Acta Dermatovenerol Croat 2009;17(3):162-165 SCIENTIFIC ARTICLE

The Role of CD4 and CD8 Lymphocytes and Macrophages in Psoriasis Vulgaris

Leo Čabrijan[1], Jasna Lipozenčić[2], Tanja Batinac[1], Sandra Peternel[1], Zrinjka Paštar[2]

[1]University Department of Dermatology and Venereology, Rijeka University Hospital Center and School of Medicine, Rijeka; [2]University Department of Dermatology and Venereology, Zagreb University Hospital Center and School of Medicine, Zagreb, Croatia

Corresponding author:
Leo Čabrijan, MD, PhD
University Department of Dermatology and Venereology
Rijeka University Hospital Center and School of Medicine
Krešimirova 42
HR-51000 Rijeka, Croatia
leo.cabrijan@ri.t-com.hr

Received: January 15, 2009
Accepted: June 10, 2009

SUMMARY Current knowledge of the immunopathogenesis of psoriasis vulgaris is based on the crucial role of CD4 and CD8 lymphocytes. Also, the connection of activated lymphocytes with macrophages, especially dendritic cells and plasmacytoid dendritic cells, is considered to be significant. In the present study, the expression of CD4+ lymphocytes as well as CD8+ lymphocytes ($P<0.001$) and macrophages ($P<0.001$) was found to be significantly increased in lesional skin epidermis and dermis in psoriasis vulgaris patients as compared with healthy skin. These findings suggested a cascade or chain reaction with cells and cytokines playing an important role to be involved in the immunopathogenesis of psoriasis vulgaris.

KEY WORDS: CD4, CD8, macrophages, psoriasis vulgaris

INTRODUCTION

T lymphocytes have an important role in epidermal alteration, angiogenesis and inflammation (1-4). On comparison of non-lesional and lesional skin, an increased number of T cells are found in both epidermis and dermis of lesional skin. Immunohistochemical studies have shown the expression of CD8+ cytotoxic lymphocytes to be increased in the epidermis, and the expression of CD4+ helper lymphocytes in the dermis of psoriasis vulgaris (PV) skin. These cells are responsible for the production and secretion of interferon gamma (IFN-γ), tumor necrosis factor alpha (TNF-α) and many other cytokines (5-7). CD3+ and CD8+ lymphocytes can express chemokine receptors like CXCR3 (8), and adhesion molecules such as integrin alfaEBeta7. Activated macrophages produce TNF-α. IFN-γ and TNF-α stimulate keratinocytes for the production of inflammatory cytokines. The aim of this study was to clarify the role of each cell type, CD4 and CD8 cells, and macrophages in the pathogenesis of PV.

Acta Dermatovenerol Croat
2009;17(3):162-165

MATERIAL AND METHODS

A total of 100 paraffin embedded specimens, 50 obtained from lesional skin of PV patients and 50 from normal skin of healthy volunteers as a control group were analyzed by immunohistochemistry. Immunohistochemistry was performed with CD4 and CD8 monoclonal antibodies for lymphocytes and CD68 antibody for macrophages. For visualization of immunohistochemical staining, LSAB+ (labeled streptavidin biotin method) was employed for CD4 and CD8 lymphocytes and Envision K5007 for macrophages. The number of each cell type was determined by counting the number in each specimen in ten fields (magnification, X400), followed by determination of the mean number of positive cells.

Patients included in the study had a chronic stationary form of PV and did not use any local or systemic treatment for at least two weeks. Patients with erythrodermic and arthropathic form or with pustular psoriasis were excluded from the study. Statistical analysis was done by use of Student's t-test and variance analysis test.

RESULTS

The present study compared the expression of CD4 and CD8 cells in the lesional skin epidermis and dermis of PV patients and in healthy skin (control group). Study results are presented in Tables 1, 2 and 3.

The expression of CD4+ lymphocytes in lesional skin epidermis and dermis of PV patients was significantly increased as compared with the expression in healthy skin of control group subjects (P<0.001) (Table 1). Also, the expression of CD8+ lymphocytes in lesional skin epidermis and dermis of PV patients was significantly greater as compared with the expression in healthy skin of control group subjects (P<0.001) (Table 2).

