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Selected Immunological Changes in Patients with Goeckerman's Therapy TNF-alpha, sE-selectin, sP-selectin, sICAM-1 and IL-8

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Summary

Psoriasis is one of the most frequent inflammatory skin diseases in which abnormal individual immune reactivity plays an important role. The aim of the present study was to describe selected immunological changes, concerning pro-inflammatory cytokines (TNF-alpha, IL-8) and adhesion molecules (sE-selectin, sP-selectin, sICAM-1), in 56 patients cured by Goeckerman's therapy (GT). GT includes dermal application of crude coal tar (containing polycyclic aromatic hydrocarbons) and exposure to UV radiation. When compared with the control group (healthy blood donors), the patients before GT had significantly increased serum levels of sE-selectin ($p<0.001$), sP-selectin ($p<0.001$), sICAM-1 ($p<0.001$) and IL-8 ($p<0.001$). Significantly decreased serum levels of sE-selectin ($p<0.05$) and significantly increased serum levels of IL-8 ($p<0.05$) were found after GT therapy. Serum levels of sICAM significantly correlated with the disease activity and with serum levels of sE-selectin. The level of PASI score (Psoriasis Area and Severity Index) significantly decreased after GT ($p<0.001$) and confirms the high efficiency GT. These findings confirmed that pro-inflammatory chemokine (IL-8) and adhesion molecules (sE-selectin, sP-selectin, sICAM-1) play an important role in the development and regulation of inflammation in psoriasis. Determination of sE-selectin and sICAM seems to be a promising marker of psoriasis's activity. Chemokine pathway (IL-8) and TNF-alpha activity seem to be modulated by Goeckerman's therapy (polycyclic aromatic hydrocarbons).

Key words

Psoriasis • Goeckerman's Therapy • TNF-alpha • sE-selectin • sP-selectin • sICAM-1 • IL-8

Introduction

Psoriasis is one of the most frequent chronic hyperproliferative skin diseases with genetic predisposition, e.g. certain HLA (Human Leukocyte Antigens) haplotype (HLA-Cw*0602) (Kundakci *et al.*

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2002). The pathogenesis of this disease remains enigmatic but numerous immunologic, bioregulatory and biochemical changes accompanying this disease were described (Svozil 2002). Psoriasis is an inflammatory T cell-mediated disease (Prinz 2001, de Rie *et al.* 2004), characterized by epidermal hyperplasia and parakeratosis, resulting in lesional areas of thick and scaling skin (Morrow 2003). Increased levels of proinflammatory cytokines are being found in psoriatic lesions, predominantly of the Th1 cell profile (Ozawa and Aiba 2004). What is responsible for the activation of T cells is still unknown, but several hypotheses exist as causal, including keratinocyte-mediated and Langerhans cell-mediated activation (Scott and Neil 2004). Both cells may also be responsible for immune activation. TNF-alpha is one of the most potent proinflammatory cytokines (inciting agents for the disease) prevalent in psoriatic lesions. TNF-alpha has many effects in the induction of an inflammatory response such as stimulating production of pro-inflammatory chemokine (e.g. IL-8) and adhesion molecules (e.g. sE-selectin, sP-selectin, sICAM-1) (Scott and Neil 2004).

Goeckerman´s therapy (GT) is often used as the first option for effective treatment of psoriasis (Lebwohl and Ali 2001, Jenner *et al.* 2002, Novotný 2002, Thami and Sarkar 2002, Borská *et al.* 2006). GT includes dermal application of crude coal tar (CCT), containing polycyclic aromatic hydrocarbons (PAHs), and exposure to UV radiation. PAHs and UV (GT) represent potentially mutagenic, carcinogenic (Gardošová *et al.* 1997, Fiala *et al.* 2000, Lüllmann *et al.* 1999, Fiala *et al.* 2004, Borská *et al.* 2004, 2006) and immunotoxic agents (Luster and Rosenthal 1993, Fiala *et al.* 2000).

The aim of the present study was to describe the serum levels of pro-inflammatory cytokine (TNF-alpha, IL-8) and adhesion molecules (sE-selectin, sP-selectin, sICAM-1) in patients undergoing the Goeckerman´s therapy.

Research Design and Methods

Subjects, therapy and sampling

A group of 56 patients aged 18-77 years, diagnosed with psoriasis and undergoing GT, was selected. The group consisted of 35 men and 21 women and includes 25 smokers and 31 non-smokers. The Ethics Committee of the Medical Faculty of Charles University, University Hospital and Purkyně Military Medical Academy in Hradec Králové reviewed and approved this study.

