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CLINICAL REPORT

Lymphopaenia, Anti-Ro/Anti-RNP Autoantibodies, Renal Involvement and Cyclophosphamide Use Correlate with Increased Risk of Herpes Zoster in Patients with Systemic Lupus Erythematosus

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Herpes zoster occurs with increased frequency in patients with systemic lupus erythematosus (SLE). The aim of this study was to identify and evaluate clinical and laboratory risk factors associated with development of herpes zoster in patients with SLE. A retrospective case-control study was performed in a population of patients with SLE. Patients were identified as cases if their first episode of herpes zoster occurred after diagnosis of SLE. Patients with SLE who never developed herpes zoster were enrolled as controls. Medical charts and laboratory data for both cases and control patients were comprehensively reviewed. A total of 65 cases and 105 controls were included. Risk factors associated with the development of herpes zoster in patients with SLE were found to be lymphopaenia, anti-Ro antibodies, anti-RNP antibodies, neuropsychiatric manifestations, renal involvement and cyclophosphamide use. Therefore, the presence of certain disease manifestations in patients with SLE represents risk factors for the development of herpes zoster.
***Key words: systemic lupus erythematosus; herpes zoster; risk factors*.**

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Herpes zoster (HZ) is caused by reactivation of the varicella zoster virus (VZV) and can occur in anyone who has had an episode of varicella in the past. It is more common with increasing age and in immunocompromised patients. The latter group includes patients with malignancies and those with autoimmune diseases, such as systemic lupus erythematosus (SLE) (1). HZ is a common viral infection in SLE, with a prevalence ranging from 13.5% to 46.6% (2). The annual incidence of HZ is approximately 1.5–3.0 cases per 1,000 persons in the general population in the United States and increases to up to 32.5 cases per 1,000 persons for patients with SLE have been reported in Korea (3).

The explanation for the high rate of HZ in patients with SLE is not completely defined. In normal individuals, the main defence against VZV reactivation is cell-mediated immunity (4–9). On the other hand, humoral immunity may not inhibit the development of HZ, since HZ infections occur in patients with antibodies against VZV (7, 10–12). In patients with SLE, immunological studies have demonstrated defective cellular immunity (13–17) and hyperactive humoral immunity (18–23). More specifically, Nagasawa et al. (12, 19) showed that lupus patients have a significantly lower frequency of positive delayed skin hypersensitivity reactions (a measure of cellular immunity) to the VZV antigen, but normal or even better antibody response to VZV compared with healthy controls. In addition, Ishikawa et al. (24) found that patients with SLE have a much lower rate of positive delayed-type hypersensitivity skin test with VZV antigen compared with patients with systemic sclerosis. Therefore, the suppression of cellular immunity in patients with SLE, related to the disease itself or the effect of immunosuppressive medications, may underlie the susceptibility to HZ.

SLE is a heterogeneous disease with great variations in the spectrum and severity of clinical and laboratory manifestations (25). Since not all patients with SLE will subsequently develop HZ, the identification of factors in patients with SLE that may increase their susceptibility to HZ is of great clinical importance. Not only would this enable clinicians to provide more accurate prognostic information to patients with SLE regarding their risk of developing HZ, but this information may also help in identifying the subgroup of people who may benefit the most from the new zoster vaccine. The prevention of HZ in this high-risk group will not only benefit the patient, but will also reduce the financial burden of HZ on the healthcare system. We therefore conducted a retrospective case-control study in order to identify and characterize the factors associated with the development of HZ in patients with SLE.

METHODS

Frequency of comorbidities in patients with herpes zoster

Clinical records from Kaohsiung Medical University Hospital over a 9-year period (December 1999 to December 2008) were

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reviewed. Cases with records of International Classification of Disease (ICD) codes for HZ (including 053, 0530, 0531, 05310, 05311, 05312, 05313, 05319, 0532, 05320, 05321, 05322, 05329, 0537, 05371, 05379, 0538 or 0539) from our institution were identified retrospectively. For these patients with HZ, the presence of a previous or concurrent diagnosis of a serious medical disorder (as defined by the Taiwanese National Health Insurance Bureau) (26) was recorded.