The expression of macrophages (CD68+ cells) in lesional skin epidermis and dermis of PV patients and in healthy skin of control subjects is shown in Table 3. The number of macrophages was significantly higher in the skin of PV patients as compared with the skin of healthy controls (P<0.001). The increased numbers of CD4+ and CD8+ lymphocytes found in the lesional skin of PV patients could be associated with the intense macrophage infiltration of lesional skin in PV patients, as illustrated in Figures 1, 2 and 3.

Table 1. Expression of CD4+ lymphocytes in lesional skin epidermis and dermis of psoriasis vulgaris patients and in healthy skin of control subjects

	CD4 cells in epidermis and dermis		
Cells	Mean	SD	Statistics
Psoriasis vulgaris patients	19.09	4.15	t=6.69 P<0.001
Control subjects	15.47	2.88	

Table 2. Expression of CD8+ lymphocyes in lesional skin epidermis and dermis of psoriasis vulgaris patients and in healthy skin of control subjects

	CD8 cells in epidermis and dermis		
Cells	Mean	SD	Statistics
Psoriasis vulgaris patients	32.02	7.27	t=17.09 P<0.001
Control subjects	15.67	5.17	

Table 3. Expression of macrophages in the skin of psoriasis vulgaris patients and in control group

			Statistics	
	Control group	Psoriasis vulgaris patients	F	P
Macrophages (CD68+ cells) $\bar{x}$ ±SD (%)	15.3±9.5	29.4±12.9	27.46	<0.001

DISCUSSION

It is well known that T cells, CD4+ and CD8+, play an important role in the pathogenesis of PV. It should also be noted that a cascade or chain reaction between many inflammatory cells and cytokines takes place in PV (9). However, the leading molecule or antigen that is responsible for initia-

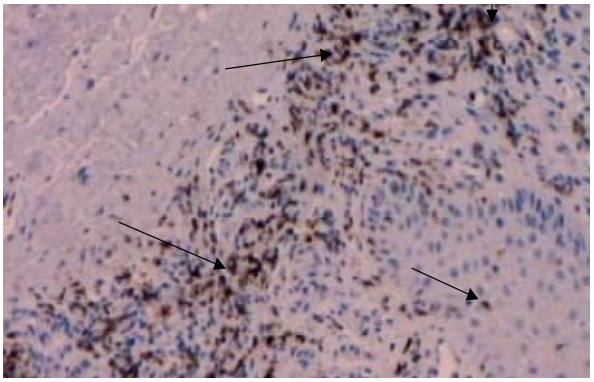

Figure 1. Immunohistochemical stain of CD4 cells in lesional skin of psoriasis vulgaris patients (X200). Intense inflammatory infiltrate of CD4 positive lymphocytes (arrows).

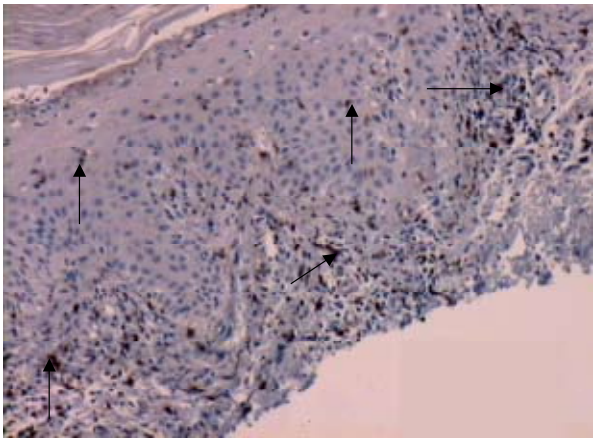

Figure 2. Immunohistochemical stain of CD8 cells in lesional skin of psoriasis vulgaris patients (X200). Intense inflammatory infiltrate of CD8+ lymphocytes (arrows).