The therapy was medicated individually (from 8 to 30 days; average time 17 days). CCT ointment (containing 5 % of CCT-Pix Lithantracis) was applied daily to the patches (32-77 % of the patient's body surface). Concurrently, the patients were daily irradiated by ultraviolet radiation-A (UV-A) and ultraviolet radiation-B (UV-B). Radiation was applied in relation to the intensity of disease activity at intervals from 1 to 15 min. Density of UV-B radiation (134.45 $\mu W/cm^2$) and UV-A radiation (245.60 $\mu W/cm^2$) was controlled by spectroradiometer Sola-Scope 2000 (Solatell Ltd., UK).

Prior to the beginning of this study, informed consent of each subject was obtained. A questionnaire was given to each subject to determine his or her co-exposures to coal tar (PAHs) and UV-radiation. Patients with positive exposure history were excluded. The efficacy of GT was assessed with respect to erythema, infiltration and desquamation by means of the Psoriasis Area and Severity Index – PASI score (de Rie *et al.* 2004). Patients were assessed before treatment and after the treatment period.

The set of selected immunological parameters (TNF-alpha, IL-8, sE-selectin, sP-selectin and sICAM-1) in the peripheral blood of patients with psoriasis before therapy were statistically compared with the results of a group of healthy blood donors (from 25 to 50 people, aged 18-77, who were examined for the individual immune parameters), denoted as the control group. Subjects from the control group were not exposed to harmful chemical compounds and they lived in the same locality as patients with psoriasis.

Immunological findings

The levels of serum sE-selectin, sP-selectin, sICAM-1, TNF-alpha and IL-8 were evaluated using the commercial ELISA technique (R&D Systems, USA).

Statistical analysis

The differences between average values of the parameters were evaluated by two-tailed Student's t-test. To assess the treatment effect, appropriate samples before and after the GT were compared by the paired t-test, while the probability of significant differences between the control and patient group were calculated by using the t-test for independent samples. The associations between selected parameters were evaluated by Pearson's correlation coefficient. The statistical significance was assessed on a probability level $p<0.05$ in all calculations.

Table 1. Serum levels in patients before and after GT

Serum levels	n	Before GT	n	After GT	p
TNF-alpha (pg/ml)	56	1.68 ± 0.83	56	1.51 ± 0.72	NS
sE-selectin (ng/ml)	56	91.03 ± 59.85	56	85.36 ± 49.83	P<0.05
sP-selectin (ng/ml)	56	111.23 ± 33.35	56	108.42 ± 34.37	NS
sICAM-1 (ng/ml)	56	337.77 ± 126.71	56	328.30 ± 119.37	NS
IL-8 (ng/ml)	56	51.93 ± 22.33	56	88.06 ± 111.21	P<0.05

Values are expressed as arithmetic means ± SD; n = number of samples,NS - non-significant difference

Table 2. Serum levels in patients before GT and healthy controls

Serum levels	n	Before GT	n	Controls	P
TNF-alpha (pg/ml)	56	1.68 ± 0.83	40	1.80 ± 1.10	NS
sE-selectin (ng/ml)	56	91.03 ± 59.85	70	42.90 ± 37.20	P<0.001
sP-selectin (ng/ml)	56	111.23 ± 33.35	70	84.30 ± 40.90	P<0.001
sICAM-1 (ng/ml)	56	337.77 ± 126.71	70	121.70 ± 53.40	P<0.001
IL-8 (ng/ml)	56	51.93 ± 22.3	55	33.70 ± 12.90	P<0.001

For legend see Table 1.

Results

Immunological findings in psoriatic patients before GT when compared with control group are presented in Table 2. The results showed increased serum levels of sE-selectin, sP-selectin, sICAM-1 and IL-8 in the groups of patients before GT. The serum level of TNF-alpha was not significantly different between patients before GT and the controls.

Immunological findings in psoriatic patients before and after GT are presented in Table 1. Significantly decreased serum levels of sE-selectin and significantly increased serum levels of IL-8 were found after the therapy. The changes of other immunological findings were not significant.

We found some significant correlation between the serum level of immunological parameters and the basic characteristics of GT (Table 3). Serum levels of sICAM significantly correlated with activity of the disease, expressed as the PASI score, and with serum levels of sE-selectin.

The PASI score before and after GT was 22.2±6.9 and 6.3±3.7, respectively. The results showed significant improvement in the clinical state of psoriatic patients treated by GT ($p<0.001$).

