Disease duration and herpes zoster infection related to neutropenia in patients with systemic lupus erythematosus

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Received January 16, 2023; Accepted May 15, 2023

DOI: 10.3892/br.2023.1636

Abstract. Systemic lupus erythematosus (SLE) is an autoimmune disease involving several organs. Neutropenia in patients with SLE may be a factor associated with infection leading to higher morbidity and mortality. There are several inconsistent predictors of neutropenia in patients with SLE. The present study is a retrospective, analytical study, which aimed to identify other predictors of neutropenia in patients with SLE. Patients with SLE who had been regularly followed up for ≥1 year were included in this study. Clinical factors, including history of disease, comorbidities, previous infection, laboratory results and treatment, were collected. The primary analyzed indicator was the occurrence of neutropenia. Factors associated with neutropenia were calculated by multivariate logistic regression analysis. A total of 84 patients met the study criteria. Of those 84 patients, 36 (42.86%) developed neutropenia. There were seven factors placed in the predictive model for neutropenia. Two factors were independently associated with the presence of neutropenia: Disease duration and herpes zoster infection. The first factor was negatively related with neutropenia with an adjusted odds ratio of 0.70 (95% confidence interval, 0.54, 0.92), whereas herpes zoster infection was an independent risk factor for neutropenia with an adjusted odds ratio of 8.46 (95% confidence interval, 1.30, 54.80). In conclusion, the present study revealed that short duration of disease and herpes zoster infection are predictors of neutropenia in patients with SLE.

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease associated with high morbidity and mortality. A report from the United States reported that the prevalence of SLE is 72.8/100,000 person-years, with women predominantly affected (women to men ratio, 9:1) (1). Compared with the general population, patients with SLE have a higher all-cause standardized mortality ratio of 2.6, mostly caused by renal disease, cardiovascular disease or infection (2). A cohort study from Ontario, Canada, also demonstrated that mortality is higher in younger patients (<40 years), and is mostly caused by malignancy and infection; for these patients, the mortality ratios are 31.9 and 30.2, respectively (3).

Neutropenia in patients with SLE may be one of the factors associated with infection leading to higher morbidity and mortality. Patients with SLE and neutropenia may have a 2.368 times increased risk of infection, with the highest risk being 11.366 times for serious infection (4-6). A previous meta-analysis revealed that the prevalence of neutropenia in patients with SLE is 20-40% (4). Additionally, neutropenia in patients with SLE may be related to proteinuria with a hazard ratio of 2.54 (95% confidence interval, 1.14, 5.65) (7).

Several studies have been performed that predict the occurrence of neutropenia. A study from Mexico reported that low platelet count or central nervous system involvement are associated with neutropenia, with an adjusted odds ratio of 4.72 and 5.04 (P=0.002 and 0.025), respectively. In addition, a study from France revealed that thrombocytopenia, lymphopenia and low C3 are independent factors for neutropenia (8,9). As there are inconsistent data for the predictors of neutropenia in patients with SLE, the present study aimed to identify other predictors of neutropenia in patients with SLE.

Patients and methods

Study design. The present study is a retrospective, analytical study, which was conducted at Panyananthaphikkhu Chonprathan Medical Center, an affiliated center of Srinakarinwirot University (Nonthaburi, Thailand). The inclusion criteria were as follows: Adult patients aged ≥18 years diagnosed with SLE, according to the 2012 diagnostic criteria (10), and treated at the SLE clinic for ≥1 year with regular follow-ups. Patients who were pregnant, had other

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Key words: herpes zoster, predictors, risk factors

Table I. Baseline characteristics and clinical manifestations of patients with systemic lupus erythematosus categorized by presence of neutropenia.

Factor	No neutropenia (n=48)	Neutropenia (n=36)	P-value
Age at diagnosis, years[a]	42 (32-51)	41 (29-58)	0.807
Age at present, years[a]	48 (37-59)	51 (33-59)	0.914
Male	4 (8.33)	2 (5.56)	0.696
Occupation: Laborer	37 (77.08)	25 (69.44)	0.461
Disease duration, years[a]	4.8 (1.8-6.0)	2.4 (0.6-3.7)	0.003
Hypertension	24 (50.00)	17 (47.22)	0.829
Diabetes mellitus	15 (31.25)	9 (25.00)	0.628
Dyslipidemia	22 (45.83)	16 (44.44)	0.999
First presentation			
Hematological	9 (18.75)	9 (25.00)	0.594
Vascular	1 (2.08)	1 (2.78)	0.999
Mucocutaneous	19 (39.58)	11 (30.56)	0.492
Arthritis	7 (16.28)	4 (11.11)	0.746
Autoimmune hemolytic anemia	5 (10.42)	8 (22.22)	0.222
Lupus nephritis	11 (22.92)	8 (22.22)	0.999
Pulmonary	2 (4.17)	3 (8.33)	0.647
Neuropsychiatric	3 (6.25)	3 (8.33)	0.999
Cardiac	4 (8.33)	1 (2.76)	0.386
Follow-up presentation			
Skin	33 (68.75)	20 (55.56)	0.257
Alopecia	7 (14.58)	9 (25.00)	0.269
Vascular	8 (16.67)	4 (11.11)	0.543
Neuropsychiatric	6 (12.50)	10 (27.78)	0.096
Pleuritis	5 (10.42)	3 (8.33)	0.999
Pulmonary	9 (18.75)	9 (25.00)	0.594
Idiopathic thrombocytopenic purpura	8 (16.67)	12 (33.33)	0.119
Evans syndrome	5 (10.42)	10 (27.78)	0.048
Autoimmune hemolytic anemia	19 (39.58)	22 (61.11)	0.077
Hematological	26 (54.17)	25 (69.44)	0.181
Nephrological	18 (38.30)	17 (47.22)	0.503
Musculoskeletal	31 (64.58)	24 (66.67)	0.999
Gastrointestinal	1 (2.08)	4 (11.11)	0.159
Cardiac	5 (10.42)	2 (5.56)	0.693
BILAG[a]	1 (0-8)	2 (1-13)	<0.001
Previous infection			
Any herpes infection	4 (8.33)	10 (27.78)	0.036
Herpes simplex infection	2 (4.17)	0	0.504
Herpes zoster infection	2 (4.17)	7 (19.44)	0.034
Chickenpox	0	3 (8.33)	0.075
Tuberculosis	2 (4.17)	0	0.504

