

Letter to the Editor

Possible role of T_H17 cells in the pathogenesis of Stevens-Johnson syndrome and toxic epidermal necrolysis

To the Editor:

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare but life-threatening forms of the same mucocutaneous diseases.¹ The pathogenesis of SJS/TEN is still unclear; however, drugs are the most important etiologic agents. SJS/TEN is believed to involve an immune-mediated cytotoxic reaction against keratinocytes, leading to massive apoptosis. Accumulating evidence has shown that the extensive keratinocyte apoptosis might be mediated by granulysin, perforin/granzyme B, and Fas ligand, which can be released by cytotoxic $CD8^+$ T lymphocytes, natural killer T cells, and macrophages.¹⁻³ A variety of cytokines, including IFN- γ , TNF- α , IL-6, IL-10, and IL-13, have also been reported to be involved in the immune reaction of SJS/TEN.^{2,3} T_H17 cells are a recently described effector $CD4^+$ T-cell subset that produces IL-17 and IL-22 and that has been implicated in the pathogenesis of various autoimmune and allergic diseases.⁴ However, little information is available regarding the role of T_H17

cells in the pathogenesis of SJS/TEN. In this study we examined T_H17 cells in the circulation and blister fluid of patients with SJS/TEN.

Patients with SJS/TEN ($n = 7$) and those with erythema multiforme major (EMM; $n = 7$) were enrolled in this study after providing informed consent. Seven healthy subjects served as control subjects. The diagnosis of SJS/TEN and EEM was made on the basis of clinical and histopathologic criteria.¹ All patients with SJS/TEN and those with EEM were treated with systemic prednisolone. Blood samples, blister fluids, or both were obtained from the patients with SJS/TEN and those with EEM before treatment with prednisolone. This study was approved by the ethics committee of Saitama Medical University, Saitama Medical Center.

Flow cytometric assessment of cytokine production in $CD4^+$ and $CD8^+$ T cells was performed as described previously.⁵ Briefly, T cells from the circulation and blister fluid of patients with SJS/TEN were stimulated for 4 hours with phorbol 12-myristate 13-acetate and ionomycin, followed by staining for intracellular cytokines. The results are expressed as means $\pm$ SEMs. Statistical analyses were performed with the Mann-Whitney U test, the paired

