Association of Reduced CD4 T Cell Responses Specific to Varicella Zoster Virus with High Incidence of Herpes Zoster in Patients with Systemic Lupus Erythematosus

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ABSTRACT. ***Objective.*** To examine whether the high incidence of herpes zoster in patients with systemic lupus erythematosus (SLE) is associated with the frequency of memory T cells specific to varicella zoster virus (VZV).

Methods. Whole blood samples from 47 subjects [24 patients with SLE, 11 with rheumatoid arthritis (RA) as a disease control, and 12 healthy negative controls] were stimulated with VZV antigen, stained for surface CD4 and CD8 and intracellularly stained for the cytokines interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α), interleukin 4 (IL-4), and IL-10, followed by flow cytometry analyses. Correlations of VZV-specific T cell frequencies with the clinical status of patients were analyzed.

Results. Percentage of IFN-γ-positive CD4 T cells was significantly lower in patients with SLE (0.043 ± 0.009%) than in RA (0.102 ± 0.019%) and healthy controls (0.126 ± 0.025%) upon VZV stimulation. A similar pattern was seen in TNF-α-positive CD4 T cell responses. These low frequencies of VZV-specific CD4 T cells in patients with SLE were significantly related with disease activity ($r = -0.435$, $p = 0.043$).

Conclusion. These data suggest that the high incidence of herpes zoster in patients with SLE was related to the intrinsic defects in controlling VZV reactivation, and thus VZV-specific CD4 T cell frequency could be another practical risk factor of herpes zoster in patients with SLE. (J Rheumatol 2004;31:2151–5)

Key Indexing Terms:
HERPES ZOSTER
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Varicella zoster virus (VZV) is a human herpesvirus that causes varicella (chickenpox) during primary infection, establishes latency in sensory ganglia, and may reactivate as herpes zoster (shingles)[1,2]. At least 90% of the population may be infected with VZV by the age of 20 years[3], and these persons acquire cellular immunity after recovery from the primary infection. The annual incidence of herpes zoster was estimated to be less than 0.5% of the general population, mostly in elderly or immunocompromised persons[3-5]. But in patients with systemic lupus erythematosus (SLE), the incidences were dramatically increased and reported to be between 3.2% and 21.0% in Western countries[6,7].

The suppression of cellular immunity has been implicated in the pathogenesis of reactivation of VZV, because recurrent VZV infections occurred in patients with antibodies against VZV. Several studies have reported the risk factors of increased incidence of herpes zoster in patients with SLE. Nagasawa, *et al* reported that lupus patients with or without a history of zoster had a significantly lower frequency of positive delayed skin reactions to the VZV antigen than healthy individuals, suggesting that lupus patients show decreased cellular immunity against VZV[8]. Manzi, *et al* reported that patients who developed zoster were more likely to have experienced serious manifestations of SLE, including nephritis, hemolysis, and thrombocytopenia, and to have required treatment with cyclophosphamide[9]. Kahl suggested that the primary reason for high incidence of zoster in patients with SLE might be the intrinsic immunologic imbalance of lupus, rather than some distinct immuno-

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logic abnormality associated only with disease flares or their treatment[10]. But most of these reports resulted from epidemiological studies or immunological analyses determining only antibody titers and delayed skin reactions. We wished to ascertain if the decreased cellular immunity against VZV in patients with SLE was associated with high incidence of herpes zoster, by comparing a population based epidemiological survey with VZV-specific memory T cell frequency.

We examined the incidence of herpes zoster in patients with SLE and rheumatoid arthritis (RA), and then compared the persistence of VZV-specific memory T cells using intracellular cytokine flow cytometry among disease groups. Our results revealed that the patients with SLE showed significantly lower VZV-specific CD4 T cell frequencies than RA patients and healthy controls, and these decreased VZV-specific CD4 T cell responses were related to disease activity of patients with SLE.

MATERIALS AND METHODS

Patients and controls for epidemiological study. A total of 303 patients diagnosed as having SLE according to the 1997 revised American College of Rheumatology (ACR) criteria[11] and 1748 patients with RA fulfilling 1987 revised ACR criteria[12] as a control group, who were evaluated or treated in the Hospital for Rheumatic Diseases, Hanyang University, from January 1990 to December 2000, were enrolled in this epidemiological study. The history of herpes zoster was confirmed retrospectively from chart review.