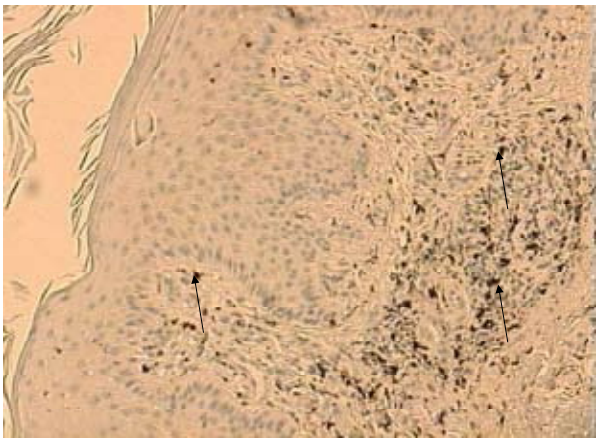

Figure 3. Immunohistochemical stain of CD68+ macrophages in lesional skin of psoriasis vulgaris patients (X200). Strong macrophage infiltrate in lesional skin of psoriasis vulgaris patients (arrows).

tion of the inflammatory process and development of skin lesions in PV remains unknown. Some authors believe that immune events in PV make important distinction between lesional and non-lesional skin (9). Indeed, lesional skin can thus be clinically and histopathologically differentiated from non-lesional skin in PV patients, whereas there is only little or no difference on immunohistochemistry (10).

As expected, we found more CD4+ lymphocytes in the skin samples of lesional PV skin in comparison with control group (P<0.001). CD8+ lymphocytes were also present in a significantly greater number in PV lesional skin as compared with control group (P<0.001). Vissers *et al.* (11) compared the expression of CD4 and CD8 lymphocytes in the center and at the inner and outer margin of PV plaque and found a greater number of CD4+ cells than CD8+ cells in the dermis of the plaque center as well as in the inner and outer margin of PV plaque. In the epidermis, they observed greater expression of CD8+ cells as compared with CD4+ cells in the center of psoriatic lesion, as well as on the inner margin of psoriatic lesion. CD8+ cells were considered to be important in the early phase of PV, along with CD25+ cells, CD2+ cells and CD45RO+ cells (11). There also are opposite reports on a greater number of CD4+ lymphocytes than CD8+ cells, which are activated late (12). In our study, we found an increased number of CD4+ lymphocytes in epidermis and dermis of psoriatic lesions in comparison with control group. de Boer *et al.* report on the predominance of CD8+ lymphocytes in the epidermis of PV patients (12), whereas Onuma (13) found CD4+ cells to prevail in the epidermis in the early phase, followed by the predominance of CD8+ cells in the later or chronic phase. This author also reports on the predominance of CD4+ lymphocytes in dermal infiltrate in the early and later phase of psoriatic lesions (13).

CD68 is a myelomonocytic marker that identifies dermal macrophages (14). We detected a significantly higher expression of CD68+ cells in PV patients than in control group (P<0.001). The major role of these molecules was demonstrated in many studies in association with the obvious role of T lymphocytes, neutrophils and dendritic cells (14). Other authors found CD68+ dendritic epidermal cells in normal skin, and in a greater number in lesional skin of PV patients, in association with the increased monocyte chemoattractant protein-1 (MCP-1), which is important in migration of CD68+ cells (14). CD68+ dendritic cells are a subpopulation of C1a+ Langerhans cells (14).

In comparison with our results, some authors did not find an increased number of CD68+ macrophages in PV skin (15), whereas others, like de Boer *et al.* (12), found a higher number of CD68+ cells in lesional and non-lesional skin of PV patients in comparison with healthy skin. There also are reports on CD83+ dendritic cells that play an important role in the immune response in the dermis, along with lymphocytes, but are rare in the epidermis (16). Activated dendritic cells capture and present antigens to the immune cells, leading to initiation of immune response in PV, and also play an important role in both non-lesional and lesional PV skin (17,18). Studies of plasmacytoid dendritic cells detected an increased number of these cells in lesional skin of PV patients in comparison with healthy skin (19). Interactions of dendritic cells and T cells could be a new target of biologic therapy in PV (20).

In conclusion, CD4+ and CD8+ lymphocytes are important in the pathogenesis of PV, but it is clear that only their interaction with other cells such as neutrophils and dendritic cells, in association with a cascade of interleukins and cytokines, can lead to the development of PV. It is well known that topical and systemic therapy is very useful in PV management, but biologic agents open a new era in the treatment of these patients and systemic therapy may replace topical treatment in the times to come.