Selection of herpes zoster cases and controls

Clinical records from 1999 to 2008 were evaluated. Patients were classified as cases if their first episode of HZ occurred after the diagnosis of SLE. During the same time period, patients with SLE who had never had zoster were eligible as controls.

SLE was diagnosed if patients fulfilled at least 4 out of 11 criteria devised by the American College of Rheumatology (ACR) (27). Patients with mixed connective tissue disease (combined features of lupus, systemic sclerosis and myositis) were excluded. HZ was clinically diagnosed when there was a clear history of a vesicular eruption developing in a dermatomal distribution. Duration of SLE was measured from the date of SLE diagnosis to the time of HZ infection (for cases) or the date of the last follow-up (for controls).

Collection of clinical and laboratory data

In total, 65 cases and 105 controls were included in the present study, and their medical records and laboratory data were comprehensively reviewed. At the time of HZ infection (for cases) or at the time of last follow-up (for controls), information was collected with regards to age, gender, duration of SLE, complement levels (C3, C4), anti-nuclear antibody (ANA) titre, and use of prednisolone or other immunosuppressive medications.

The past history was comprehensively reviewed for the presence of severe disease manifestations of lupus. Information regarding renal and neuropsychiatric involvement was collected from the time of SLE diagnosis up to the time of HZ infection (for cases) or the date of the last follow-up (for controls); data for haematological complications were examined over a 2-year period preceding the time of HZ infection (for cases) or the date of the last follow-up (for controls). Renal involvement was diagnosed when patients showed persistent proteinuria >0.5 g/day in 24-h urine collection or lupus-related glomerulonephritis on renal biopsy. Neuropsychiatric complications were diagnosed when patients had a history of seizures or psychosis in the absence of offending drugs or known metabolic derangements (as per the ACR criteria for neurological disorder in SLE) (27). Haematological complications were diagnosed when there was one or more episode of leucopaenia (white blood cell count $< 4000/mm^3$), lymphopaenia (lymphocyte count $< 1,500/mm^3$), haemolytic anaemia (with positive direct Coombs test), or thrombocytopaenia (platelet count $< 100,000/mm^3$), which were not obviously related to medications or viral infection.

In addition, the past history and laboratory data were evaluated for the presence of various autoantibodies, including anti-dsDNA, anti-Ro (SS-A), anti-La (SS-B), anti-RNP and anti-Sm.

Statistical analysis

The disease manifestations and treatments of patients with and without HZ were compared in order to identify any associated risk factors. Statistical analyses were performed using SPSS version 12.0 software package. The χ^2 test or Fisher's exact test was used for categorical data analysis. The two-sample *t*-test was used for continuous data, which were expressed as means ± standard deviations (SD). All variables that were significant from univariate analysis were included in a stepwise multivariate analysis using logistic regression. The risk was expressed as the adjusted odds ratio (aOR). A p-value < 0.05 was regarded as statistically significant.

RESULTS

Frequency of comorbidities in patients with herpes zoster

From 1999 to 2008, a total of 2,306 cases with HZ were diagnosed in our hospital. Among these patients with HZ, the most frequently found serious medical disorders (as defined by the Taiwanese National Health Insurance Bureau) (26) were malignant cancers (14.8%), followed by connective tissue diseases (4.4%), liver cirrhosis (1.7%), chronic renal failure (1.7%), stroke (0.9%), and human immunodeficiency virus (HIV) infection (0.9%) (Table I). The 3 most commonly found malignancies in those with HZ were cancers of the lung (1.9%), liver (1.7%) and breast (1.6%). SLE (occurring in 2.8% of patients with HZ) accounted for the great majority of connective tissue diseases associated with HZ, and is a more common comorbidity in HZ patients than any single cancer individually.