Discussion

Psoriasis is an immune-mediated skin disease in which chronic T-cell stimulation by still unknown antigens is mediated by antigen presenting cells (APC), localized in the skin (Novotný 2002, Scott and Neil 2004). Langerhan's cells and dermal dendritic cells are specialized APC present in epidermis and dermis. APC mature upon capture of the antigen and migrate to the skin-draining lymph node, where they can activate antigen-specific naive T-cells. Naive T-cells (CD45RA+) can be either CD4+ (T-helper cells) or CD8+ (cytotoxic, suppressor) (Štork and Klubal 2001, Ozawa and Aiba 2004, Vašků 2004) and recognize the antigen, presented by APC, in contex of the major histocompatibility complex (MHC) proteins II or I. The mature T-cells proliferate and express the skin-homing marker, cutaneous lymphocyte-associated antigen, which can allow binding to the transmembrane endothelial cell adhesion molecules, E-selectins and P-selectins. When the activated T-cells release cytokines such as TNF-alpha, a complex immune response can be initiated and other immune effector cells are being recruited, including neutrophils. Neutrophils and other immune cells can be recruited from the blood vessels into the dermis in response to immune activation, provided by activated

Table 3. Relationships between immunological changes and PASI score

Parameters	TNF-alpha	sE-selektin	sP-selektin	sICAM-1	IL-8
PASI	n=56 r=-0.013	n= 56 r=0.101	n=56 r=0.944	n=56 r=0.263	n=56 r=0.039
Score	NS	NS	NS	p<0.05	NS
TNF-alpha		n=56 r=-0.095	n=56 r=0.037	n=56 r=0.024	n=56 r=0.197
(pg/ml)		NS	NS	NS	NS
sE-selektin	n=56 r=-0.095		n=56 r=0.128	n=56 r=0.582	n=56 r=-0.054
(ng/ml)	NS		NS	p<0.001	NS
sP-selektin	n=56 r=0.037	n=56 r=0.128		n=56 r=0.121	n=56 r=0.213
(ng/ml)	NS	NS		NS	NS
sICAM-1	n=56 r=0.024	n=56 r=0.582	n=56 r=0.121		n=56 r=0.088
(ng/ml)	NS	p<0.001	NS		NS
IL-8	n=56 r=0.197	n=56 r=-0.054	n=56 r=0.213	n=56 r=0.088	
(ng/ml)	NS	NS	NS	NS	

n = number of samples, r = Pearson's correlation coefficient. p<0.05 and **p<0.1 and ***p<0.001, NS indicates statistically insignificant difference.

endothelial cells, keratinocytes or T-cells. TNF-alpha induced keratinocytes to produce IL-8, which is chemotactic for neutrophils. TNF-alpha released from T-cells also induces keratinocytes to produce the vascular endothelial cell growth factor, resulting in neighboring endothelial cell proliferation, resulting in enhanced expression of ICAM (Victor and Gottlieb 2002, Scott and Neil 2004).

TNF-alpha

TNF-alpha is one of the key cytokines in the innate immune response and is increased in psoriatic lesions (Bonifati *et al.* 1995, Terajima *et al.* 1998, Krejsek and Kopecký 2004). Recent data clearly indicated that TNF-alpha production is increased in psoriatic lesions of the skin as compared to non-lesioned and healthy skin (Ettehadi *et al.* 1994, Groves *et al.* 1995, de Rie 2004). For example, Mussi *et al.* (1997) analyzed the serum TNF-alpha (by ELISA) in plaques of psoriatic patients. Serum TNF-alpha levels of the patients were significantly higher than those of the controls. After effective treatment, both the PASI scores and the cytokine TNF-alpha levels concomitantly decreased (p<0.001). A significant correlation was observed between circulating TNF-alpha and E-selectin in agreement with a possible functional activity of these cytokines.

In our study we did not find differences between patients with psoriasis and the control group in serum levels of TNF-alpha (Table 2). Likewise, observed therapy did not affect the level of TNF-alpha in psoriatic patients (Table 1). Our results are in good agreement with Tigalonova *et al.* (1994) but they are not consistent with the results described in the previous paragraph.

The results of experimental studies are inconsistent. The inhalation exposure of rats to asphalt fumes (containing PAHs) did not activate alveolar macrophage to produce pro-inflammatory cytokine TNF-alpha (Ma *et al.* 2003, Legret *et al.* 2005). On the other hand, "in vitro" exposure of rat alveolar macrophages to diesel exhaust particles containing PAH decreased the ability of lipopolysacharide (LPS) to stimulate the production of proinflammatory cytokine TNF-alpha (Castranova *et al.* 2001).

sE-selectin, sP-selectin

As in other organs, leukocyte adhesion molecules and their ligands play a major role in cutaneous inflammatory events, both by directing leukocyte trafficking and by their effects on antigen presentation (Krejsek and Kopecký 2004). Skin biopsies, taken from inflamed skin of patients with diseases such as psoriasis, reveal up-regulation of endothelial cell expression of P-selectin, E-selectin and intercellular adhesion molecule 1 (ICAM-1) (Barker 1995). When cutaneous inflammation is severe (e.g. in erythroderma), soluble forms of these molecules begin to be detectable in the serum. (Barker 1995, Andrýs *et al.* 1999).

