, spongiosis, suprapapillary thinning, dilated dermal vessels and dermal lymphocytic infiltrate was seen in all 50 cases (100%), followed by parakeratosis 49 (98%), hypogranulosis 48 (96%), micro munro abscess 18 (36%) and kogoj pustules 4 (8%) cases, respectively [Table/Fig-1]. The perilesional part of the biopsy showed a variable distribution of the above features [Table/Fig-1]. Few of the features were retained in perilesional tissue of some patients such as dermal lymphocytic infiltrate in 21 (42%) cases, dilated dermal vessels in 8 (16%), mild acanthosis in 7 (14%), spongiosis in 3 (6%) and hypogranulosis in 2(4%) cases, respectively.

Histopathological features	Psoriatic lesional area, n (%)	Perilesional area of the biopsy, n (%)
Acanthosis	50 (100%)	7 (14%)
Parakeratosis	49 (98%)	0 (0%)
Munro microabscesses	18 (36%)	0 (0%)
Hypogranulosis	48 (96%)	2 (4%)
Spongiosis	50 (100%)	3 (6%)
Kogoj pustules	4 (8%)	0 (0%)
Suprapapillary thinning	50 (100%)	0 (0%)
Dilated dermal blood vessels	50 (100%)	8 (16%)
Dermal lymphocytic infiltrate	50 (100%)	21 (42%)

[Table/Fig-1]: Histopathological features of lesions (N=50).

On immunohistochemistry, the difference between p53 expression score values in keratinocytes (p=0.014) of the lesional epidermis (mean score=1.02) compared from the perilesional region (mean score=0.62), were statistically significant (p<0.05) [Table/Fig-2]. The basal cells and lymphocytes of the lesional skin, expressed bcl-2 in few of the cases with a mean score value of 0.32 and 0.2, respectively, though the expression was not statistically significant when compared with the perilesional skin (p-value>0.05) [Table/Fig-3]. The mean score value of p53 expression in the epidermis, basal cells and lymphocyte of the lesional skin was 1.02, 0.32 and 0.1, respectively. The mean score value of bcl-2 expression in epidermal cells, basal cells and dermal lymphocytes of lesional skin was 0.18, 0.18 and 1.76 respectively. On comparison between lesional and perilesional skin, the difference between the bcl-2



[Table/Fig-2]: (a) Predominant epidermal distribution of p53 positive cells in the psoriatic skin (Immunohistochemistry using p53 as primary antibody at 100X magnification); (b) Scattered/dispersed cells showing immunohistochemical nuclear positivity of p53 in the keratinocytes of the psoriatic lesional skin, with a sum score of 4 (2+2). (Immunohistochemistry using p53 as primary antibody at 400X magnification); (c) Predominant distribution of bcl-2 positivity in the lesional psoriatic skin chiefly in the dermal lymphocytes.(Immunohistochemistry using bcl-2 as primary antibody at 100X magnification); (d) Dermal lymphocytes express bcl-2 in the lesional skin with score of 3. (Immunohistochemistry using bcl-2 as primary antibody at 400X magnification).

p53 expression						
Variables	**Epidermis-L**	**Epidermis-PL**	**Basal cell-L**	**Basal cell-PL**	**Lymphocytes-L**	**Lymphocytes-PL**
Range	0-4	0-2	0-2	0-2	0-2	0-2
Mean	1.02±0.999	0.62±0.779	0.32±0.551	0.2±0.495	0.1±0.364	0.08±0.340
p-value	<0.05 (S)		>0.05 (NS)		>0.05 (NS)	
bcl-2 expression						
Variables	**Epidermis-L**	**Epidermis-PL**	**Basal cell-L**	**Basal cell-PL**	**Lymphocytes-L**	**Lymphocytes-PL**
Range	0-2	0-1	0-1	0-1	0-4	0-3
Mean	0.18±0.482	0.06±0.239	0.18±0.274	0.04±0.198	1.76±1.04	0.42±0.836
p-value	>0.05 (NS)		>0.05 (NS)		<0.001 (HS)	

[Table/Fig-3]: Expression of p53 and bcl-2 in lesion skin and perilesional skin.
Statistical test used: Student's t-test; S: Significant; NS: Non significant; HS: Highly significant

expression of dermal lymphocytes was statistically highly significant. The difference between the epidermal p53 expression of the lesional skin and perilesional skin was found to be statistically significant.

The difference between the immunohistochemical expression of bcl-2 in dermal lymphocytes of the lesional skin showing a mean score of 1.76, while the perilesional skin showed a mean score of 0.42 was highly significant (p<0.001) [Table/Fig-2c,d]. The epidermis and the basal cells of the lesional skin showed bcl-2 expression in few of the cases with a mean score value of 0.18 in each of them respectively, but none of them showed a statistically significant expression (p-value>0.05) when compared with the perilesional epidermis [Table/Fig-3].

DISCUSSION

Psoriasis is a common chronic, relapsing, inflammatory papulosquamous skin disorder clinically characterised by variably sized well demarcated dry scaly plaques covered with fine silvery scales [11-13]. A histopathological examination is required for confirmatory diagnosis, which is based on evaluation of histopathological features such as uniform elongation of rete ridges, dilated blood vessels, thinning of the suprapapillary plates, intermittent parakeratosis, perivascular infiltration of lymphocytes and presence of occasional neutrophil aggregates in the epidermis [12]. The presence of evenly elongated and slender rete ridges along with equally long dermal papillae is quite specific for psoriasis [14]. There are many disease conditions which form the differential diagnosis of psoriasiform hyperplasia. The histopathological features are specific and characteristic in psoriasis, pityriasis rubra pilaris, pityriasis rosea and inflammatory linear verrucous epidermal nevus. There is some overlap in lesions like prurigo nodularis, lichen simplex chronicus and allergic contact dermatitis for which diagnosis has to be based upon a combination of proper clinical and histopathological observation [15]. The present study includes 50 histopathologically confirmed cases of psoriasis including a small part of the perilesional skin. The perilesional region retained some of the above histopathological features such as dermal perivascular lymphocytic inflammatory infiltrate, dilated dermal vascular channels and mild acanthosis in few of the cases. Occasional cases showed hypogranulosis and mild spongiosis [Table/Fig-1].

