Journal of Clinical & Experimental Dermatology Research

Nakamura et al., J Clin Exp Dermatol Res 2013, 4:2
DOI: 10.4172/2155-9554.1000175

Case Report Open Access

Levels of Tumor Necrosis Factor-Alpha, Interleukin-6, and Interferon-Gamma during the Active Phases of Bechet's Disease, Pustular Psoriasis, Palmoplantar Pustulosis, and Stevens-Johnson Syndrome: A Pilot Study

Satoshi Nakamura[1-3]*, Keiko Takeda[3], Yoshio Hashimoto[2], Toshihiro Mizumoto[2], Hajime Iizuka[3] and Demitsu Toshio[1]

[1]*Department of Dermatology, Jichi Medical University Saitama Medical Center, Amanumacho1-847, Omiya-ku, Saitama, 330-8503, Japan*
[2]*Department of Dermatology, Asahikawa Kousei Hospital, 1-joudori 24-chome 111, Asahikawa, Hokkaido 078-8211, Japan*
[3]*Department of Dermatology, Asahikawa Medical University, Midorigaoka Higashi 2-1-1-1, Asahikawa, Hokkaido, 078-8510, Japan*

Abstract

Inflammatory serum cytokines are produced by lymphocytes and target organs in inflammatory skin diseases. Changes in cytokines fluctuate daily during disease activity. Comparisons of serum cytokine levels, cytokine species, or flow cytometric changes during the disease course might not be adequate. In addition, daily target organ examinations are difficult.

In this report, we determined disease-specific cytokine balances by continuously measuring the levels of inflammatory cytokines (Interleukin-6 [IL-6], interferon gamma [IFN-gamma], and Tumor Necrosis Factor-alpha [TNF-alpha, TNF-a]) in patients with Bechet's Disease (BD), Pustular Psoriasis (PP), Palmoplantar Pustulosis (PPP), and Stevens-Johnson Syndrome (SJS) during the course of the disease activity. We compared these cytokines in various cutaneous inflammatory diseases activities. Furthermore, participations of inflammatory lymphocytes subsets were considered.

Keyword: Bechet's disease; Pustular psoriasis; Palmoplantar pustulosis; Stevens-Johnson syndrome; Tumor necrosis factor-alpha; Interleukin-6; Interferon-gamma

To the Editor

Inflammatory serum cytokines are produced by lymphocytes and target organs in inflammatory skin diseases [1-3]. Changes in cytokines fluctuate daily during disease activity. Comparisons of serum cytokine levels, cytokine species, or flow cytometric changes during the disease course might not be adequate. In addition, daily target organ examinations are difficult.

In this report, we determined disease-specific cytokine balances by continuously measuring the levels of inflammatory cytokines (interleukin-6 [IL-6], interferon gamma [IFN-gamma], and tumor necrosis factor-alpha [TNF-alpha, TNF-a]) in patients with Bechet's Disease (BD), Pustular Psoriasis (PP), Palmoplantar Pustulosis (PPP), and Stevens-Johnson Syndrome (SJS) during the course of the disease. We compared these cytokines in various cutaneous inflammatory diseases activities. Furthermore, participation of inflammatory lymphocyte subsets was considered.

All 4 patients showed typical clinical appearances, blood and serological tests, and histopathologies. The BD patient was treated with colchicine; the PP patient was treated with cyclosporine MEPC. The PPP patient was treated with etretinate, and the SJS patient was treated with methylprednisolone pulse therapy and oral prednisolone.

IL-6, TNF-alpha, and IFN-gamma levels were measured with an enzyme-linked immunosorbent assay (Figure 1). Maximal TNF-alpha and IL-6 levels were 40 pg/mL and 7.2 pg/mL, respectively, in the BD patient. Maximal TNF-alpha and IL-6 levels were 77 pg/mL and 21.2 pg/mL in the PP patient. Maximal TNF-alpha and IL-6 levels were 24.8 pg/mL and 4.2 pg/mL, respectively, in the PPP patient. Levels of TNF-alpha, IL-6, and IFN-gamma were 93 pg/mL, 33.9 pg/mL, and 8.6 IU/mL, respectively, in the SJS patient (Figure 2). Although the maximal TNF-alpha levels were not disease-specific, they most correlated with clinical severity like as fever, arthralgia, skin rash, elevation of CRP and so on, in SJS, which was followed by PPP, BP, and PP (Figure 1).

