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Psoriasis Vulgaris – An Inflammatory Skin Disease and/or Benign Epidermal Hyperplasia

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SUMMARY Psoriasis vulgaris (PV) is a systemic inflammatory disease in which immune and genetic factors are involved in the pathogenesis. Some treatment approaches in PV patients have been similar to therapy of some tumors. This fact has led to a new scientific approach to PV not only as an inflammatory disease, but also as a benign epidermal hyperplasia or a benign tumor. In this article, we hypothesize that there has been a parallel between some benign tumors and neoplasms and PV. The aim of this article is to present the approach to PV as an inflammatory disease as well as benign epidermal hyperplasia or tumor, and to introduce a new meaning.

KEY WORDS: psoriasis vulgaris, epidermal hyperplasia, benign tumor

INTRODUCTION

Psoriasis vulgaris (PV) is an inflammatory skin disease that affects skin and joints. In its most severe, erythrodermic variant, it affects the whole skin. Recently, the role of many tumor growth factors in the pathogenesis of PV has been identified. Prominent epidermal hyperplasia has been one of the dermatohistopathologic signs of PV. This could explain the fact why psoriasis affects some parts of the skin, while the other parts are spared. This clinical picture is similar to benign tumors like fibropapillomas and seborrheic keratoses or verrucae vulgaris, as found in verrucous PV (1). Considering this fact, PV could be included in differential diagnosis of some benign epidermal tumors. Therapy for PV includes cytostatics and immunosuppressants, suggesting that PV could be a variant of an epidermal tumor. In flaring clinical picture of PV, histopathology shows dense perivascular infiltrate in the upper part of the dermis, edema of papillary dermis, dilated capillaries, psoriasiform hyperplasia with equal epidermal tracks, with little or no spongiosis in the lower parts of the dermis, spongiform pustule of Kogoj, no stratum granulosum and confluent parakeratosis with collection of neutrophils in stratum corneum (2). Acanthotic epidermis is thickened four to five times in contrast to normal epidermis. Furthermore, by light microscopy one can see acanthosis in spinous layer and enlarged epidermal papillae with mitoses in basal and suprabasal layers. These data suggest hyperproliferation of keratinocytes and disorder of their differentiation. The control of keratinocyte growth is performed by different growth factors like epidermal growth factor (EGF) and transforming growth factor α2 (TGFα2) (3). By investigating the culture of keratinocytes and PV

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patients *in vivo*, it has been demonstrated that more mitoses were present in the epidermis of psoriatic patients than in healthy population.