Patients and controls for immunological study. Blood samples were obtained from 24 SLE patients, 11 RA patients, and 12 healthy subjects, who had immunity to VZV after recovery from chickenpox or herpes zoster and showed positive serum level of IgG antibodies to VZV and human cytomegalovirus (CMV). In total, 24 SLE patients were selected in our clinic within a certain period of time; patients with severe cases of lymphopenia were excluded. The Systemic Lupus Activity Measure–Revised (SLAM-R) was used to measure SLE activity and severity[13,14]. The SLAM-R data were prospectively collected at blood sampling. Patients and controls with a history of herpes zoster within the previous 6 months were excluded. Clinical details of patients with SLE are summarized in Table 1.

Patients and healthy controls selected for immunological studies were all female; the mean age of patients with RA (35.55 ± 9.98 yrs) was higher than other groups (28.58 ± 5.13 in healthy controls and 27.42 ± 6.63 in patients with SLE).

Intracellular cytokine detection. Heparinized whole blood (1 ml) was incubated with whole cell lysates of VZV and CMV (BioWhittaker, Walkersville, MD, USA). Because CMV reactivation had frequently been reported in other immunocompromised patients such as transplant recipients and patients with acquired immunodeficiency syndrome (AIDS), we used CMV lysate as a virus control antigen. Staphylococcal enterotoxin B (Sigma, St. Louis, MO, USA) and phosphate buffered saline (PBS) were used as positive and negative controls, respectively. Anti-CD28 antibody (2 µg/ml; BD PharMingen, San Diego, CA, USA) and CD49d (1 µg/ml; Becton Dickinson, San Jose, CA, USA) were added to each sample as a costimulator. After 2 h incubation, brefeldin A (10 µg/ml; Sigma) was added to stop the transport of cytokines to the cell surface. After additional 4 h incubation, 100 µl of PBS containing 20 mM EDTA was added for 15 min to remove adherent cells.

Activated cultures were stained with CD4-peridinin chlorophyll A protein (PerCP) or CD8-PerCP for 15 min, and red blood cells were lysed with FACS lysing solution (Becton Dickinson) and fixed with 2% paraformaldehyde solution. The fixed cells were washed, permeabilized with 0.5% saponin solution for 5 min, and stained in the dark for 30 min with monoclonal antibodies against 2 combinations of cytokines, interferon-γ (IFN-γ)-fluorescein isothiocyanate (FITC)/interleukin 4 (IL-4)-phycoerythrin (PE) or tumor necrosis factor (TNF-α)-FITC/IL-10-PE[15,16]. Samples were analyzed using a FACSCalibur flow cytometer (Becton Dickinson). Data for 40,000 events of CD4 or CD8 T cells were analyzed using CellQuest version 3.11 (Becton Dickinson).

Statistical analysis. Analyses were performed with SPSS v. 9.0 (SPSS Inc., Chicago, IL, USA). Differences in the means and standard error of the mean (SEM) among groups were analyzed by Student independent t-test. The statistical significance of the relationship between the percentage of VZV-specific CD4 T cells and the SLAM-R was tested using Spearman correlation analysis.

To exclude the nonspecific preactivated T cell responses from virus-specific memory responses, the percentage of virus-specific memory T cells was defined as the percentage observed in virus-stimulated blood cultures after subtracting the percentage of T cells detected in negative controls. P values less than 0.05 were considered significant. Data are given as mean ± SEM unless otherwise noted.

RESULTS

Patients with SLE showed a higher incidence of herpes zoster than patients with RA. We found 42 of the 303 patients with SLE (13.86%) had a history of herpes zoster and the annual incidence of zoster was 32.5/1000 patient-years of followup. On the other hand, herpes zoster had only occurred in 14 (0.80%) of the 1748 patients with RA and the overall incidence of zoster was 3.9/1000 patient-years.

Patients with RA had higher mean age and longer disease duration than those with SLE, but significant differences were not detected in patients with or without history of herpes zoster within each disease group. There were no significant differences in dermatome distribution of herpes zoster in patients with SLE and RA.

