

Altered distribution of leukocyte subsets and cytokine production in response to acute psychosocial stress in patients with psoriasis vulgaris

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Received 11 January 2006; received in revised form 9 March 2006; accepted 22 March 2006

Available online 22 May 2006

Abstract

Psoriasis (PSO) is a mainly T helper-type 1 (TH₁) cell mediated chronic inflammatory skin disease characterized by epidermal hyperproliferation and psoriatic plaques. There is ample evidence that stress may trigger psoriatic eruption, however, the underlying mechanisms of stress-induced exacerbation of PSO are poorly understood. The specific goal of the present study was to investigate the impact of acute stress on pathologically relevant immune functions in PSO patients. PSO patients ($n = 23$) and healthy controls ($n = 25$) were exposed to a standardized laboratory stressor (“Trier Social Stress Test”, TSST) including a free speech and mental arithmetics in front of an audience. Blood samples were collected 10 min before and 1, 10, 20, and 60 min after the TSST as well as 24 h after the experiment at identical time points under resting conditions. Analyses of leukocyte subsets indicated a significantly increased number of leukocyte subpopulations (lymphocytes, granulocytes, CD3⁺, CD8⁺, CD16⁺/CD56⁺, and CD3⁺/HLA-DR⁺) after the TSST (all $p < .01$) with no significant between-group differences. However, monocyte number ($F(3, 120) = 2.7$; $p < .01$) and number of CD4⁺ cells ($F(3, 120) = 3.09$; $p < .05$) were found to be significantly higher in PSO sufferers than in controls. Moreover, a significant decrease of CD3⁺/CD25⁺ cells was observed in the PSO, but not in the control group ($F(3, 120) = 3.46$; $p < .05$). After exposure to the TSST, stimulation of peripheral blood mononuclear cells (PBMCs) with phytohemagglutinin (PHA) resulted in elevated production of IFN- γ ($F(3, 126) = 6.9$; $p < .001$) and IL-2 ($F(3, 123) = 6.6$; $p < .001$), and moreover, a decreased production of IL-10 ($F(3, 132) = 5.22$; $p < .01$) and IL-4 ($F(3, 129) = 3.9$; $p < .01$). No difference in stress-induced changes of cytokine production to PHA could be identified between the two experimental groups (all $p > .05$). The present findings suggest that acute psychosocial stress is associated with changes of immune functions known to be involved in PSO which may be one potential explanation of how stress may trigger psoriatic eruption.

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Keywords: Stress; Leukocyte subsets; Psoriasis; Cytokines; Inflammation

1. Introduction

Psoriasis (PSO) is a chronic, genetically determined inflammatory skin disease affecting approximately 2% of the northern population (Langley et al., 2005). Beside allergic contact dermatitis and atopic dermatitis, PSO is the most common chronic skin disease. PSO can start at any age, however, disease onset is most frequently observed in the second decade of life. Typical features of PSO are ery-

thematous and solid skin plaques with sharply defined borders, covered with fine silvery scales. Around 30% of the psoriatics suffer from itch and pain mostly due to the dryness and cracking of the plaque (Gottlieb, 2005). Although not life-threatening, PSO can be a disabling disease with a considerable impact on the patient’s psychological and social well-being. Psoriatics often feel stigmatized and psychologically stressed by the disfiguring skin disease which can lead to increased anxiety and depression (Rapp et al., 1999; Griffith and Richards, 2001).

The pathophysiology of PSO is not fully understood, however, there is growing evidence that T cell mediated

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autoimmune processes and action of proinflammatory cytokines cause hyperproliferation of keratinocytes and assume the psoriatic phenotype (Krueger and Bowcock, 2005). The antigenic peptide responsible for the initial T cell activation in PSO has not been established yet. However, one current model is that bacterial proteins (streptococcal M proteins) resulting from a preceding infection may act as superantigens. Regions of streptococcal M6 proteins have been found to share sequence homology with epidermal keratins in PSO patients. It is assumed that recruitment of M protein-specific T cells in the skin and crossreaction with the psoriatic keratin may lead to T cell activation and release of proinflammatory mediators (Prinz, 1997; Valdimarsson et al., 1997).