DISCUSSION

Research on proliferating cell nuclear antigen (PCNA) and administration of monoclonal antibody Ki-67 to psoriatic patients has demonstrated that the epidermis in psoriatic patients was characterized by hyperproliferation of keratinocytes (4). Other investigations demonstrated that *in vitro* psoriatic dermal fibroblasts could initiate hyperproliferation of keratinocytes. Similar role could belong to Langerhans and other dendritic cells, which can release tumor necrosis factor α (TNF-α) and interleukin-12 (IL-12) (5). The expression of vascular endothelial growth factor (VEGF), which is coded by genes on 6th chromosome, is increased in psoriatic lesion. According to the experiments, keratinocytes and fibroblasts secrete VEGF. Recent researches confirm that psoriatic plaque demonstrates a differentiated lymphoid organ. These theses could be important in the tendency of stopping the development of lymphoid tissue in psoriatic skin for future treatments of PV. Admission of vascular reserves into the skin is provided by chemotactic protein derivatives, including IL-8 and growth-regulated oncogene-α (GRO-α) (6). Serum levels of interferon-gamma (INF-γ) correlate with the intensity of the disease, and it was observed that therapy with cyclosporine A or etretinate rapidly decreased serum levels of IFN-γ (7). Depending on the stimulation, it has been demonstrated that the connection leukocyte function-associated antigen-1/intracellular adhesion molecule-1 (LFA-1/ICAM-1) played an important role in T-cell proliferation (8). Keratinocytes treated with IFN-γ are capable of interposing bacterial superantigen induced T-cell proliferation by superficial ICAM-1. Immunostimulative function of keratinocytes is primarily provided through ICAM-1 and LFA-1 signal on T-cells (8). In PV, there is expression of angiogenic factors like VEGF and basic fibroblast growth factor (BFGF), which raise the levels of angiopoietin 2 and tyrosine kinase-2 (Tie2) expression on endothelial cells (9). There are many data proved by the authors that adhesion molecules such as ICAM-1, vascular cell adhesion molecule-1 (VCAM-1) and E selectin play an important role in pathogenesis of PV. But, there are many papers which prove that the same molecules also play important roles in the pathogenesis of tumors. Kobayashi *et al*. also confirmed that cell adhesion molecules (CAMs) such as ICAM-1, VCAM-1, E-selectin and P selectin are important in the pathogenesis of inflammation (10). This fact may explain the connection between inflammation and tumorigenesis (10). Indirectly, it has already been proven by the benefit of anti-inflammatory drugs used in cancer treatment (10). Natural killer/T lymphocyte (NK/T) cells play their role in the development of psoriatic plaques. NK/T cells and their receptors are important in the late phase of psoriatic process (11). INF-γ and TNF-α stimulate the expression of ICAM-1 in *in vitro* keratinocytes (12). These authors have demonstrated stronger expression in hyperproliferative keratinocytes induced by IL-1α (12). There were many studies indirectly supporting this hypothesis. Brody *et al*. showed that epidermal hyperplasia was present in 2-day psoriatic plaque (13). PUVA bath therapy *ex juvantibus* reduces epidermal hyperplasia in 90% of treated patients. Epidermal acanthosis was reduced in 40% of patients after 2-week therapy and in 66% of patients by the end of PUVA treatment (14). Other authors found decreasing expression of the adhesion molecules ICAM-1 and VCAM-1 in psoriatic patients after PUVA and UVB therapy (15). The importance of the adhesion molecules proved the hypothesis and papers reporting increased expression of the ICAM-1 and VCAM-1 in lesional and non-lesional skin of psoriatic patients (16). Murphy *et al*. demonstrated that epidermal hyperplasia was the most prominent histopathologic disorder in the early and resolving psoriasiform lesion (17). Dermatoscopy allows diagnosing of malignant tumors, especially pigmented, although it has its advantages in diagnosing inflammatory diseases. Blum *et al*. demonstrated dermatoscopic picture of PV as symmetrically homogeneous and bunch-like arranged. Pinpoint-like capillaries had the same appearance in PV and in clear-cell acanthoma, a tumor characterized as benign epidermal hyperplasia (18). Papules and plaques, which resemble verruca vulgaris, a benign epidermal hyperplasia caused by HPV viruses, could be seen in the clinical picture of PV. Khalil *et al*. have supported this hypothesis and demonstrated prominent epidermal hyperplasia in the histopathologic picture of papules and plaques in psoriatic patients (1). Some authors showed that proliferation of the bcl-2, Ki-67 and TUNEL markers was significantly higher in psoriatic epidermis as compared with the healthy one (19). Zippin *et al*. examined soluble adenylyl cyclase (sAC) in hyperproliferative disorders of the skin like PV, verruca vulgaris and squamous cell carcinoma *in situ* on sun damaged skin and demonstrated that keratinocytes were stained predominantly nuclear (20). The authors conclude that sAC could play a role in the pathogenesis of hyperproliferative disorders like PV (20). Putative human homologue of yeast CDC47 is member of the mini-chromosome maintenance protein family (hCDC47) and is a component of the regulatory mechanism in cell proliferation. Hiraiwa *et al*. compared the pat-

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terns of distribution of putative human homologue of yeast CDC47 and (hCDC47) positive cells in tumors and PV (21). In keratoacathomas and PV, distribution was similar as peripheral type of location positive cells, which also supports our hypothesis that PV may also be a benign epidermal hyperplasia (21).

CONCLUSION

We suggest that PV and some tumors have in part equal pathogenesis and that PV could be both a variant of hyperproliferative benign tumor as well as an inflammatory disease. We can conclude that PV, although characterized as a systemic inflammatory disease, has elements of benign epidermal hyperplasia and further researches are needed to elucidate this hypothesis.

