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Review Article

Role of Vascular Endothelial Growth Factor and Survivan Expression in Pathogenesis of Psoriasis

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Abstract: The Bundelkhand region of central India is different geographically, socially and economically. It is a semi-arid plateau area. This region is marked by extremes of temperature. The climatic and geographical conditions in this region favours the development of skin diseases. Studies have shown that several variants of psoriasis are developed in this region. **Aims:** The aim of this present study was to investigate the immunohistochemical expression of VEGF and Survivin in psoriatic skin and to detect their role in the pathogenesis of Psoriasis so that therapy could be targeted against suvivan and angiogenesis in the treatment of psoriasis patients. **Settings**: A retrospective case control study in a tertiary referral centre. **Material & methods**: A total of 54 cases were taken who visited the Dermatology OPD from January 2016 to october2017. These cases were diagnosed as Psoriasis after histopathological examination. Each case was subjected to general examination, H&E staining (Culling 1975) and immunohistochemistry with VEGF and Survivin. **Results:** Maximum 37% cases shows cytoplasmic VEGF staining in epidermis, dermis & blood vessels. 13% cases shows VEGF staining in epidermis and blood vessels. 30 cases showed nuclear and cytoplasmic SURVIVIN staining in epidermis. 26 cases shows Survivin staining in epidermis + sweat glands .The value of |Z| obtained is 5.04216 and $p<0.0001$ implies that there is high significant difference between Psoriasis studied with age and duration of Psoriasis. **Conclusion**: Over expression of survivin in psoriasis denotes its important role in the apoptosis suppression as a possible mechanism in the pathogenesis of Psoriasis so that survivin targeted therapies can be benifited in the treatment of psoriasis.

Keywords: skin diseases. Suvivan and angiogenesis in the treatment of psoriasis patients.

INTRODUCTION:

Psoriasis is a complex immune – mediated chronic skin disease affecting approximately 2% of the worldwide population. Psoriasis (PS) is a common chronic, relapsing, immune-mediated disease involving the skin and joints of genetically predisposing individuals, which potentially shares the disease pathways with other chronic inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease (Nickoloff, B. J., & Nestle, F. O. 2004).Several variants of Psoriasis (PS) are well characterized, including chronic plaque psoriasis which is the most common variant , guttate psoriasis , erythrodermic psoriasis , pustular psoriasis , and inverse psoriasis (Griffiths, C. E. M. *et al*., 2007). Despite numerous studies, the pathogenesis of psoriasis has not been fully elucidated. However, many pathogenic mechanism have been suggested (Pietrzak, A. T. *et al*., 2008). There is much evidence that Psoriasis is a polygenic disease modified to expression by triggering factors. Psoriasis is characterized by hyperproliferation and abnormal differentiation of epidermal keratinocytes, lymphocyte infiltration consisting mostly of T lymphocytes, and various endothelial vascular changes in the dermal layer, such as angiogenesis, dilation, and high endothelial venule formation, T lymphocytes and the released cytokines and chemokines appear to be the principal driver of lesion development and persistence. In addition, endothelial cells (EC), neutrophils, and natural killer T cells may play an adjunctive role along with other cytokines such as intercellular adhesion molecule-1 (Guenther, L. C., & Ortonne, J. P. 2002). It

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is suggested that Psoriasis is an angiogenesis-dependent disease, and vasoproliferation is suggested as a suitable target for the development of antipsoriatic drugs (Creamer, D. *et al*., 2002). Several angiogenic factors have been identified in psoriatic epidermis, including IL-8, TNF-α, transforming growth factor-a, EC-stimulating angiogenesis factor, thymidine phosphorylase ,and VEGF cell survival, upregulation of cell survival pathways, and suppression of apoptosis, which are implicated in blood vessel maintenance and tissue inflammation. Vascular endothelial growth factor (VEGF) is a major regulator of physiological and pathological angiogenesis, causing aberrant angiogenesis and vascular leakage in the upper dermis. It may also contribute to keratinocyte proliferation and epidermal barrier homeostasis in psoriasis. VEGF also known as vascular permeability factor and vasculoprotein, is an endothelial –specific growth factor. In addition, it is a potent angiogenic agent and very potent hyperpermeability factor being 50000 times more potent than histamine. Survivin is one of the inhibitor of apoptosis (IAP) that have been discovered, it is a bifunctional protein that regulates cell division and suppresses apoptosis (Altieri, D. C. 2008). This function is mediated by the inhibition of the caspase pathway. Survivin was abundantly expressed in fetal tissues but completely down regulated in most normal terminally differentiated adult tissues, in addition to its up regulation in most human cancers (Ambrosini, G. *et al*., 1997). The aim of this study was to investigate the immunohistochemical expression of VEGF and Survivin in psoriatic skin and to detect their role in the pathogenesis and therapy of Psoriasis.