References

1. Pašić A. Eritematoskvamozne i papulozne dermatoze. In: Lipozenčić J, *et al.* Dermatovenerologija. Zagreb: Medicinska naklada; 2004. pp. 197-207.
2. Springer TA. Adhesion receptors of the immune system. Nature 1990;346:425-34.
3. Hisashi W, Masahiro T. E-selectin and vascular cell adhesion molecule-1 are critical for initial trafficking of helper-inducer/memory T cells in psoriatic plaques. Arch Derm 1994;130:457-63.
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;39:S129-32.
5. Asadullah K, Döcke WD, Ebeling M, Friedrich M, Belbe G, Audring H. Interleukin 10 treatment of psoriasis: clinical results of a phase 2 trial. Arch Dermatol 1999;135:187-92.
6. Asadullah K, Sterry W, Stephanek K, Jasulaitis D, Leupold M, Audring H, *et al.* IL-10 is a key cytokine in psoriasis. Proof of principle by IL-10 therapy: a new therapeutic approach. J Clin Invest 1998;101:783-94.
7. Boehm U, Klamp T, Groot M, Howard JC. Cellular responses to interferon-gamma. Annu Rev Immunol 1997;15:749-95.
8. Rottman J, Smith T, Ganley K, Kikuchi T, Krueger J. Potential role of the chemokine receptors CXCR3 CCR4 and the integrin alfaEbeta7 in the pathogenesis of psoriasis vulgaris. Lab Invest 2001;81:335-47.
9. Čabrijan L, Batinac T, Lenković 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. Epub 2008. Nov 20.
10. Čabrijan L, Lipozenčić J, Batinac T, Lenković M, Stanić Zgombić Z. Influence of PUVA and UVB radiation on expression of ICAM-1 nad VCAM-1 molecules in psoriasis vulgaris. Coll Antropol 2008;32 Suppl 2:53-6.
11. Vissers WM, 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. de Boer OJ, Visser C, Bos A, Pranab K. Cellular interactions and adhesion molecules in psoriatic skin. Acta Derm Venereol Suppl (Stockh) 1994;186:15-8.
13. Onuma S. Immunohistochemical studies of infiltrating cells in early and chronic lesions of psoriasis. J Dermatol 1994;21:223-32.
14. Nakamura K, Yasaka N, Asahina A, Kato M, Miyazuno K, Furue M, *et al.* Increased numbers of CD68 antigen positive dendritic epidermal cells and upregulation of CLA (cutaneous lymphocyte-associated antigen) expression on these cells in various skin diseases. J Dermatol Sci 1998;18:170-80.
15. Deguchi M, Aiba S, Ohtani H, Nagura H, Tagami H. Comparison of the distribution and numbers of antigen-presenting cells among T lymphocyte-mediated dermatoses: CD1a+, factor XIIIa+, and CD68+ cells in eczematous dermatitis, psoriasis, lichen planus and graft-versus-host disease. Arch Dermatol Res 2002;294:297-302.
16. Koga T, Duan H, Urabe K, Furue M. In situ localization of CD83-positive dendritic cells in psoriatic lesions. Dermatology 2002;204:100-3.
17. Zhu Kj, Cheng H, Mao Xh, Lao LM, Cen JP, Ye J. Increased endocytic activity in monocyte-derived dendritic cells in patients with psoriasis vulgaris. Indian J Med Res 2006;123:43-50.
18. Chamian F, Krueger JG. Psoriasis vulgaris: an interplay of T lymphocytes, dendritic cells, and inflammatory cytokines in pathogenesis. Curr Opin Rheumatol 2004;16:331-7.
19. Chen J, Tan Z, Liu Z, Wu Y, Li J. Expression of plasmacytoid dendritic cells, IRF-7, IFN-alpha mRNA in the lesions of psoriasis vulgaris. J Huazhong Univ Sci Technol Med Sci 2006;26:747-59.
20. Jariwala SP. The role of dendritic cells in the immunopathogenesis of psoriasis. Arch Dermatol Res 2007;299:359-66.