References

1. Khalil FK, Keehn CA, Saeed S, Morgan MB. Verrucous psoriasis: a distinctive clinicopathologic variant of psoriasis. Am J Dermatopathol 2005;27:204-7.
2. Ackerman AB. Histologic diagnosis of inflammatory skin diseases. Baltimore, Maryland: Williams & Wilkins; 1997. pp. 663-4.
3. Pašić A. Eritematoskvamozne i papulozne dermatoze. In: Lipozenčić J, *et al*., editors. Dermatovenerologija. Zagreb: Medicinska naklada; 2004. pp. 197-207.
4. Duvic M, Asanao A, Hager C, Mays S. The pathogenesis of psoriasis and the mechanism of action of tazarotene. J Am Acad Dermatol 1998;129:32.
5. Koga T, Duan H, Urabe K, Furue M. *In situ* localization of IFN-gamma-positive cells in psoriatic lesional epidermis. Eur J Dermatol 2002;12:20-3.
6. Gillitzer R, Ritter U, Spandau U, Goebeler M, Bröcker EB. Differential expression of GRO-alpha and IL-8 mRNA in psoriasis: a model for neutrophil migration and accumulation *in vivo*. J Invest Dermatol 1996;107:778-82.
7. Paukkonen K, Naukkarinen A, Horsmanheimo M. The development of manifest psoriatic lesions is linked with the appearance of ICAM-1 positivity on keratinocytes. Arch Dermatol Res 1995;287:165-70.
8. Nickoloff BJ, Mitra RS, Green J, Zheng X-G, Shimizu Y, Thompson C, *et al*. Accessory cell function of keratinocytes for superantigens: dependence on lymphocyte function-associated antigen-1/intercellular adhesion molecule-1 interaction. J Immunol 1993;150:2148-59.
9. Kuroda K, Sapadin A, Shoji T, Fleischmajer R, Lebwohl M. Altered expression of angiopoietins and Tie2 endothelium receptor in psoriasis. J Invest Dermatol 2001;116:713-20.
10. Kobayashi H, Boelte KC, Lin PC. Endothelial cell adhesion molecules and cancer progression. Curr Med Chem 2007;14:377-86.
11. Vissers WH, Arndtz CHM, Muys L, Van Erp PEJ, Jong EMG, van de Kerkohf PCM. Memory effector (CD45RO+) and cytotoxic CD8+ T cells appear early in the margin zone of spreading psoriatic lesions in contrast to cells expressing natural killer receptors, which appear late. Br J Dermatol 2004;150:852-9.
12. Sebök B, Bonnekoh B, Mahrle G. Il-1 alpha-induced expression of ICAM-1 on cultured hyperproliferative keratinocytes: suppression by antipsoriatic dimethyl-fumarate. Int J Dermatol 1994;33:367-70.
13. Brody I. Dermal and epidermal involvement in the evolution of acute eruptive guttate psoriasis vulgaris. J Invest Dermatol 1984;82:465-70.
14. Coven TR, Murphy FP, Gilleaudeau P, Cardinale I, Krueger JG. Trimethylpsoralen bath PUVA is a remittive treatment for psoriasis vulgaris. Evidence that epidermal immunocytes are direct therapeutic targets. Arch Dermatol 1998;134:1263-8.
15. Cabrijan L, Lipozencić J, Batinac T, Lenković M, Stanić Zgombić Z. Influence of PUVA and UVB radiation on expression of ICAM-1 and VCAM-1 molecules in psoriasis vulgaris. Coll Antropol 2008;32 (Suppl 2):53-6.
16. Cabrijan L, Batinac T, Lenkovic M, Gruber F. The distinction between lesional and non-lesional skin in psoriasis vulgaris through expression of adhesion molecules ICAM-1 and VCAM-1. Med Hypotheses 2009;72:327-9.
17. Murphy M, Kerr P, Grant-Kels JM. The histopathologic spectrum of psoriasis. Clin Dermatol 2007;25:524-8.
18. Blum A, Metzler G, Bauer J, Rassner G, Garbe C. The dermatoscopic pattern of clear-cell acanthoma resembles psoriasis vulgaris. Dermatology 2001;203:50-2.
19. Doger FK, Dikicioglu E, Ergin F, Unal E, Sendur N, Uslu M. Nature of cell kinetics in psoriatic epidermis. J Cutan Pathol 2007;34:257-63.
20. Zippin JH, Chadwick PA, Levin LR, Buck J, Magro CM. Soluble adenylyl cyclase defines a nuclear cAMP microdomain in keratinocyte hyperproliferative skin diseases. J Invest Dermatol 2010;130:1279-87.
21. Hiraiwa A, Fujita M, Adachi A, Ono H, Nagasaka T, Matsumoto Y, *et al*.. Specific distribution patterns of hCDC47 expression in cutaneous diseases. J Cutan Pathol 1998;25:285-90.