Material and Method: The present study was conducted in Pathology Department in collaboration with Department of Dermatology MLB Medical College, Jhansi. The tissue material for the study was obtained from various out patients and inpatients admitted in Department of Dermatology.

Study Sample:

A total of 54 cases diagnosed in Histopathology laboratory between year 2016-17 were included as follows: INCLUSION AND EXCLUSION CRITERIA: Only cases proven by histopathology patients were included in the study. Selection of cases with skin lesions: All patients with suspected skin lesions of psoriasis were worked up with histopathological examination after detailed clinical examination.

Clinical Assessment:

Detailed clinical history including age, sex, symptoms, duration of illness, history of hypertension, diabetes and family history of diabetes, clinical details of the lesion.

General Examination:

SEVERITY OF DISEASE – On the basis of body surface area (BSA).

MILD- <3%BSA

MODERATE- 3-10% BSA

SEVERE ->10% BSA

LAB Assessment:

Histological Examination Slides prepared after biopsy (formalin fixed) were stained with haematoxylin and Eosin stain and then studied for histological changes. By automatic tissue processor paraffin blocks were prepared. Sections were cut at 5 microns thickness and were stained with Haematoxylin and Eosin stain (Clayden *et al*., 1971) All cases with psoriatic skin lesions were subjected for Immunohistochemical analysis with Anti VEGF : staining and evaluation using ready-to-use VEGF165 polyclonal primary antibody, supplied by Biogenex. Anti Survivin: staining and evaluation using ready to use Survivin [EP2880Y] antibody , supplied by Biogenex. (Clayden *et al*., 1971) FOR IHC: POSITIVE CONTROL: For VEGF and SURVIVIN – Placenta, NEGATIVE CONTROL: Sections stained omitting primary antibody were taken as negative control.

INTERPRETATION:

Anti VEGF IHC: The antibody stains cytoplasm in positive cells. Intensity of staining: To evaluate the intensity of staining in epithelium semiquantative grading was done.

0- Negative. 1- Mild (<10% expression of cells). 2- Moderate (10–20% expression of cells). 3- Strong (expression in >50%). A score of 2 or higher was considered positive.

Immunostainingm for Survivin Was Semiquantitatively Scored as Follows:

The mean percentage of positive cells for the expression of survivin was determined in at least five areas at 400- fold magnification, and patients with less than 10% positively stained cells were defined as negative. Patients with 10–29% positively stained cells were defined as +,

30–59% as ++, and 60% or more as +++ .

Statistical Analysis

Calculation of mean, standard deviation and Z test.

RESULTS:

The present study was conducted in Department of Pathology and dermatology MLB Medical College, The performed study included a total of 54 cases of skin biopsy which were diagnosed as Psoriasis after histopathological examination. Maximum psoriatic patients were found in 51-60 yr age group. Males predominates over females with M:F ratio 1.8:1. Most of the cases showed duration of 7-9yrs

of disease in our study.(table1). Expression of VEGF were found in 61% (33/54) of psoriatic lesions. [table2] In psoriasis, expression of VEGF was strong (38.9%) throughout the epidermis and dermis (dermal cells + endothelial cells) and moderate in 22.2% cases.[table3] Expression of survivin were found in 72.2% (39/54) of psoriatic lesions.[table4] Maximum 30 cases shows nuclear and cytoplasmic SURVIVIN staining in epidermis. 26 cases shows Survivin staining in epidermis + sweat glands.(table5) The value of |Z| obtained is 5.04216 and $p<0.0001$ implies that there is high significant difference between Psoriasis studied with age and duration of Psoriasis (Table 6).