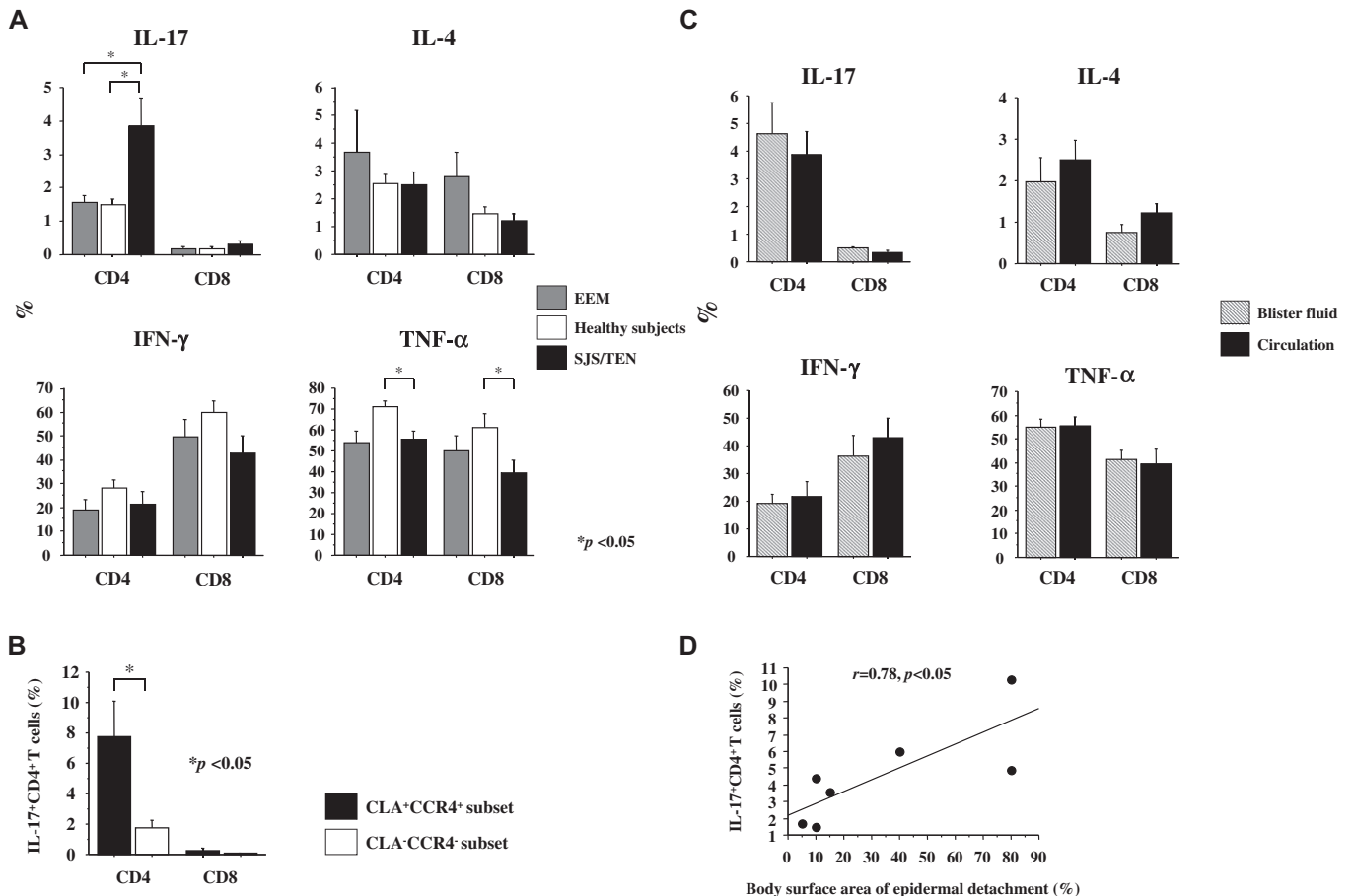


FIG 1. A, The proportions of cytokine-producing circulating T cells in patients with SJS/TEN, patients with EMM, and healthy subjects. B, A significantly higher proportion of IL-17 $^+$ CD4 $^+$ T cells is observed in the CLA $^+$ CCR4 $^+$ subset in patients with SJS/TEN. C, The proportions of cytokine-producing T cells in the circulation and blister fluid of patients with SJS/TEN. D, Correlation between the proportion of IL-17 $^+$ CD4 $^+$ T cells in blister fluid and the severity of SJS/TEN.