A number of studies focused on endothelial activity described increased serum levels of soluble E-

selectin (sE-selectin) in psoriatic patients compared to healthy controls (Bonifati *et al.* 1995, Czech *et al.* 1996, D´Auria *et al.* 1998, Szepietowski *et al.* 1999). These studies reported decreasing sE-selectin serum levels after therapy. Both these effects were also observed in our study (Tables 1 and 2).

sICAM-1

ICAM-1 is an immunoglobulin-like adhesion molecule expressed on the surface of several cell types, including endothelial cells and cells involved in the immune response. It plays an important role in the adhesion and migration of leukocytes to the site of inflammation (Andrýs *et al.* 2000, Pietruczuk *et al.* 2004). ICAM-1 is expressed as membrane-bound and soluble form (Rothlein *et al.* 1991). The levels of sICAM-1 are increased in numerous diseases (Pietruczuk *et al.* 2004), including psoriasis (Kowalzick *et al.* 1993, Lee *et al.* 1994). In our study the serum levels of sICAM significantly increased in patients in comparison to the control group (Table 2). Our results are in good agreement with those of Schopf *et al.* (1993). Ameglio *et al.* (1994) found significant correlation between the serum levels sICAM and PASI score which was also found in our study (Table 3). Zhang *et al.* (2004) detected ICAM-1 by immunohistochemistry directly in lesions of 26 patients with psoriasis before and after treatment. The sICAM-1 concentration showed no significant differences between active disease and static phase of psoriatic lesions ($p>0.05$). Likewise, we did not find significant differences in sICAM levels before and after GT (Table 1)

IL-8

IL-8 is one of the best characterized chemotactic and proinflammatory cytokines from the large group of chemokines (Parkin and Cohen 2001, Krejsek and Kopecký 2004). Many studies indicate that IL-8 may be involved in the imunopathogenesis of psoriasis (Konstantinova *et al.* 1996, Bonifati and Ameglio 1999, Duan *et al.* 2001). In fact, currently available data suggest that this cytokine exerts a critical role as a potent chemoattractant for neutrophils and T-lymphocytes, as well as the factor stimulating keratinocyte proliferation (Bonifati and Ameglio 1999, Prinz 2001). Jacob *et al.* (2003) investigated serum levels of IL-8 in psoriatic patients. IL-8 was significantly increased in psoriatic patients compared to the controls and positively correlated with disease activity. Abanmi *et al.* (2005) compared the serum levels of IL-8 in patients with psoriasis and healthy controls recruited from the Saudi Arabia population. Results showed significantly higher levels of serum IL-8 in psoriatic patients when compared with healthy controls. Our results are in good agreement with their observations (Table 2).

All previous studies mentioned above confirmed decreasing serum IL-8 levels after the therapy. However, we found significantly increased serum IL-8 levels after GR (Table 1). We suppose that this effect might be induced due to exposure to PAHs (contained in coal tar). PAHs such as benzo(a)pyrene are toxic environmental contaminants, known to enhance production of pro-inflammatory cytokines (Lecureur *et al.* 2005). PAHs are associated with diesel exhaust particles that are able to enhance the serum activity of IL-8 (Fahy *et al.* 1999, 2000). Healthy subjects developed airway inflammation 6 hours after exposure to diesel exhaust. The inflammation was related to airways neutrophilia and lymphocytosis, together with an increase of IL-8 in the lavage fluid and upregulation of the endothelial adhesion molecules (Stenfors *et al.* 2004). In our previous study we investigated the group of 23 patients with psoriasis, treated by GT (Fiala *et al.* 2004). The content of 15 selected PAHs in samples of used coal tar varied from 29-36 %. In the presented study we found significantly increased serum levels of IL-8 (Table 1). These findings suggest that the chemokine pathways (IL-8) are modulated by GT and that the development of inflammatory reactions might be affected by coal tar (polycyclic aromatic hydrocarbons).

Conclusion

Our results confirmed enhanced endothelial activity in patients with psoriasis. We found significantly increased levels of pro-inflammatory chemokines and adhesion molecules sICAM-1, IL-8, sP-selectin and sE-selectin in psoriatic patients before therapy. After the therapy we found significantly decreased levels of sE-selectin and non-significantly decreased levels of sICAM and sP-selectin. On the contrary, the levels of IL-8 were significantly increased after the therapy. This fact indicated that the chemokine pathway of IL-8 activity can be modulated by Goeckerman's therapy (polycyclic aromatic hydrocarbons).

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