Table1: Duration wise distribution of patients

DURATION (in month)	No. of cases	Percentage
0-12	1	1.9%
13-24	5	9.3%
25-36	7	13%
37-48	9	16.7%
49-60	7	13%
61-72	8	14.8%
73-84	4	7.4%
85-109	12	22.2%
110-121	1	1.9%
Total	**54**	**100%**

TABLE – 2 Presence of VEGF in Psoriasis

Result	No. of cases	Percentage
Absent (negative and mil expression)	21	38.80
Positive (moderate and strong expression	33	61.10
Total	54	100%

Table3: Distribution of cases according to groups and pattern of staining for VEGF antibody

LOCATION OF VEGF(+)		No. of cases	Percentage
	Epidermis	6	11.1
Positive cases	Epidermis+Dermis+Blood Vessels	20	37.0
	Epidermis +blood vessels	7	12.96
Negative case		21	38.80
Total case		54	100

TABLE - 4Presence of Survivin in Psoriasis

Result	No. of cases	Percentage
Absent	15	27.80
Positive (Mild and Moderate and severe expression)	39	72.2
Total	54	100

Table: 5 Distribution of cases according to groups and pattern of staining for survivin antibody

Location of Survivin		No. of cases	Percentage
	Epidermis	16	29.60
Positive cases	Epidermis+ sweat gland	14	25.90
	Epidermis +blood vessels	6	11.10
	Sweat Gland	3	5.50
Negative case		15	27.70
Total case		54	100

Table 6: Comparison of Mean and standard deviation of Age and duration of Psoriasis

Parameters	N	Mean	Standard deviation	Z test / |Z|	P value
Age (in years)	54	37.31	16.241	5.04216	<0.0001
Duration of Psoriasis (in months)	54	58.69	26.592		highly significant

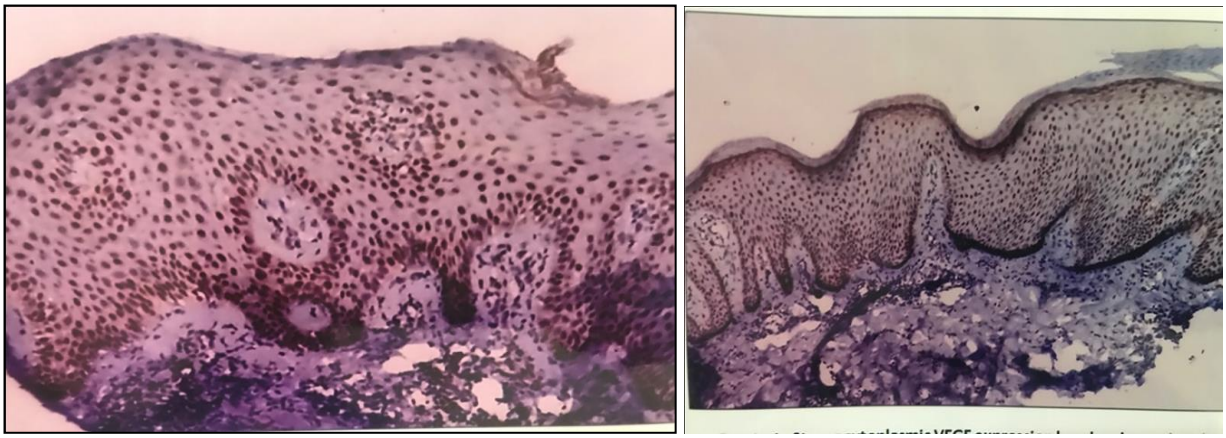

Fig1&2. Shows strong cytoplasmic VEGF expression in basal and suprabasal layer of epidermic (IHCVEGF 400X)

