High incidence of herpes zoster in patients with systemic lupus erythematosus: an immunological analysis

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Abstract
The incidence of herpes zoster was determined in patients with systemic lupus erythematosus (SLE) and the cellular and humoral immunity to varicella zoster virus (VZV) investigated in 45 of these 92 patients.

The incidence of herpes zoster was high, occurring in 40 patients (43%), though it was benign in all. Patients with SLE who had had zoster showed significantly higher antibody titres than normal subjects. On the other hand, only 13 of 43 (30%) patients with SLE showed positive delayed hypersensitivity skin reactions to VZV antigen, despite a history of infections with VZV, whereas all 15 normal subjects had positive reactions. Skin reactions to VZV correlated directly with the ratio of OKT4+ to OKT8+ T cells and inversely with the dose of corticosteroids.

These results suggest that the high incidence of herpes zoster in patients with SLE is probably due to defects in cellular immunity and that normal or higher titres of antibodies to VZV will not act as a preventive against zoster. In addition, reactivation of VZV, whether symptomatic or not, seemed often to occur in patients with SLE.

Patients and methods
PATIENTS WITH CONTROLS
Ninety two patients (89 women, three men) who fulfilled the criteria of the American Rheumatism Association for SLE20 were enrolled in this study. They had a mean age of 36-8 (range 19-68) years. The history of herpes zoster was obtained at interview with the patients and was confirmed by doctors’ records. Cellular and humoral immunity to VZV was evaluated in 45 of these 92 patients (44 women and one man with a mean age of 37-2 (range 22-68) years) and in 15 healthy subjects with no history of zoster (11 women and four men with a mean age of 35-0 (23-52) years). Patients with a history of herpes zoster within the last six months were excluded from the immunological study. At the time of the immunological study 36 patients were receiving corticosteroids alone (1-25-30 mg/day of prednisolone) and nine were receiving corticosteroids and immunosuppressants (50 mg/day of cyclophosphamide or azathioprine).

ANTIBODY TO VZV
Serum antibody titres to VZV antigen were measured by both the standard complement fixation technique21 and the neutralisation test, using the Kawaguchi strain of VZV and human embryonic lung cells as indicators.

SKIN TESTING
Varicella zoster virus antigen was prepared from the Oka strain.22 Skin testing with purified protein derivative (0-5 μg/ml, Nippon BCG Co, Tokyo, Japan) was also performed. A volume of 0-1 ml of VZV antigen, purified protein derivative, and normal serine (control) was separately injected intradermally into the forearms and reactivity was measured at 48 hours. The response was recorded as millimetres of diameter of erythema or induration. A reaction was considered positive if the erythema or induration was 5 mm or more for VZV antigen and 10 mm or more for purified protein derivative.

STATISTICS
Categorical data were analysed by χ² test with Yates’s correction, and Student’s t test was used for the group comparisons.

Results
INCIDENCE OF HERPES ZOSTER IN PATIENTS WITH SLE
Forty of the 92 patients with SLE (43%) had a history of herpes zoster and eight patients (9%)
had its multiple episodes. The annual incidence of zoster in these 92 patients was 9.1% (57 episodes of zoster in 623.1 cumulative years from the onset of SLE). The zoster was benign and localised in every patient and in no patient was there a generalised zoster. About half the patients had zoster in the year after the diagnosis of SLE had been made and many of the remaining patients had it in the chronic or inactive stage of SLE. It should be noted that four patients had zoster 1-5 to 10 years before SLE was diagnosed (fig 1). Their ages ranged from 21 to 32 (mean 24.7) years, younger than the average age of all the patients studied.

### SERUM ANTIBODY TITRES TO VZV

To evaluate the humoral immunity to VZV in patients with SLE we measured the serum antibody titres to VZV by complement fixation and the neutralising test. Antibody determined by complement fixation is known to be detected rather transiently. Table 1 shows that the antibody to VZV determined by complement fixation was detectable (>4) in only three of 13 (23%) normal subjects, an incidence lower than the 45% (10/22) in patients with SLE and no history of herpes zoster (p<0.05). In contrast, as many as 20 of 23 (87%) patients with SLE and a history of zoster had antibody detected by complement fixation with titres up to 1/256.