Epidermal hyperproliferation along with incomplete and accelerated maturation of the epidermal keratinocytes is the characteristic feature of psoriasis [13,16].

According to previous studies, p53 accumulation has been a frequent finding in the hyperproliferative non neoplastic skin lesions [17,18], similar to the findings of p53 staining being significantly associated with epidermal keratinocytes, in the present study. While Hussein MR et al., reported that intact p53 nuclear localisation in such hyperproliferative non neoplastic skin lesions, allows mutant p53 protein to stay in the nucleus and exert its dominant negative function, Moles JP et al., have disregarded the TP53 mutation theory in the pathogenesis of psoriasis [17,19]. According to Ren Z et al., a dispersed pattern of p53 staining suggests the wild type status of TP53 protein, as also seen in our study [20].

The p53 is a marker of active cycling cells and it has been reported that though the cycling time in psoriasis is normal, only increased recruitment of epidermal cells is responsible for psoriatic lesions [21]. Unique mechanisms of keratinocytes for establishing cutaneous homeostasis and maintaining structural integrity, in response to DNA damage may be responsible for p53 expression (wild type) in psoriatic epidermis due to cell cycle disturbance [22,23]. The increased p53 expression hence may also be a physiological response to counteract the proliferation and repair of DNA errors [24].

Blockage of the normal apoptotic pathways has been proposed in the pathogenesis of Psoriasis. Increased bax and bcl-x expression but decreased bcl-2 has been postulated [25]. The limited expression of bcl-2 in psoriasis does not appear to have a direct association with cell proliferation or apoptotic resistance [26]. The previous data on bcl-2 expression in psoriatic epidermis by some authors, has been conflicting [5,27,28], while others proposed a relatively unimportant role of bcl-2 protein in the pathogenesis of psoriasis [9,10,29]. Recently, Shi HJ et al., studied the effect of oxymatrine or acitretin treatment and found that it significantly reduces psoriatic lesions, decreases the proliferative index value possibly by inhibiting epidermal cell proliferation. However, oxymatrine has been shown to inhibit cell apoptosis by increasing the expression of the anti-apoptotic bcl-2 protein [30].

Moorchung N et al., reported a linear correlation between immunohistochemical expression of anti-apoptotic bcl-2 in the basal cells with expression of pro-apoptotic p53 in epidermal cells, basal cells as well as lymphocytes [9]. The kinetics of basal cells differs from the rest of the epidermis and a simultaneous activation of both the pro-apoptotic and anti-apoptotic processes was postulated which has also been previously reported by Takahashi H et al., [5].

The increased bcl-2 expression in the dermal lymphocytes as also found in the present study suggests increased lymphocyte survival, which may contribute to the chronic, inflammatory and relapsing nature of psoriasis as failure to remove the excess cells after an immune or inflammatory process, is crucial in the regulation of the inflammatory response. Whether the anti-apoptotic changes in the dermal lymphocytes is a primary or secondary process in the pathogenesis is still an unanswered question and requires studies on bcl-2 expression in the circulating peripheral blood lymphocytes in cases of psoriasis for further clarification [6].

On review of recent literature, studies by Kokolakis G et al., showed a marked decrease in the expression of genes encoding anti-apoptotic proteins bcl-2, bcl-xL, and transcription factor NF-kB and also an increase in the expression of genes encoding the proapoptotic proteins p53, bax, and Apoptosis Inducing Factor (AIF) in the patients treated with Infliximab [31]. These changes correlated with a decrease in epidermal thickness as well as a decrease in the value of surface indicators and the severity of psoriatic lesions, which indicates a positive effect of the use of TNF-alpha antagonists in patients with psoriasis [31]. Similarly remarkable efficacy of biological drugs in the treatment of psoriasis was also obtained by Yu Q et al., [32]. Methotrexate monotherapy, has also been shown

to significantly increase the expression of caspase 9 and decreases the expression of genes encoding bcl-xL, c-FLIP, NFkBp65, and pAkt1, which indicates a beneficial effect of methotrexate on the induction of the mitochondrial apoptosis pathway, thus controlling acanthosis [33]. These studies show that normalisation of apoptosis process in the course of psoriasis may lead to the reduction of clinical changes. For this purpose, biological drugs appear to be the therapeutic future [34], hence, a need for more extensive studies on the apoptotic pathophysiological mechanisms in psoriasis.

Limitation(s)

Only two easily available, popular as well as significant immunohistochemical markers of cell cycle regulation and apoptosis were used as these were significant in the evaluation of possible apoptotic process in psoriatic lesions. These could not be further worked up to study its molecular basis and hence was a major limitation to our study. A tiny part of perilesional tissue included in the biopsy was taken for comparison, also formed a drawback of the study.

CONCLUSION(S)

The nuclear positivity of p53 in the epidermal keratinocytes of psoriatic lesional skin may indicate the retention of wild type TP53 as a response to increased frequency of DNA errors taking place during the rapid proliferation of keratinocytes or an expression of cell cycle disturbance. The insignificant expression of bcl-2 in psoriatic epidermis indicates that it does not play an important role in its pathogenesis, on the other hand, increased expression of bcl-2 in the dermal lymphocytes of psoriatic skin points towards its possible important antiapoptotic role responsible for the chronic inflammatory and relapsing nature of psoriasis.

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