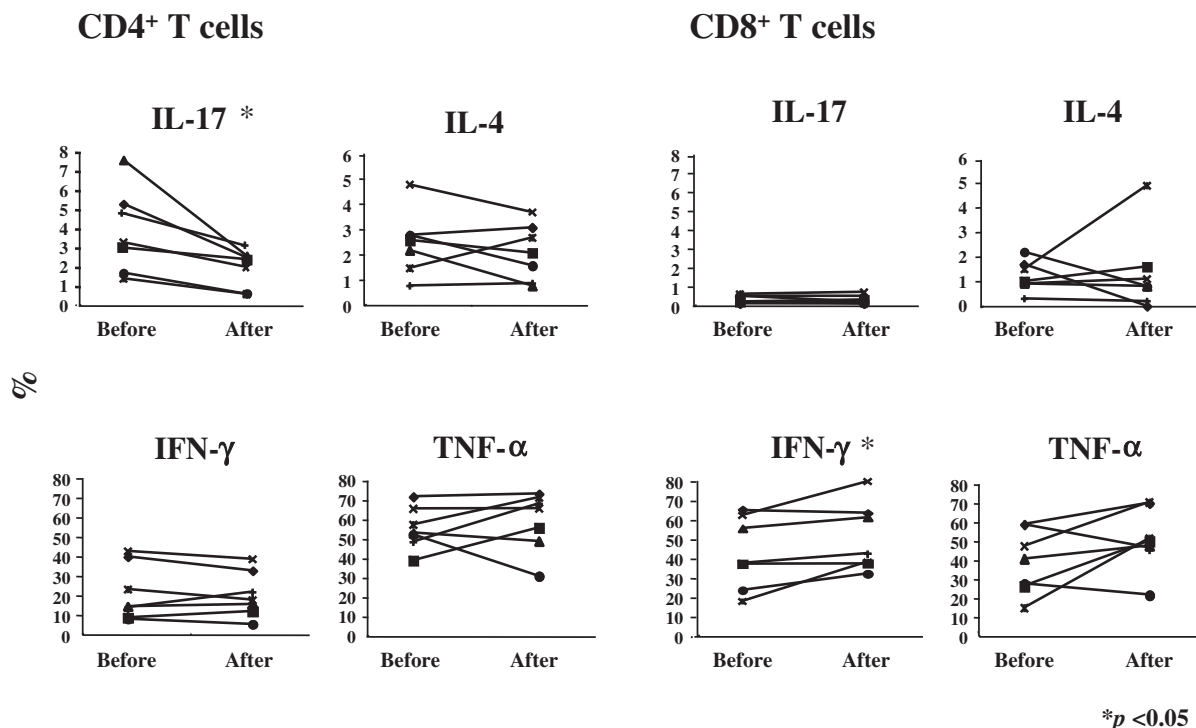


FIG 2. The proportion of circulating IL-17⁺CD4⁺ T cells significantly decreased after improvement of SJS/TEN.

t test, and nonparametric Spearman rank correlation. *P* values of less than .05 were considered significant.

The percentages of CD4⁺ and CD8⁺ T cells in the circulation of patients with SJS/TEN were $28.6\% \pm 4.9\%$ and $27.7\% \pm 4.0\%$, respectively, and in the blister fluid the percentages were $22.7\% \pm 4.5\%$ and $51.2\% \pm 7.3\%$, respectively. The number of lymphocytes in the blister fluid from 2 patients with SJS/TEN were $2.3 \times 10^6/\text{mL}$ and $7.3 \times 10^6/\text{mL}$, respectively. Our results indicate that the blister fluid of patients with SJS/TEN contains not only CD8⁺ T cells but also a significant number of CD4⁺ T cells, which is consistent with a previous report.² The percentages of CD4⁺ and CD8⁺ T cells in the circulation of patients with EMM were $43.8\% \pm 5.9\%$ and $21.7\% \pm 4.6\%$, respectively.

As shown in Fig 1, A, the proportion of circulating IL-17-producing CD4⁺ T cells, but not CD8⁺ T cells, was significantly higher in patients with SJS/TEN than in patients with EMM, as well as healthy subjects (*P* < .05). No significant differences in the proportions of circulating IL-17-producing CD4⁺ and CD8⁺ T cells were observed between patients with EMM and healthy subjects. There were no significant differences in the proportions of circulating IL-4- and IFN-γ-producing T cells among patients with SJS/TEN, patients with EMM, and healthy subjects, although the proportions of circulating TNF-α-producing CD4⁺ and CD8⁺ T cells were lower in patients with SJS/TEN than in healthy subjects (*P* < .05). We also examined IL-17-producing CD4⁺ T cells in a CLA⁺CCR4⁺ subset with skin-homing properties and found a significantly higher proportion of such cells existed in this subset in patients with SJS/TEN (*P* < .05; Fig 1, B).

We next examined cytokine-producing T cells in the blister fluid of patients with SJS/TEN. Although IL-17-producing CD4⁺ T cells were present in the blister fluid of patients with SJS/TEN, there were no significant differences between the proportion of

such cells in the circulation and blister fluid (Fig 1, C). There were no significant differences in the proportions of IL-4-, IFN-γ-, and TNF-α-producing CD4⁺ and CD8⁺ T cells between the circulation and blister fluid of patients with SJS/TEN. The proportion of IL-17-producing CD4⁺ T cells in the blister fluid was positively correlated with the percentage of the body surface area showing epidermal detachment in patients with SJS/TEN (*r* = 0.78, *P* < .05; Fig 1, D), suggesting that IL-17-producing CD4⁺ T cells infiltrating the skin lesions are related to disease severity.

Finally, the proportion of circulating cytokine-producing T cells was examined after improvement of skin lesions in patients with SJS/TEN to determine which cytokines contribute to the outcome of SJS/TEN. The proportion of circulating IL-17-producing CD4⁺ T cells decreased significantly after disease improvement (*P* < .05), whereas that of circulating IFN-γ-producing CD8⁺ T cells increased (*P* < .05, Fig 2). There were no significant differences in the proportions of circulating IL-4- and TNF-α-producing T cells before and after disease improvement. Collectively, these results suggest that skin-homing T_H17 cells are involved in the pathogenesis of SJS/TEN.