IL-6 is produced by macrophages and/or target organ chronic inflammation and is synchronized with TNF-alpha [1,2]. The IL-6 and IL-17 produced by Th17 was suppressed by IFN-gamma from Th1 stimulated by IL-12 from macrophages [1,2]. In addition, IL-6 induction was promoted by IL17A by positive feedback loop in autoimmune diseases [3] and IL-6 levels from keratinocytes were up-regulated by IL-17 stimulation [4]. The relative ratio of IL-6 and TNF-alpha might show a disease-specific pattern of changes among IL-6, TNF-alpha, and IL-17A during the disease course (Figure 3). If maximal IL-6 and TNF-alpha levels were synchronized, the expected ratio would be 2.74, 5.9, 5.56, and 3.63 in SJS, PPP, BD, and PP, respectively. Approximately similar these values that were evaluated by calculating the ratio between IL-6 and TNF-alpha showed to remove the specificity of each disease.

However, the actual measurements were 56, 22.6, 12.5, and 3.63, respectively (Figure 2). The most marked difference was detected in SJS. SJS is assumed to be a disease of Th1 cytokines. The difference between the expected and actual TNF-alpha/IL-6 values might be explained by scattering produced Th1 cytokines. Interestingly, the PP patient exhibited actual values that were similar to the expected value. This result is consistent with the close relationship between psoriasis and Th17 lymphocytes [5]. Furthermore, in psoriasis, there is the paper that

***Corresponding author:** Satoshi Nakamura, Department of Dermatology, Jichi Medical University Saitama Medical Center, Amanumacho1-847, Omiya-ku, Saitama, 330-8503, Japan, Tel: +81-48-647-2111; Fax: +81-48-648-5166; E-mail: namu@jichi.ac.jp

Received May 03, 2013; **Accepted** May 20, 2013; **Published** May 24, 2013

Citation: Nakamura S, Takeda K, Hashimoto Y, Mizumoto T, Iizuka H, et al. (2013) Levels of Tumor Necrosis Factor-Alpha, Interleukin-6, and Interferon-Gamma during the Active Phases of Bechet's Disease, Pustular Psoriasis, Palmoplantar Pustulosis, and Stevens-Johnson Syndrome: A Pilot Study. J Clin Exp Dermatol Res 4: 175. doi:10.4172/2155-9554.1000175