Figure 2 shows the antibody titre to VZV detected by the neutralising test. All patients with SLE and normal subjects had titres of antibodies detectable by the neutralising test. The mean titres in patients with SLE without herpes zoster and normal subjects were 2^5.5 and 2^5 respectively, with no statistically significant difference. On the other hand, the mean titre in patients with SLE and a history of zoster was 2^5.9, a significantly higher value than in the other two groups (p<0.05).

### DELAYED SKIN REACTIONS TO VZV ANTIGEN

Figure 3 shows the results of delayed skin test with VZV antigen. When a diameter of ≥5 mm of erythema or induration at 48 hours was taken as positive, all of 15 (100%) normal subjects showed positive reactions. In contrast, only eight of 21 (38%) patients with SLE and a history of herpes zoster and five of 22 (23%) patients with no history had positive reactions (p<0.01). The size of the erythema was larger in the normal subjects than in the group with SLE. To determine whether the depressed skin reactivity would be limited to or specific for VZV antigen a skin test was carried out using the purified protein derivative antigen. The results were similar to those with VZV—only five of 42 (12%) patients with SLE showed positive reactions to purified protein derivative, in contrast with the high incidence of 13/15 (87%) in the normal subjects (p<0.01). In no patient tested was there a history of tuberculosis. These results indicate that the delayed hypersensitivity is generally depressed in patients with SLE and that herpes zoster does not augment the delayed skin reactivity to VZV antigen in these patients when tested more than six months after experiencing zoster. All the patients with SLE were receiving corticosteroids, compounds considered to exert an inhibitory effect on skin reactions. In the patients receiving less than 10 mg/day of
Table 2: Effect of corticosteroids on skin reactions to varicella zoster virus

<table>
<thead>
<tr>
<th>Dose of prednisolone (mg/day)</th>
<th>No of patients</th>
<th>No (%) of positive skin reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥10</td>
<td>27</td>
<td>3 (11)*</td>
</tr>
<tr>
<td>&lt;10</td>
<td>16</td>
<td>10 (65)</td>
</tr>
</tbody>
</table>

*Significantly lower (p<0.05).

Table 3: Correlation between OKT4/8 ratio and skin reactions to varicella zoster virus

<table>
<thead>
<tr>
<th>OKT4/8 ratio</th>
<th>No of patients</th>
<th>No (%) of positive skin reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.5</td>
<td>17</td>
<td>3 (18%)</td>
</tr>
<tr>
<td>0.5–1.0</td>
<td>15</td>
<td>5 (33%)</td>
</tr>
<tr>
<td>&gt;1.0</td>
<td>11</td>
<td>6 (55%)*</td>
</tr>
</tbody>
</table>

*Significantly different (p<0.05) from each other.

The OKT4/8 ratio was assessed using peripheral lymphocytes when the skin test was performed.

Prednisolone 10 of 16 (63%) had positive skin reactions to VZV, whereas only three of 27 (11%) patients receiving 10 mg/day or more prednisolone showed positive reactions (table 2). Nine of 45 patients were treated with immunosuppressive drugs (cyclophosphamide or azathioprine, 50 mg/day for each) together with corticosteroids. There was no difference, however, in skin reactions to VZV between the patients receiving immunosuppressive drugs and those not receiving them (data not shown).

In delayed hypersensitivity skin reactions T cells, preferentially CD4 (OKT4+) cells, and macrophages are considered to be involved. We investigated the correlation between skin reactions to VZV and the OKT4/8 ratio in patients with SLE (table 3). As shown, the positivity of skin reactions correlated with the T4/T8 ratio. In patients with a T4/T8 ratio of 1:0 or more the number of those with positive skin test was higher than that in those with a T4/T8 ratio of less than 0:5 (p<0.05).

Discussion

The annual incidence of herpes zoster is estimated to be less than 0.5% of the general population, and most are elderly or immunosuppressed subjects. In patients with SLE the incidence of zoster reported in Western countries is 3.2–21%. We found that herpes zoster occurred in patients with SLE with an incidence of 43% and an annual incidence of 9%. These figures are extremely high compared with those mentioned above.