Table I. *Association of herpes zoster (HZ) with serious medical disorders (as defined by the Taiwanese National Health Insurance Bureau) (26)*

	Patients $n = 2,306$ n (%)[a]
Malignant cancers	
Lung cancer	43 (1.86)
Liver cancer	39 (1.69)
Breast cancer	36 (1.56)
Acute myeloid leukaemia	25 (1.08)
Colorectal cancer	24 (1.04)
Acute lymphoid leukaemia	22 (0.95)
Lymphoma	22 (0.95)
Oral cancer	21 (0.91)
Nasopharyngeal carcinoma	21 (0.91)
Oesophageal cancer	10 (0.43)
Multiple myeloma	9 (0.39)
Cervical cancer	9 (0.39)
Ovarian cancer	8 (0.35)
Gastric cancer	8 (0.35)
Prostate cancer	7 (0.30)
Other cancers	37 (1.60)
Subtotal	341 (14.79)
Connective tissue diseases	
Systemic lupus erythematosus	65 (2.82)
Rheumatoid arthritis	20 (0.87)
Systemic sclerosis	6 (0.26)
Sjögren's syndrome	6 (0.26)
Dermatomyositis	3 (0.13)
Polymyositis	2 (0.09)
Subtotal	102 (4.42)
Liver cirrhosis	39 (1.69)
Chronic renal failure	38 (1.65)
Stroke	21 (0.91)
Human immunodeficiency virus infection	20 (0.87)

[a]Percentage of total number of patients with HZ who had an underlying serious medical disorder.

Demographic characteristics of patients with systemic lupus erythematosus with and without herpes zoster

A total of 65 cases (59 women and 6 men) and 105 controls (94 women and 11 men) were identified. The mean age was 33.92 ± 12.68 years for cases and 35.03 ± 13.31 years for controls. The mean duration of SLE was 6.40 ± 6.29 years for cases and 7.02 ± 6.61 years for controls. There were no statistically significant differences in age, sex or disease duration between patients with and without zoster (Table II).

Comparison of severe disease manifestations of lupus between patients with and without herpes zoster

Patients who developed zoster had significantly higher cumulative frequencies of lymphopaenia, neuropsychiatric manifestations and renal involvement, during their SLE course prior to HZ infection, compared with patients who did not develop zoster ($p < 0.05$). There were no statistically significant differences in the cumulative frequencies of leucopaenia, haemolytic anaemia, and thrombocytopaenia in patients with zoster compared with patients without zoster (Table II).

Comparison of immunological parameters between patients with and without herpes zoster

A higher proportion of HZ patients had a cumulative history of positive anti-Ro, anti-RNP, and anti-Sm antibodies compared with non-HZ patients ($p < 0.05$). However, there were no significant differences in the cumulative frequencies of positive anti-dsDNA and anti-La antibodies between the 2 groups (Table II). In addition, there were no significant differences in the ANA titre or complement (C3 and C4) levels, at the time of zoster reactivation (for cases) or at the time of last follow-up (for controls).

Comparison of immunsuppressive treatments between patients with and without herpes zoster

A higher proportion of patients with HZ had received cyclophosphamide compared with non-HZ patients ($p < 0.05$). There were no significant differences in the rates of prednisolone (≥ 30 mg/day), hydroxychloroquine, azathioprine, or methotrexate administration between the 2 groups (Table II).

Comparative risks of various predisposing factors for the development of herpes zoster in patients with systemic lupus erythematosus

All variables that were significant from univariate analysis were included in a stepwise multivariate analysis using logistic regression. The risk of developing HZ (expressed as the aOR) was calculated for patients with SLE with various predisposing factors. The following disease manifestations were found to be risk factors for the development of HZ in patients with SLE: lymphopaenia (aOR 2.9), anti-Ro antibodies (aOR 3.4), anti-RNP antibodies (aOR 3.0), neuropsychiatric manifestations (aOR 4.0), renal involvement (aOR 2.2) and cyclophosphamide use (aOR 5.0) (Table III). These disease manifestations may therefore act as predictors for the development of HZ in patients with SLE.

Table II. *Comparison of demographic, clinical and laboratory features between herpes zoster (HZ) cases and controls*