A higher incidence of herpes zoster in patients with SLE was not related to the mean or cumulative dosage of corticosteroid used as a treatment for SLE. In contrast, immunosuppressants, especially cyclophosphamide, were found to have an increased association with high incidence of herpes zoster. The azathioprine-treated group did not show significant differences in the incidence of herpes zoster (13.0%) from untreated groups, but the methotrexate- (26.1%) and cyclophosphamide- (53.6%, treated groups exhibited increased susceptibility to zoster ($p < 0.05$).

Patients with SLE had decreased VZV-specific memory CD4 T cell responses compared to healthy controls and patients with RA. CD4 T cells that responded to short-term (6 h) *in vitro* exposure to VZV or CMV antigen with production of cytokines were regarded as VZV- or CMV-specific memory CD4 T cells. Short term stimulation confined the proliferation of naive T cells, and surface coexpression patterns of CD45RA, CD45RO, and CD69 in responding CD4 T cells confirmed the memory T cell responses against VZV or CMV antigens (data not shown).

Patients with SLE had a marked decrease in VZV-specific IFN-γ-positive CD4 T cells. But the patients with RA showed only a slight decrease in CD4 T cell responses to

Table 1. Demographic information and clinical variables for patients with SLE.

Patient	Age, yrs	Disease, Duration, wks	Pred Daily Dosage, mg	CYC Pulse, no. times	Anti-VZV IgG	Anti-CMV IgG	WBC, cells/μl	Nephritis	SLAM-R Score
1	33	204	15.3	9	+	+	3900	1	4
2	34	6	20	0	+	+	8500	0	4
3	32	264	5.2	3	+	+	6900	1	4
4	31	156	23.4	6	+	+	11100	1	5
5	35	30	8.7	0	+	+	7900	1	5
6	23	16	31.6	0	+	+	5400	0	5
7	38	184	9.5	0	+	+	7500	0	6
8	19	260	13	8	+	+	7500	1	6
9	18	158	9.5	2	+	+	9100	1	7
10	28	10	20.8	3	+	+	5900	1	8
11	19	32	13.2	0	+	+	6500	0	9
12	31	4	0	0	+	+	4400	0	9
13	23	10	15	0	+	+	4100	0	10
14	33	141	10.8	0	+	+	6000	0	11
15	22	172	16.8	8	+	+	6700	1	11
16	22	385	10.7	6	+	+	3600	1	11
17	21	256	3.9	0	+	+	4500	1	11
18	31	2	0	0	+	+	2400	0	11
19	24	60	29.3	6	+	+	3900	1	11
20	26	23	8.6	0	+	+	5900	0	13
21	23	6	12.8	1	+	+	6000	0	14
22	31	570	12.75	1	+	+	3200	1	16
23	15	8	12.3	0	+	+	7300	1	17
24	38	8	104.1	0	+	+	7200	0	21

Pred: prednisolone, CYC: cyclophosphamide, VZV: varicella zoster virus, CMV: human cytomegalovirus, WBC: white blood cell count, SLAM-R: SLE Activity Measure-Revised.

VZV compared to healthy controls. The mean percentage of IFN-γ-positive CD4 T cells specific for VZV was 0.126 ± 0.025% in healthy individuals, 0.102 ± 0.019% in RA patients, and 0.043 ± 0.009% in SLE patients ($p = 0.007$; Figure 1A). Another similar finding was a decreased percentage of VZV-specific TNF-α-positive CD4 T cells in patients with SLE (0.065 ± 0.013%; $p = 0.002$) compared with healthy controls (0.144 ± 0.023%). There were no differences between RA patients (0.130 ± 0.025%) and healthy controls (Figure 1B). In the case of CD8 T cells, significant differences were not detected among groups ($p > 0.05$, data not shown).

In contrast to VZV-specific T cell responses, the patients with SLE showed higher frequencies of IFN-γ- or TNF-α-positive CD4 T cells against CMV antigen. Although significant relations in CMV-specific T cell frequencies were not detected in each group, we did observe higher frequencies of CMV-specific CD4 T cells in patients with SLE and confirmed that the immune surveillance against viral antigens was not entirely declined in patients with SLE.

