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Acute Phase Proteins in Psoriasis

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A B S T R A C T

Psoriasis is a chronic, relapsing, inflammatory and hyperproliferative skin disorder. The levels of acute phase proteins are suggested to be elevated in those patients with acute disease. The expression of selected acute phase proteins as the parameters of humoral immunity has been analyzed in 70 patients with acute psoriasis and 40 healthy controls. The aim was to evaluate the inflammatory response in the exacerbation of psoriasis and to determine the correlation of these objective inflammatory parameters with clinical features of disease activity. Main demographic and epidemiologic features were, as well, analysed. The plasma levels of C-reactive protein (CRP) (χ^2 = 23.61; p<0.005), and alpha1-acid glycoprotein (α1-AGP) (χ^2 = 7.,42; p<0.01) were significantly increased in those patients with acute phase of the disease compared to healthy controls. Our results suggest that psoriasis is an inflammatory disease and therefore its worsening seemed to be linked to the increase in the inflammatory response. It seems that CRP and al-AGP levels could serve as important prognostic factors for the worsening of psoriasis.

***Key words**: alpha1-acid glycoprotein, alpha2-macroglobulin, alpha1-antitrypsin, C-reactive protein, psoriasis*

Introduction

Psoriasis is histologically characterized by significant epidermal keratinocyte hyperplasia and it has been suggested that impaired epidermal proliferation and keratinocyte differentiation, as well as increased epidermal turnover play a role in the pathogenesis of the disease[1,2]. Psoriasis is defined as a chronic, relapsing, inflammatory and hyperproliferative skin disorder characterized by sharply defined erythematosquamous lesions[3]. The pathogenesis of the disease remains enigmatic. It is an inflammatory disease in which abnormal individual immune response plays an important role[4]. The genetic predisposition, certain Human Leukocyte Antigens (HLA) haplotype (HLA-Cw*0602) in association with environmental factors are involved in the immunopathogenesis of psoriasis[5]. The environmental triggering factors are largely unknown, but it is well known that bacterial infections, such as Streptococcal infection, may induce or aggravate psoriasis by antigen-mediated induction of immunopathological reactivity.

An acute phase of psoriasis can be induced by inflammatory cytokines that play an important role in the pathogenesis of the disease. Activation of the acute phase reaction by pro-inflammatory cytokines is responsible for the development of systemic symptoms, such as increased temperature, arthropaty and general pruritus, in severe forms of psoriasis, like arthorpatic and pustular psoriasis. It has been suggested that acute phase proteins are mostly elevated in the acute phase of the disease, while still present in phases of clinical remission. Among the large group of acute phase reactants, C-reactive protein (CRP), alpha2-macroglobulin (α2-MG), alpha1-antitrypsin (α1-AT), and alpha1-acid glycoprotein (α1-AGP) may be of special interest in psoriasis.

In this study, we examined the expression of selected acute phase proteins as the parameters of humoral immunity in acute phase of the disease in order to determine the correlation of the inflammatory response and

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the exacerbation of psoriasis. We have also analyzed demographic and epidemiologic features of psoriatic patients in order to determine a genetic predisposition for the disease.

Materials and Methods

We included in this study 110 patients, of which 40 healthy volunteer blood donors (6 female, 34 male) and 70 patients diagnosed with psoriasis (34 female, 36 male), treated at the Department of Dermatovenerology, University Hospital Osijek, Department of Dermatovenerology, University Hospital Zagreb and Department of Dermatovenerology, Clinical Hospital »Sestre Milosrdnice«, Zagreb, between 2005 and 2007, irrespective of age and sex. Diagnostic criteria for psoriasis included typical clinical features which were then confirmed histologically.

The average age of psoriatic patients was 51.0 ± 12.6 years (48.7 ± 12.5 years for male, 53.4 ± 12.4 years for female) and of healthy controls 36.7 ± 10.0 years (37.2 ± 9.4 years for male, 33.7 ± 13.8 years for female). The healthy control group consisted of significantly younger patients compared to the group of patients with psoriasis ($p< 0.05$).