Variable	HZ cases $n = 65$ (%)	Controls $n = 105$ (%)	p-value
Age, years, mean ± SD	33.92 ± 12.68	35.03 ± 13.31	0.593
Sex, *n* (%)			0.793
Male	6 (9.2)	11 (10.5)	
Female	59 (90.8)	94 (89.5)	
Duration, years, mean ± SD	6.40 ± 6.29	7.02 ± 6.61	0.548
Renal involvement, *n* (%)			0.006
Absent	23 (35.4)	60 (57.1)	
Present	42 (64.6)	45 (42.9)	
Neuropsychiatric manifestations, *n* (%)			0.003
Absent	44 (67.7)	91 (86.7)	
Present	21 (32.3)	14 (13.3)	
Leucopaenia within 2 years, *n* (%)			0.136
No	21 (32.3)	46 (43.8)	
Yes	44 (67.7)	59 (56.2)	
Lymphopaenia within 2 years, *n* (%)			0.019
No	9 (13.8)	31 (29.5)	
Yes	56 (86.2)	74 (70.5)	
Haemolytic anaemia within 2 years, *n* (%)			0.455
No	55 (84.6)	93 (88.6)	
Yes	10 (15.4)	12 (11.4)	
Thrombocytopaenia within 2 years, *n* (%)			0.859
No	50 (76.9)	82 (78.1)	
Yes	15 (23.1)	23 (21.9)	
Anti-dsDNA, *n* (%)			0.620
Negative	26 (41.3)	47 (45.2)	
Positive	37 (58.7)	57 (54.8)	
Anti-Ro, *n* (%)			0.009
Negative	21 (33.9)	53 (55.2)	
Positive	41 (66.1)	43 (44.8)	
Anti-La, *n* (%)			0.528
Negative	51 (82.3)	75 (78.1)	
Positive	11 (17.7)	21 (21.9)	
Anti-RNP, *n* (%)			< 0.001
Negative	30 (50.0)	75 (77.3)	
Positive	30 (50.0)	22 (22.7)	
Anti-Sm, *n* (%)			0.019
Negative	43 (71.7)	85 (86.7)	
Positive	17 (28.3)	13 (13.3)	
ANA titre, mean ± SD	687.29 ± 834.95	559.29 ± 824.65	0.366
C3 level, mg/dl, mean ± SD	79.13 ± 31.92	76.58 ± 31.96	0.618
C4 level, mg/dl, mean ± SD	16.81 ± 9.25	14.40 ± 8.45	0.084
Prednisolone (≥ 30 mg), *n* (%)			0.264
No	50 (76.9)	88 (83.8)	
Yes	15 (23.1)	17 (16.2)	
Hydroxychloroquine use, *n* (%)			0.940
No	27 (41.5)	43 (41.0)	
Yes	38 (58.5)	62 (59.0)	
Cyclophosphamide use, *n* (%)			0.001
No	50 (76.9)	99 (94.3)	
Yes	15 (23.1)	6 (5.7)	
Azathioprine use, *n* (%)			0.324
No	58 (89.2)	88 (83.8)	
Yes	7 (10.8)	17 (16.2)	
Methotrexate use, *n* (%)			0.676
No	62 (95.4)	102 (97.1)	
Yes	3 (4.6)	3 (2.9)	

Table III. *Results of the multivariate logistic regression analysis, showing the adjusted odds ratio (aOR) for the different risk factors*

		95% CI		
Variables	aOR	Lower	Upper	*p*-value
Lymphopaenia within 2 years	2.867	1.067	7.707	0.037
Anti-Ro	3.405	1.526	7.595	0.003
Anti-RNP	3.035	1.377	6.690	0.006
Neuropsychiatric manifestations	3.980	1.483	10.677	0.006
Renal involvement	2.199	1.002	4.827	0.049
Cyclophosphamide use	5.016	1.531	16.431	0.008

CI: confidence interval

DISCUSSION

In our hospital, the serious medical disorders found most frequently in patients with HZ were malignant cancers, connective tissue diseases (including SLE), liver cirrhosis, and chronic renal failure. In fact, SLE (an underlying disease in 2.82% of patients with HZ) is a more frequent comorbidity in patients who develop HZ compared with any single cancer individually, such as cancers of the lung, liver, or breast. Since SLE is a frequent underlying disease in patients with HZ, there is great importance in identifying and evaluating the factors that may predispose patients with SLE to the development of HZ.

Recently, HZ vaccination has been shown to be effective in reducing the incidence and severity of HZ and post-herpetic neuralgia in adults ≥ 60 years (28–32). Despite the efficacy of the zoster vaccine, it has limited availability and has a high financial cost. This may prohibit non-selective use of the vaccine, particularly in less wealthy countries. By identifying risk factors associated with the development of HZ in patients with SLE, clinicians may be more capable of selecting patients who may benefit the most from HZ vaccination.