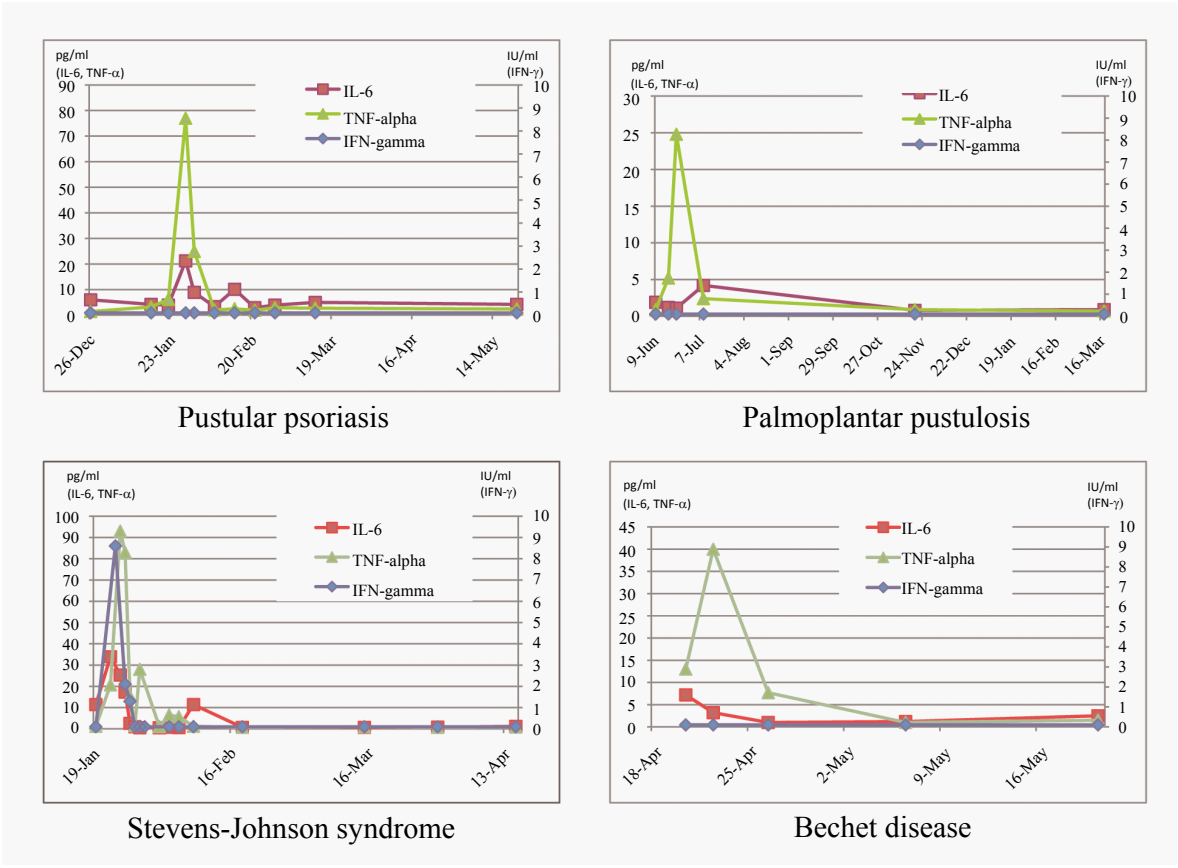
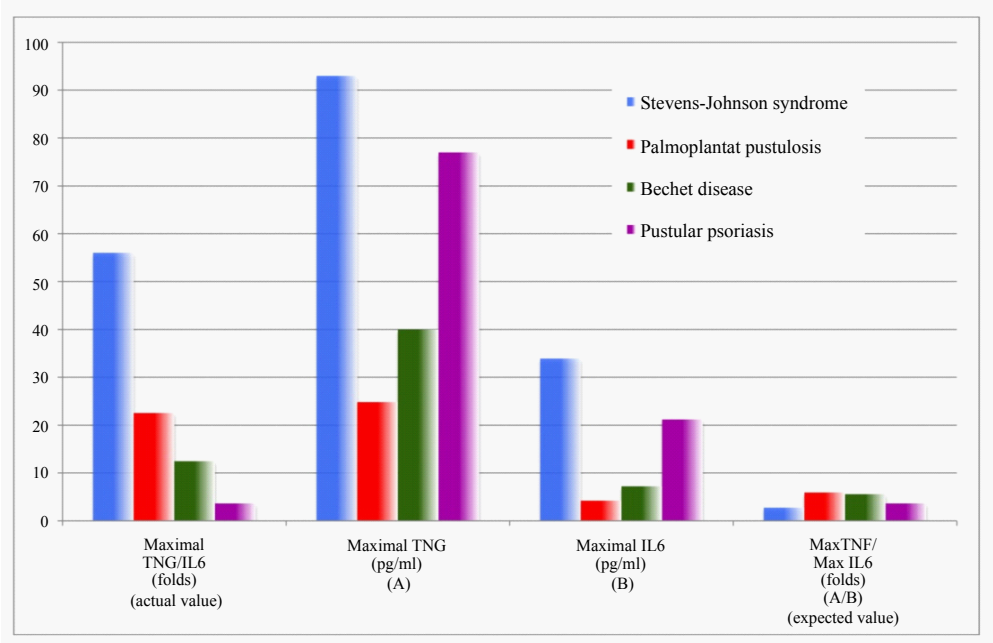


Figure 1: Cytokine patterns of each patient with pustular psoriasis, palmoplantar pustulosis, Stevens-Johnson syndrome, and Bechet's disease. We measured cytokine levels until they were undetectable.



Values at the start and after improvement are shown for each cytokine measured

Figure 2: Tumor necrosis factor (TNF)-alpha/interleukin (IL)-6 calculated values.