Patients with psoriasis were clinically carefully evaluated. Severity of psoriasis was determined quantitatively based on the percentage of skin involvement and was graded as follows: minimal skin involvement (less than 9% of skin involved), average skin involvement (between 10% and 29% of skin involved) and extreme skin involvement (more than 30% of skin involved). The average percentage of the involved skin in psoriatic patients was 51.4% (36) and the extreme skin involvement was observed in 48.6% (34) patients. The estimated median skin involvement in psoriasis was 32.93% (SD 21.63). The pustular psoriasis was not included in the research.

Blood samples were obtained from patients with psoriasis in the active stage of the disease and healthy control group. Plasma concentrations of CRP, α2-MG, α1-AT and α1-AGP were analyzed. In vitro diagnostic methods were used for the quantitative determination of α1-AT, α2-AGP and α2-MG in human serum such as nephelometry using the Nephelometer- BN ProSpec (BN*Systems, Dade Behring Marburg GmbH, USA). The assay protocols for BN*Systems are given in the Instruction Manual and software of the instrument. All steps are performed automatically by the system. (Reagents-materials provided: N Antiserum to Human α1-Antitrypsin, Code No. OSAZ; N Antiserum to Human α2-Macroglobulin, Code No. OSAM or N Antiserum to Human α1-acid Glycoprotein, Code No. OSAW).

CRP was determined by immuno-turbidimetric test for the quantitative determination of C-reactive protein (CRP) in human serum and plasma on OLYMPUS analyses (CRP Latex-OSR6199). Calibration was for Normal application with calibrator: Olympus CRP Latex Calibrator Normal Set (Cat. No.ODC0026). The calibrator CRP values are traceable to IFCC (International Federation of Clinical Chemistry) standard CRM 470.

The differences between groups were analysed using the Mann-Whithey U test and Chi-square test. *P* values of less than 0.05 were considered statistically significant.

Results

A familiar distribution pattern for psoriasis has been found in 26 (37.14%) patients with psoriasis. A significantly higher genetic prevalence was found in patients with type I psoriasis (22 patients, 31.4%), compared to patients with type II psoriasis (4 patients, 5.7%) ($\chi^2= 9.92$; $p<0.05$). It was observed that heredity is more often related to the father's side of the family (11 of totally 26 patients) compared to mother's side (6 of totally 26 patients) but the difference was not statistically significant ($\chi^2=1,39$; $p>0.05$) due to the small group of patients.

TABLE 1
PLASMA LEVELS OF ACUTE PHASE PROTEINS IN PSORIASIS AND HEALTHY CONTROL GROUP

	Diagnosis	Normal		Decreased		Increased		p*
		N	%	N	%	N	%	
α2-MG	Psoriasis	51	72.9	16*	22.9	3*	4.3	>0.05
	Control	37	92.5	3	7.5	0	0.0	
α1-AT	Psoriasis	58	82.9	7*	10.0	5*	7.1	>0.10
	Control	35	87.5	5	12.5	0	0.0	
α1-AGP	Psoriasis	48	68.6	2	2.9	20*	28.6	<0.01
	Control	36	90.0	2	5.0	2	5.0	
CRP	Psoriasis	38	54.3	–	–	32*	45.7	<0.005
	Control	40	100.0	–	–	–	–	

α1-AGP – Alpha1- acid glycoprotein, α2-MG – Alpha2-macroglobulin, α1-AT – Alpha1-antitrypsin
χ^2 test * *p* values of less than 0.05 were considered statistically significant.

The detected plasma levels of CRP, α2-MG, α1-AT and α1-AGP in the psoriatic patients during the acute disease and in healthy controls are shown in Table 1. There was a significant increase in the plasma level of CRP (χ^2= 23.61; p<0.005), and α1-AGP (χ^2=7.42; p<0.01) in acute phase of the disease compared to control group. On the other hand, levels of alpha1-AT (χ^2=1.57; p>0.1 for increased values and χ^2=0.008; p>0.1 for decreased values) and 2-MG (χ^2=0.51; p>0.1 for increased values and χ^2=3.19; p>0.05 for decreased values) were generally within the normal ranges and were not significantly different from the levels detected in the control group.

There was no difference observed in clinical findings between patients with the type I and type II psoriasis (p>0.05).

Discussion

Psoriasis is a chronic and recurrent inflammatory skin disease. It is a common skin disorder, affecting about 1–3% of the population[3,5]. Some 7–42% of patients with psoriasis develop either a peripheral or axial inflammatory arthritis[6]. The inflammatory response represents a fundamental ability of the organism to protect itself from different infectious agents and injury. In order to evaluate the inflammatory response in the acute phase of psoriasis and to determine a possible prognostic significance of acute phase proteins, we have analyzed their expression during the exacerbation of the disease. Analyzed acute phase proteins and cytokines involved in the development of skin inflammation are closely related.