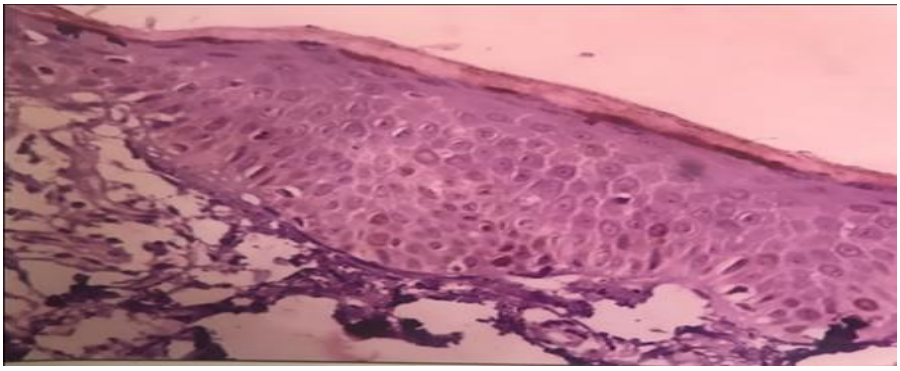

Fig3: This Photomicrograph shows mild cytoplasmic and nuclear survivan expression in basal and suprabasal layer of epidermis (IHC Survivan 400

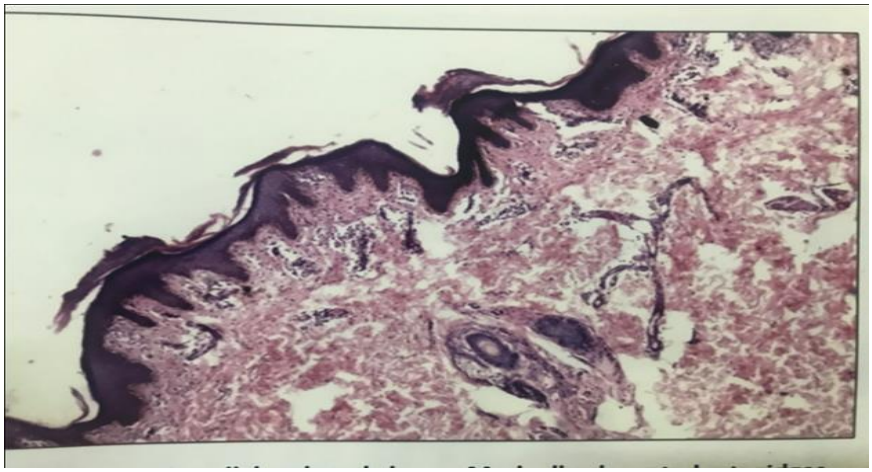

Fig4: This Photonicrograph show epidermal acanthosis papillomatosis with marked elongated rere ridges parakeratotic mounds and dilated vessels in the dermis (H&E400X)

DISCUSSION

Psoriasis is considered to be a T cell-mediated disease with active hyperproliferation of keratinocytes and abnormal vascular expansion within the superficial dermis. This expansion is mediated by angiogenesis; an active vasoproliferative process that appears to be a key inflammatory response early in the pathogenesis of psoriasis [(Hern, S. *et al*., 2005).VEGF is a major regulator of physiological and pathological angiogenesis. The receptors for VEGF (VEGFR-1 or VEGFR-2) are primarily expressed by vascular Endothelial Cells. VEGF binds to either of these receptors, leading to receptor activation and intracellular signal transduction (Ferrara, N. 2009). VEGF signalling often represents a critical rate limiting step in physiological angiogenesis. Besides its potential role in causing aberrant angiogenesis and vascular leakage in the upper dermis, VEGF may also contribute to keratinocyte proliferation and epidermal barrier homeostasis. In psoriatic skin, the VEGF receptors, VEGFR-1 and VEGFR-2, are detectable and functional in the keratinocytes (Man, X.Y. *et al*., 2006). As VEGF is secreted by the keratinocytes and induces VEGFR expression in the same cells, VEGF may also contribute to keratinocyte hyperproliferation in Psoriasis in an autocrine manner.