The risk factors for developing HZ in patients with SLE have been explored previously in only a small number of studies (2, 3, 33, 34). These studies were limited in terms of the number of variables examined, and some of the results were inconsistent between different studies. In particular, previous studies had only examined leucopaenia, but not lymphopaenia, despite the fact that lymphopaenia is one of the ACR criterion for the diagnosis of SLE (27), and that lymphopaenia is a more specific reflection of defective cellular immunity compared with leucopaenia (35). Moreover, previous studies had rarely investigated the presence or absence of various SLE-related autoantibodies in those with and without HZ. In addition, statistical analyses in previous reports were limited and the comparative risks for each of the different predictors (as expressed by the odds ratio) had not been specifically determined.

Our results showed that lymphopaenia is a risk factor for HZ in patients with SLE, but there was no statistically significant difference in the occurrence of leucopaenia between patients with SLE with and without zoster. Previously, Kang et al. (3) also demonstrated that in patients with SLE who developed zoster, the frequency of leucopaenia was not increased compared with those without zoster. However, the lymphocyte count is a variable that had not been specifically examined in previous reports. The leukocyte count in the peripheral blood examination is mainly composed of the neutrophil count and the lymphocyte count. Lymphocytes are associated with adaptive immunity (cell-mediated and humoral), whereas neutrophils are part of innate immunity (35). Although the exact mechanisms involved in VZV reactivation is not clear, it is well recognized that decreased cell-mediated immunity plays a large role (4–9). On the other hand, neutrophils play a much lesser role in the suppression of VZV reactivation. It is therefore possible that lymphopaenia (with resulting impairment in cellular immunity) is a stronger predictor for HZ infection than leucopaenia. Lymphopaenia in patients with SLE has been found to be associated with anti-lymphocyte antibodies (36–42).

Intriguingly, we also identified anti-Ro and anti-RNP antibodies as risk factors for HZ. These antibodies are directed against extractable nuclear antigens (more specifically ribonucleoproteins) (43–46). Previously, lymphopaenia in patients with SLE had been found to be associated with anti-Ro and anti-RNP antibodies (47–51), suggesting that these autoantibodies might have an antilymphocyte effect. Interestingly, anti-Ro and anti-RNP antibodies had been shown to bind and penetrate lymphocytes, which could lead to lymphocyte apoptosis, or cause impairment in lymphocyte function without actually killing lymphocytes (47, 48, 52–55). Therefore, the presence of these autoantibodies may interfere with cellular immunity and thus explain the higher risk of HZ in these patients. The exact relationship between anti-Ro/anti-RNP and anti-lymphocyte antibodies and how these autoantibodies affect lymphocyte viability and function remain to be clarified.

Our results also showed that renal involvement and neuropsychiatric manifestations are risk factors associated with the development of HZ in patients with SLE. Since renal involvement and neuropsychiatric manifestations in patients with SLE were known to be mediated by autoantibodies produced as a result of hyperactive humoral immunity, the involvement of these organ systems may indicate greater disease severity and greater immune dysfunction (56–61), which may explain the susceptibility to HZ infection.

Finally, we had shown that patients with SLE who developed HZ were more likely to have received cyclophosphamide compared with those who did not develop HZ. There are several possible explanations for this. Firstly, cyclophosphamide use may worsen the immune suppression that is already inherent in patients with SLE, which may therefore increase the risk of HZ. Secondly, the use of cyclophosphamide may reflect a more severe

disease course or act as a marker for lupus activity, which explains its association with HZ infection. Thirdly, cyclophosphamide is often used to treat lupus nephritis. Since the cumulative frequency of renal involvement is higher in patients with zoster than those without zoster, cyclophosphamide use may merely reflect the association between renal involvement and HZ.

A limitation of this study is that the exact frequency of chickenpox in our study subjects (patients with SLE with and without HZ) was not specifically determined and compared. However, most of the patients with SLE in our study were adult females >20 years old. Previous epidemiological studies in Taiwan have shown a high seroprevalence of VZV in adults (>90%) (62, 63). Therefore, the frequency of chickenpox in controls (patients with SLE without HZ) in this study would be expected to be close to that found in SLE cases with HZ (expected to be 100%). Hence, the impact of this confounder should be small.

The authors declare no conflicts of interest.

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