Another important process in PSO pathogenesis is the trafficking of the activated T cell into the skin which is mediated by the cutaneous lymphocyte antigen (CLA) on the migrating T cell, and adhesion molecules such as E-selectin on the endothelial cells. Activated T cells generated from psoriatic lesions secrete high concentrations of interleukin-2 (IL-2), tumor necrosis factor- α (TNF- α) and interferon-gamma (IFN- γ) indicating a significant role of TH₁-mediated inflammatory processes in the psoriatic skin (Lowe et al., 2004). Accordingly, significant elevated serum levels of TH₁-derived cytokines such as IFN- γ , TNF- α , IL-12 or IL-18 has been described by others (Segedi et al., 2003; Arican et al., 2005) suggesting a local as well as a systemic dysregulation of cytokines towards a TH₁ dominance in psoriatics. Circulating TNF- α , IFN- γ , IL-10, IL-12 or IL-18 levels have been found to be significantly correlated with disease severity (Jacob et al., 2003; Arican et al., 2005). The significant role of TH₁-derived circulating cytokines is further supported by the finding that TNF- α and IFN- γ increase expression of ICAM-1 promoting infiltration of T cells and other inflammatory cells such as monocytes into the skin. Locally, IFN- γ stimulates epidermal cell proliferation and keratinocyte hyperplasia leading to the psoriatic phenotype (Krueger and Bowcock, 2005). TNF- α has also been identified to increase the expression of interleukin-8 (IL-8) which provides a strong chemotactic signal for neutrophil recruitment (Gillitzer et al., 1996).

Although PSO has been conceptualized as an autoimmune disease primarily mediated by an inappropriate function of T cells, it is widely accepted that psychosocial stress has an impact on PSO and may trigger exacerbation of the disease. For example, 31% of PSO sufferers reported the onset of PSO in times of increased everyday life stress, and for 71%, PSO symptomatology has worsened during stressful life episodes (Griffith and Richards, 2001; Zachariae et al., 2004). Others have identified increased levels of anxiety, worry, and depression in PSO sufferers with the latter being linked to pruritus and sleep difficulties (Fortune et al., 2000; Buske-Kirschbaum et al., 2004). The importance of stress in PSO has been further highlighted by reports suggesting that psychological distress affects treatment outcome in PSO patients. In these studies it could be demonstrated that the level of stress may predict the time

taken for photochemotherapy (PUVA) to clear PSO symptomatology (Fortune et al., 2003). Accordingly, stress reduction by stress management, relaxation or cognitive techniques shortened the time to clear PSO symptoms by PUVA and moreover, improved clinical severity of PSO (Kabat-Zinn et al., 1998; Fortune et al., 2002).

Despite the relevance of stress in PSO is broadly accepted, the underlying mechanisms that are involved in the contribution of stress to PSO are not understood. The specific goal of the present study was to investigate the impact of acute stress on TH₁ (IFN- γ , IL-2) and TH₂ (IL-4, IL-10) cytokine production and (re)distribution of PSO-relevant leukocyte subsets in psoriatic patients. As mentioned earlier, serum IFN- γ , IL-4, and IL-10 have been found to significantly correlated with disease severity (Segedi et al., 2003; Arican et al., 2005). Moreover, improvement of psoriatic skin condition after local treatment with dithranol ointment is associated with a decrease of TH₁-related cytokines, i.e., IFN- γ and TNF- α (Chodorowska, 1998) suggesting that fluctuations in disease activity may be closely linked to the secretion pattern of circulating cytokines. In addition, the impact of stress on leukocyte distribution should be studied. It is well documented that increased mobilization of monocytes, CD4⁺ cells and granulocytes precede psoriatic eruption and represent a key event in the skin pathology of PSO.

2. Methods

2.1. Subjects

PSO patients (psoriasis vulgaris; $n = 23$; 12 male, 11 female; mean age: 32.7 ± 7.5 years) were recruited by local dermatologists and informed that the effect of stress on PSO should be investigated. PSO severity was determined using the Psoriasis Area and Severity Index (PASI; Fredriksson and Pettersson, 1978). The PASI score in our patient group ranged from 1 to 39 indicating a moderate clinical activity in our subjects. None of the PSO patients were under current steroid medication, phototherapy or immune therapy. For a control group, sex- and age-matched healthy subjects ($n = 25$; 11 males, 14 females; mean age: 28.5 ± 10 years) participated in the study. The control subjects were medication free and did not suffer from a chronic or acute illness. To control for potential effects of sex hormones on immunological measures, all female subjects were matched for menstrual cycle phase. Additionally, all subjects of the study were non-smokers. Female subjects using the pill were excluded. No between-group differences in educational or socioeconomic background ($p > .05$) could be determined. Participants of the study received a compensation of 100 Euro upon completion of the experiment.

2.2. Experimental protocol ("Trier Social Stress Test"; TSST)

All subjects were studied on two consecutive days; experimental sessions were run between 10 a.m. and 12 a.m. On experimental day 1, a catheter (Vasofix, Braun-Melsungen, Melsungen, Germany) was inserted in an antecubital vein. After a 30-min rest period, a first blood sample was obtained. Ten minutes thereafter, all subjects were exposed to the 'Trier Social Stress Test' (TSST) which has been described elsewhere (Kirschbaum et al., 1993). Briefly, the TSST is a standardized laboratory stressor that consists of a free speech (5 min) and mental arithmetics (serial subtraction) in a role-playing approach in front of an audience. In previous work, the TSST has been repeatedly shown to induce significant endocrine and immunological stress responses (Kirschbaum and Hellhammer, 1994).

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