The pathogenic role of T_H17 cells in patients with SJS/TEN is unclear. Existing evidence suggests that IL-17 induces proinflammatory cytokines, such as IL-6 and TNF-α, and neutrophil chemoattractant chemokines, such as CXCL8.⁴ Caproni et al⁶ reported that myeloperoxidase-positive neutrophils are easily detectable in the lesional skin of patients with SJS/TEN and suggested that neutrophils might contribute to the tissue damage through release of reactive oxygen species and lysosomal enzymes. T_H17 cells might be involved in inflammation and tissue damage in patients with SJS/TEN through regulation of the recruitment of neutrophils and other inflammatory leukocytes.

Pennino et al⁷ recently demonstrated that the IL-17 infiltrating skin lesions of patients with allergic contact dermatitis strongly enhance the display of adhesion molecules, such as intercellular adhesion molecule 1, on keratinocytes, thereby promoting T cell–keratinocyte adhesion and T cell–mediated cytotoxicity and resulting in keratinocyte apoptosis. Similarly, T_H17 cells might contribute to the immune responses of patients with SJS/TEN as enhancers. Thus, T_H17 cells appear to be involved in the inflammation of SJS/TEN, as well as in psoriasis⁸ and bullous pemphigoid.⁹

Both SJS/TEN and EEM are characterized by cutaneous eruptions, such as typical or atypical target lesions, with mucosal involvement; however, the 2 diseases are now considered distinct entities on the basis of clinical, histopathologic, and etiologic differences.¹ Our results suggest that SJS/TEN is different from EEM in terms of cellular cytokine pattern.

In conclusion, T_H17 cells might play a role in the pathogenesis of SJS/TEN. Our results provide new insight into the pathogenesis and possible treatment of this serious disease.

Yuichi Teraki, MD
Misaki Kawabe, MD
Seiichi Izaki, MD

From the Department of Dermatology, Saitama Medical University, Saitama Medical Center, Saitama, Japan. E-mail: teraki@saitama-med.ac.jp.

Disclosure of potential conflict of interest: The authors declare that they have no relevant conflicts of interest.

REFERENCES

1. Mockenhaupt M. The current understanding of Stevens-Johnson syndrome and toxic epidermal necrolysis. *Expert Rev Clin Immunol* 2011;7:803-13.
2. Borchers AT, Lee JL, Naguwa SM, Cheema GS, Gershwin ME. Stevens-Johnson syndrome and toxic epidermal necrolysis. *Autoimmun Rev* 2008;7:598-605.
3. Downey A, Jackson C, Harun N, Cooper A. Toxic epidermal necrolysis: review of pathogenesis and management. *J Am Acad Dermatol* 2012;66:995-1003.
4. Louten J, Boniface K, de Waal Malefyt R. Development and function of TH17 cells in health and disease. *J Allergy Clin Immunol* 2009;123:1004-11.
5. Teraki Y, Shiohara T. IFN-gamma-producing effector CD8+ T cells and IL-10-producing regulatory CD4+ T cells in fixed drug eruption. *J Allergy Clin Immunol* 2003;112:609-15.
6. Caproni M, Torchia D, Schincaglia E, Volpi W, Frezzolini A, Schena D, et al. The CD40/CD40 ligand system is expressed in the cutaneous lesions of erythema multiforme and Stevens-Johnson syndrome/toxic epidermal necrolysis spectrum. *Br J Dermatol* 2006;154:319-24.
7. Pennino D, Eyerich K, Scarponi C, Carbone T, Eyerich S, Nasorri F, et al. IL-17 amplifies human contact hypersensitivity by licensing hapten nonspecific Th1 cells to kill autologous keratinocytes. *J Immunol* 2010;184:4880-8.
8. Krueger JG, Fretzins S, Suárez-Farinas M, Haslett PA, Phipps KM, Cameron GS, et al. IL-17A is essential for cell activation and inflammatory gene circuits in subjects with psoriasis. *J Allergy Clin Immunol* 2012;130:145-54.
9. Arakawa M, Dainichi T, Ishii N, Hamada T, Karashima T, Nakama T, et al. Lesional Th17 cells and regulatory T cells in bullous pemphigoid. *Exp Dermatol* 2011;20:1022-4.

<http://dx.doi.org/10.1016/j.jaci.2012.08.042>