IL-4 and IL-10-positive CD4 T cell percentages were too low to infer meaningful results in this short term culture condition and were excluded in subsequent analyses.

VZV-specific CD4 T cell responses were significantly related to disease activity rather than the immune modulating drugs. Next, the correlations of VZV-specific T cell frequencies with the clinical status of patients with SLE were analyzed. Like the epidemiological study results, CD4 T cell frequencies between the patients with SLE taking low (< 12 mg/day) or high (> 12 mg/day) doses of prednisolone were not different (data not shown). VZV-specific CD4 T cell frequencies were decreased in the cyclophosphamide-treated group (0.033 ± 0.010% vs 0.048 ± 0.015% using IFN-γ and 0.048 ± 0.017% vs 0.076 ± 0.018% using TNF-α as marker; $p > 0.05$) compared to the untreated group.

VZV-specific IFN-γ-positive CD4 T cell frequencies correlated significantly with disease activity of SLE. Regression analyses yielded significant correlations between the SLAM-R and VZV-specific IFN-γ-positive CD4 T cell frequencies ($r = –0.435$, $p = 0.043$). Similar but statistically insignificant results were observed using TNF-α as the marker ($r = –0.340$, $p = 0.121$).

DISCUSSION

Generally, patients with SLE have similar or higher antibody responses to VZV than healthy subjects. This may be consistent with the hypothesis that polyclonal B cell activation usually occurs in patients with SLE or suggests that reactivation of VZV without overt clinical manifestations might occasionally occur in patients with SLE because of impairment of cellular immunity. The high incidence of herpes zoster despite the presence of VZV-specific antibody may indicate that the presence of the antibody to VZV will

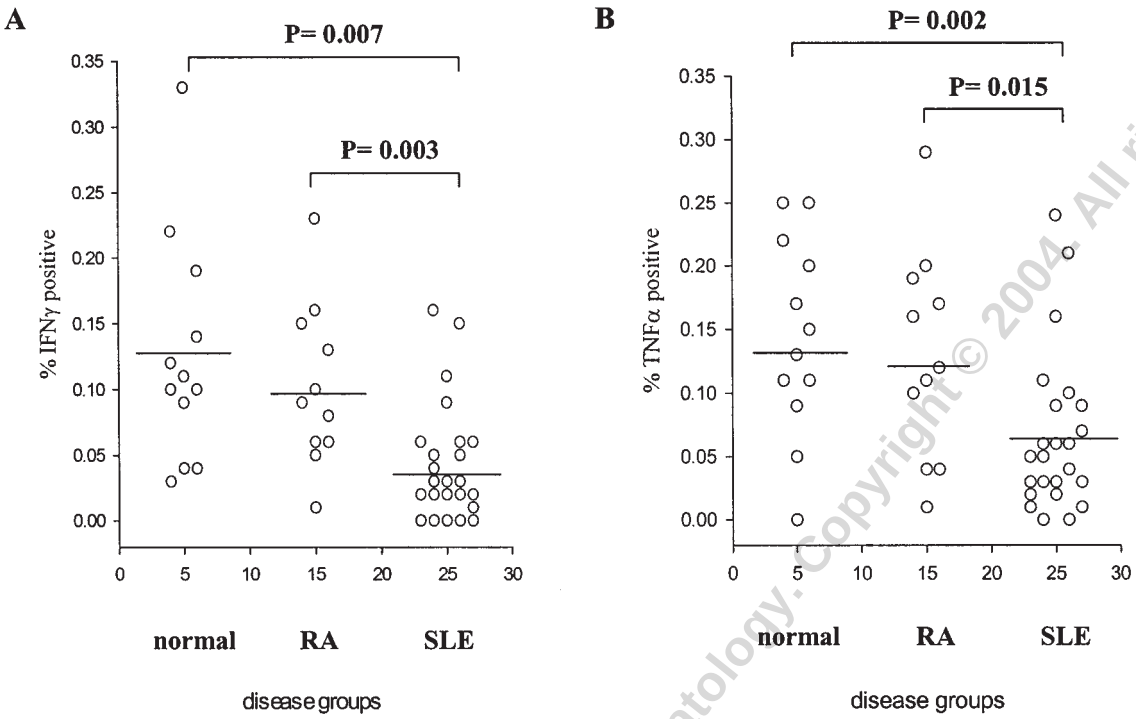

Figure 1. Distribution of individual values of VZV-specific IFN-γ (A) and TNF-α-positive (B) CD4 T cell frequencies in the 3 study groups. Individual ratio values are plotted; horizontal bars indicate the mean ratio for each group. P values calculated by Student independent t-test.