Our patients were consecutively followed up in the outpatient clinic of Kyushu University Hospital and were not specifically selected. Two other groups of investigators in Japan have reported that the incidence of zoster was 43% and 40% respectively, similar to the findings for our patients. Thus Japanese patients with SLE seem to be much more susceptible to herpes zoster than their white counterparts.

In developed temperate regions over 90% of the population are infected with VZV by the age of 20, and these subjects show a delayed type skin reaction to VZV antigen with an antibody to VZV when assessed by a sensitive technique. Suppression of cellular immunity has been implicated in the pathogenesis of reactivation of this virus, a form of herpes zoster. To evaluate cellular immunity to VZV techniques used include T cell transformation, interferon production, killer cell activity, and delayed hypersensitivity skin reactions. The delayed skin test is of great value in the overall assessment of cellular immunity. This method enables assessment of the function of T cells, mainly CD4 (OKT4+), cells, as well as of macrophages. Immuno-

ological studies in patients with SLE have shown defective delayed type hypersensitivity skin reactions and, conversely, hyperactive humoral immunity.

We found that the delayed skin reactions to VZV antigen were depressed in patients with SLE and even in those who had had herpes zoster, yet all the normal subjects showed strongly positive reactions. As four young patients had had zoster before the development of SLE, immune dysfunctions might have occurred long before SLE became apparent, though there is no direct evidence.

Corticosteroids, which are prescribed for most patients with SLE, also affect the immune states of patients. Corticosteroids suppress delayed hypersensitivity skin reactions probably by inhibiting the effect of macrophage migration inhibition factor, produced by CD4 (OKT4+) cells, on macrophages. According to our study, 10 mg/day of prednisolone seems to be the borderline dose. Although immunosuppressive drugs such as cyclophosphamide and azathioprine given to nine patients in a dose of 50 mg/day seemed to have little effect on the skin test and antibody response, the evaluation was difficult because of small numbers. Our results also indicate that the skin reactions correlated with the OKT4/8 ratio in patients with SLE. In untreated patients with SLE decreased CD4 and normal or increased CD8 cells are often noted. Corticosteroid treatment preferentially decreases CD4 cells and thus decreases the T4/T8 ratio. In our study the number of patients with SLE with a T4/T8 ratio over 1:0 accounted for only 11 of the 43 tested (26%). This low ratio may explain the poor skin reactions to VZV and the high incidence of zoster.

Sensitivity of the antibody detected by complement fixation is poor compared with that detected by the neutralising test, and in normal subjects the former disappears within one year after infection whereas the latter is detectable for a lifelong period. Our results indicated, however, that the increased antibody titre detected by complement fixation was found more often in patients with SLE, even in those with no history of zoster, than in normal subjects. Although all the patients and the normal subjects had antibody detectable by the neutralising test, patients with SLE and a history of zoster showed significantly higher titres of the antibody. These findings suggest that patients with SLE can have a normal or even better antibody response to VZV than normal subjects. This may be consistent with the hypothesis that polyclonal B cell activation usually occurs in patients with SLE or
Herpes zoster in SLE

suggest that reactivation of VZV without overt clinical manifestations might sometimes occur in patients with SLE because of impairment of cellular immunity. Corticosteroids (1-25-30 mg/day) do not seem to affect the antibody response to VZV, a finding consistent with reported data indicating that low doses of corticosteroids have no inhibitory effects on antibody formation.39 The high incidence of zoster despite the presence of humoral antibody may indicate that the presence of the antibody to VZV will probably not prevent zoster. Normal or even higher antibody titres to VZV in patients with SLE may inhibit the generalisation of zoster as Mazur et al suggested,39 which is often seen in patients with lymphoproliferative diseases.40

Taken together, we conclude that the very high incidence of herpes zoster in patients with SLE may be due to an impaired cellular immune response because of the underlying disease and as the result of corticosteroid treatment. In addition, an even higher antibody response to VZV, which is either caused by the reactivation of VZV or is a part of polyclonal B cell activation in SLE, may not inhibit the development of herpes zoster.

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