In our study VEGF expression was positive in 61%(33/54) of psoriatics. VEGF expression were seen in epidermis in 6 cases (11.1%) and also seen in epidermis+ dermis +blood vessels in 20 cases (37.0%). Only 7 cases (12.9%) shows VEGF expression in epidermis and blood vessels.[Fig1,2] Similar results were obtained in a study by Simonetti *et al*., who found that VEGF was strongly expressed in Psoriasis throughout the epidermis (mean 45.60 ± 19.84). Simonetti *et al*., found nuclear surviving expression mainly in the psoriatic suprabasal layer, while cytoplasmic survivin expression was seen in both the basal and suprabasal keratinocytes (Simonetti, O. *et al*., 2009). Survivin is the smallest member of a family of potent endogenous caspase inhibitors called the inhibitor of apoptosis proteins (Levkau, B. 2011). Apoptosis has become increasingly recognized as a key mechanism involved in the maintenance of tissue homeostasis, growth and development. Keratinocytic apoptosis plays a fundamental part in the control of epidermal morphogenesis and homeostasis (Elias, P. M. *et al*., 2008). In Psoriasis, keratinocytic differentiation and proliferation could be modulated and regulated by many cytokines, transcription factors and inflammatory mediators released from chronic inflammatory cells which accompany this lesion. Suppression of apoptosis has been proposed as a mechanism responsible for epidermal thickness in diseases like Psoriasis. Recent studies have defined a role for survivin in many different cell types including endothelial cells (ECs), T cells, neutrophils, fibroblasts, epithelial cells and melanocytes (QIN, L. Y. *et al*., 2010). Interestingly, human skin seems to be the only normal adult tissue expressing surviving. Human epidermis is characterized by a constant turnover of cells based on the presence of a population of stem cells in the basal layer that retains a high capacity of self-renewal throughout life. One could speculate that survivin, similarly to BCL -2 protects the cell viability. Survivin is responsible for inhibition of the intrinsic pathway of apoptosis by blocking both mitochondrial pathway and the death receptor pathway, by directly inhibiting terminal effector caspase-3,7 and interact with SMAC / DIABLO proteins that activate caspase-9, so it interacts with these proteins in order to antagonize their proapoptotic properties . Bowen *et al*., reported that survivin was expressed in most cases of actinic keratosis (83%), squamous cell carcinoma (100%), verruca vulgaris (91%), seborrheic keratosis (100%), and psoriasis (88%) (Bowen, A. R. *et al*., 2004). Markham *et al*., reported strong nuclear survivin expression in the basal layer of epidermis in 16 patients with psoriasis that decreased significantly with

infliximab therapy (Markham, T. *et al*., 2006). In our study 39 cases of the 54 psoriatic lesions (72.2%) showed positivity for survivin, comparable with the findings of Bowen *et al*., (2004) that reached 88% and the findings of Abdou and Hanout (2008) that reached 73%. These differences may be due to different numbers of investigated psoriatic patients, which were eight patients in Bowen. *et al*., study, 30 in Abdou and Hanout study , and 54 in this study. We detected nuclear survivin expression mainly in the psoriatic epithelial suprabasal layer, whereas cytoplasmic survivin expression was stained in the basal and suprabasal keratinocytes.[fig3,4] These results were similar to those of Simonetti *et al*., Several studies have demonstrated that angiogenic cytokines, vascular endothelial growth factor (VEGF) and angiopoietins modulate survivin expression in Endothelial Cells, disruption of which results in dysregulation of Endothelial Cell integrity and survival demonstrated that by resistance mediated by VEGF and represents a novel therapeutic target in angiogenic processes. In the study of O'Connor *et al*., (O'Connor, D. S. *et al*., 2000), survivin was massively up regulated in the newly formed blood vessels of granulation tissue in vivo while it is minimally detected in non-proliferating capillaries of normal skin and in the study of Markham *et al*., Survivin was strongly expressed in the dermal perivascular regions (Markham, T. *et al*., 2006). In our study Some lesions showed survivin expression in the hair follicles, sweat glands which was not detected in the normal skin opposite to what was mentioned in Chiodino *et al*., (1999) and Abdou and Hangout (2008).

The anti-apoptotic role of survivin not only came from its expression in epidermis but also in endothelial cells of the proliferating capillaries of the papillary dermis. Further genetic studies will be needed to confirm these findings and get benefit from survivin targeted therapies in the treatment of psoriasis.

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