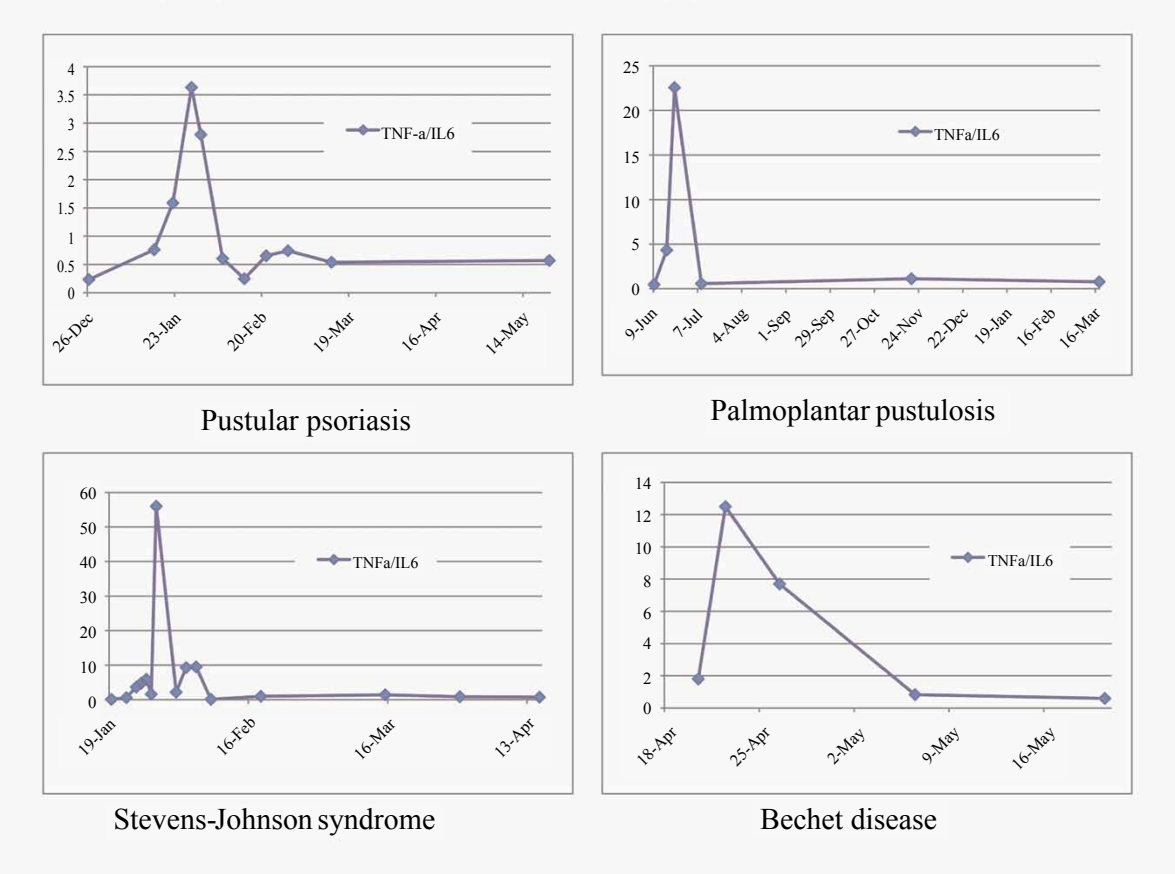


Figure 3: Comparison of the levels of each cytokine among patients with Stevens-Johnson syndrome, palmoplantar pustulosis, Bechet's disease, and pustular psoriasis. Note that the diseases that showed lower measurement values may have been affected by treatment with immunosuppressive drugs, such as anti-TNF-alpha.

clarified the relation between IL-6 and metabolic syndrome [6]. Recent reports showed that Th17 lymphocytes have been shown to be closely associated to BD [7]. Our examination is in harmony with previous report, because the actual TNF-alpha/IL-6 values were close to the expected ratio in BD. The lower actual TNF-alpha/IL-6 ratio in these diseases might be shown by the effectiveness by immuno-modulation therapy (Figure 2).

The continuous measurement of cytokines may be useful for determining disease-specific helper T-cell functions, which may fluctuate during the course of the disease. This procedure may also be useful to clarify the effectiveness of the biological drugs, for example, anti-TNF-alpha/anti-IL-6 drugs, for each disease.

References

1. Iwakura Y, Ishigame H (2006) The IL-23/IL-17 axis in inflammation. J Clin Invest 116: 1218-1222.
2. Asarch A, Barak O, Loo DS, Gottlieb AB (2008) Th17 cells: a new therapeutic target in inflammatory dermatoses. J Dermatolog Treat 19: 318-326.
3. Ogura H, Murakami M, Okuyama Y, Tsuruoka M, Kitabayashi C, et al. (2008) Interleukin-17 promotes autoimmunity by triggering a positive-feedback loop via interleukin-6 induction. Immunity 29: 628-636.
4. Fujishima S, Watanabe H, Kawaguchi M, Suzuki T, Matsukura S, et al. (2010) Involvement of IL-17F via the induction of IL-6 in psoriasis. Arch Dermatol Res 302: 499-505.
5. Caproni M, Torchia D, Schincaglia E, Frezzolini A, Schena D, et al. (2006) Expression of cytokines and chemokine receptors in the cutaneous lesions of erythema multiforme and Stevens-Johnson syndrome/ toxic epidermal necrolysis. Clin Lab Invest 155: 722-728.
6. Savastano S, Balato N, Gaudiello F, Di Somma C, Brancato V, et al. (2011) Insulin-like growth factor-1, Psoriasis, and Inflammation: A Menage a Trois?. Eur J Inflammation 9: 277-283.
7. Kim J, Park JA, Lee EY, Lee YJ, Song YW, et al. (2010) Imbalance of Th17 to Th1 cells in Behçet's disease. Clin Exp Rheumatol 28: S16-19.