We have detected elevated peripheral blood levels of two acute phase proteins, CRP and α1-AGP in psoriatic patients during the acute phase of the disease. These results are in accordance with previously published results[7–11]. Some authors detected increased values of α2-MG in patients with psoriasis[7,9,12,13]. On the contrary, we have found increased values of α2-MG in only several patients with psoriasis, but without a statistically significant difference compared to the healthy control group. Therefore, we suggest that further studies are needed in order to elucidate these differences in α2-MG values in psoriatic patients.

CRP is regarded as the most sensitive, but as well, not specific indicator of inflammation of various origins, including trauma and cancer[7]. Its significant function is in binding the altered biological material in peripheral blood, by enhancing the reactions of blocking, detoxication and elimination[7]. Since, elevated concentration of CRP in peripheral blood is a result of interaction between pro-inflammatory cytokines, their receptors and inhibitory factors, the changes in CRP concentration observed in various stages of disease activity are indirect indication of the role of cytokines in the pathogenetic process. On the other hand, α2-MG is a multifunctional binding protein that binds cytokines, toxins, bacterial and viral proteins, zinc and hormones[14]. The most importantly α2-MG has a capacity to down-regulate the activity of proteolytic enzymes whose production is increased during inflammatory response including immunopathological inflammation such as psoriasis[9].

The concentration and glycosylation of α1-AGP has been shown to alter significantly during inflammation[10,11]. A definitive physiological role of this acute phase proteins remains elusive and is the subject of extensive investigation. It has been suggested that contrary to normal plasma α1-AGP, rheumatoid α1-AGP within synovial fluid might be inadequate to prevent excessive cartilage destruction and might exacerbate the disease process[11].

Compared to the previously suggested prognostic significance of elastase/alpha1-AT levels for the worsening of psoriasis[12], we have not detected elevated level of alpha1-AT in the acute phase of disease, as well as, no correlation with clinical disease activity. These findings are in accordance with previous research showing alpha1-AT not to be as good, specific and sensitive inflammatory marker for diagnosis and follow up of the disease activity as plasma polymorphonuclear leukocyte elastase level[13].

As suggested earlier, our results confirm that genetically predisposed psoriasis (type I) is characterized by an early onset of the disease compared to the sporadic form (type II) of psoriasis, although there were no statistically significant differences found in respect to clinical and serological findings between these two groups, as shown in previous research[15], that would permit us to identify any particular subset. Our results suggest that psoriasis is an inflammatory disease and its worsening seemed to be the result of increased inflammatory response. We suggest that CRP and α1-AGP levels are of prognostic significance for the worsening of psoriasis.

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PROTEINI AKUTNE FAZE U PSORIJAZI

S A Ž E T A K

Psorijaza je kronična, recidivirajuća, hiperproliferativna bolest kože. Predloženo je da su vrijednosti bjelančevina akutne faze upale povišeni u egzacerbaciji bolesti. Analizirane su vrijednosti pojedinih bjelančevina akutne faze upale kao parametri humoralne imunosti u 70 bolesnika s pogoršanjem simptoma psorijaze i 40 zdravih ispitanika, u cilju evaluacije upalnog odgovora u pogoršanju psorijaze i utvrdila povezanost ovih objektivnih parametara upale s klinički utvrđenom aktivnosti bolesti. Također, analizirani su glavne demografske i epidemiološke karakteristike u bolesnika s psorijazom u svrhu određivanja obiteljske razdiobe bolesti. Utvrđen je značajan porast vrijednosti C-reaktivnog proteina (CRP) (χ^2 =23,61; p<0,005) i alfa1-kiselog glikoproteina (α1-AGP) (χ^2 =7,42; p<0,01) u fazi pogoršanja bolesti u usporedbi s vrijednostima u zdravih ispitanika. Naši rezultati potvrđuju da je psorijaza upalna bolest i pogoršanje kliničkih manifestacija povezano je s naglašenim upalnim odgovorom. Predlažemo da vrijednosti CRP i α1-AGP imaju prognostičko značenje u egzacerbaciji psorijaze.