probably not prevent zoster. With the exception of VZV-specific IgG antibodies, memory immunity to VZV is also characterized by the persistence of CD4 helper T cells and CD8 cytotoxic T cells. Memory T cells that recognize a broad spectrum of VZV proteins remain detectable for years after primary infection. The role of VZV-specific T cells in maintaining the equilibrium between the host and the virus during latency is implied by the association between a decline in the frequency or loss of circulating VZV-specific T cells and an increased risk of VZV reactivation, causing herpes zoster[17]. Host defense against intracellular bacterial or viral pathogens was mainly mediated by CD8 cytotoxic T cells in effector phase. But virus-specific IFN-γ or TNF-α-positive CD4 T cells can also induce persistent immunity to viral antigens. These cytokines have direct inhibitory effects on VZV replication and immune modulating effects to enhance expansion of effector T cells[18,19]. The role of CD4 T cells in the generation and maintenance of anti-viral CD8 cytotoxic T cells has been steadily introduced[20,21], and the underlying mechanism has been described[22]. VZV-specific CD4 T cells are predominantly Th1-type, producing IFN-γ and TNF-α, but IL-10 and IL-12 are produced as well[18,23,24].

Rapid progress in understanding viral immune evasion strategies took CD4 T cells into account more important than any other immune components in host defense against viral infections[25]. The blockade of IFN-γ-inducible MHC class II expression was known as the main immune evasion mechanism in herpesviruses. CMV was able to inhibit IFN-γ-inducible MHC class II transcription by disrupting IFN-γ-stimulated signal transduction through a decrease in Jak1 expression, thereby blocking activation of class II transactivator (CIITA) promoter IV and inducible MHC class II transcription[26,27]. Recently, Abendroth, *et al* reported that the same strategy was also applied in VZV, except for slight differences in the underlying mechanism. VZV infection interferes with the Jak/Stat signal transduction pathway by reducing steady-state levels of Jak2 and Stat1-α, but not Jak1 protein expression in case of CMV[28]. The capacity of VZV to evade CD4 T cells by inhibiting IFN-γ-inducible MHC class II expression is likely to be particularly important during VZV reactivation and herpes zoster activation. When VZV reactivation occurs, viral replication can spread them to adjacent dermatomes. But local release of IFN-γ should make these secondarily infected cells susceptible to activated T cells that recognize VZV antigens, and latency is reestablished within a short time. Endogenous restimulation of T cells by viral proteins that are synthesized during reactivation is thought to help sustain memory immunity to herpesviruses[28,29].

Besides a direct hide-and-seek process between VZV and its counteracting specific CD4 T cell, higher susceptibility to zoster in patients with SLE was also inferred from evidence that the CD4 T cell was a pivotal component of the current model of SLE pathogenesis. Numerous immunolog-

ical studies in murine models and patients have reported that various defects in CD4 T cell responses were observed in patients with SLE[30-33].

In our study we found that the frequencies of VZV-specific T cells were significantly decreased in patients with SLE, but not patients with RA and healthy individuals. Low frequencies of VZV-specific IFN-γ and TNF-α-positive CD4 T cells were related to disease activity in SLE. However, the high incidence of herpes zoster in patients with SLE cannot be explained merely by low frequency of VZV-specific IFN-γ and TNF-α-positive CD4 T cells. Rather, more complex genetic and environmental factors related to the pathogenesis of SLE or host immune modulation from interfering drugs might explain the high incidence rate. Nonetheless, low frequency of VZV-specific CD4 T cells in patients with SLE could be an important risk factor for the high incidence rate of herpes zoster.

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