Data are presented as number (%) or as [a]median (1st-3rd quartile range); total numbers of patients in both groups may not be 48 and 36. BILAG, British Isles Lupus Assessment Group.

connective tissue diseases, had cancer, received immunosuppressive agents, had bone marrow diseases, or had other causes of neutropenia, such as infection or medication, were excluded from the study. The study period was between September 2020 and August 2021.

Data collection. The medical records of eligible patients were reviewed for SLE diagnosis, baseline characteristics, comorbidities, clinical presentation at initial diagnosis, clinical presentation during the follow-up, laboratory results and treatments received. Clinical presentations

Table II. Laboratory results of patients with systemic lupus erythematosus categorized by presence of neutropenia.

Factor	No neutropenia (n=48)	Neutropenia (n=36)	P-value
WBC, cells/mm^3[a]	5,875 (4,955-7,340)	3,190 (2,605-3,640)	<0.001
ANC, cells[a]	3,624 (3,000-4,734)	1,630 (1,386-1,944)	<0.001
Lymphocyte, cells[a]	1,516 (1,261-2,043)	1,274 (825-1,634)	0.005
ANA	40 (93.02)	31 (93.94)	0.999
ANA titer[a]	1,280 (160-2,560)	1,280 (160-5,120)	0.326
ANA cytoplasmic	0	1 (3.70)	0.466
ANA speckle	24 (85.71)	20 (80.00)	0.719
ANA homogenous	18 (58.06)	17 (62.96)	0.791
Direct Coombs test	6 (46.15)	11 (73.33)	0.246
Rheumatoid factor	2 (25.00)	1 (33.33)	0.999
Anti-dsDNA	25 (54.35)	19 (54.29)	0.999
Anti-Sm	4 (12.50)	8 (27.59)	0.200
Anti-NRNP	3 (25.00)	7 (43.75)	0.434
Anti-Ro52	3 (30.00)	5 (71.43)	0.153
Anti-Ro60	3 (27.27)	4 (57.14)	0.332
Anti-β2	11 (30.56)	3 (12.50)	0.130
Anti-cardiolipin	6 (16.67)	4 (16.67)	0.999
Lupus anticoagulant	7 (22.78)	4 (18.18)	0.746
P-ANCA	1 (25.00)	0	0.999
C-ANCA	0	2 (50.00)	0.429
Low C3	6 (85.71)	4 (66.67)	0.559
Low C4	5 (83.33)	3 (50.00)	0.545
Erythrocyte sedimentation rate, mm/h[a]	27 (13-49)	23 (13-54)	0.668

Data are presented as the number of people with positive results (%), or as [a]median (1st-3rd quartile range). WBC, white blood cell; ANC, absolute neutrophil count; ANA, anti-nuclear antibodies; dsDNA, double-stranded DNA; Sm, Smith; NRNP, nuclear ribonucleoprotein; P-ANCA, perinuclear anti-neutrophil cytoplasmic antibodies; C-ANCA, cytoplasmic anti-neutrophil cytoplasmic antibodies.

included both major and minor organ involvement of SLE: Musculoskeletal system (arthritis), hematological system (autoimmune hemolytic anemia, thrombocytopenia, Evans syndrome), neurological system (seizure, psychosis, encephalitis), respiratory system (pleuritis, pulmonary hemorrhage), cardiovascular system (pericarditis), gastrointestinal system (vasculitis), renal system (nephritis, proteinuria), and dermatological system (alopecia, mucocutaneous involvement). Lupus organ flare, the British Isles Lupus Assessment Group (BILAG) numerical global score and any previous documented infection were also recorded. The primary analyzed indicator was occurrence of neutropenia, which was defined as an absolute neutrophil count of <2,500 cells/mm^3 (5,6). No other causes of neutropenia were identified, including herb use, immunosuppressive drug treatment for >1 month without dose change, or responses to granulocyte colony-stimulating factor, as previously reported (11). For those who developed neutropenia, clinical manifestations and laboratory results were assessed at this time point. For those who did not develop neutropenia, the studied variables were recorded at the last follow-up.

Statistical analysis. Eligible patients were divided into two groups: With and without neutropenia. Descriptive statistics, including median (1st-3rd quartile range) and number (percentage), were used to describe clinical features of studied variables, and Mann Whitney U test and Fisher's exact test were used to compare the differences between both groups. A predictive model for neutropenia was assessed by logistic regression analysis. Univariate and multivariate logistic regression analyses were used to assess predictors of neutropenia. Unadjusted and adjusted odds ratios of factors in the predictive model were reported with their 95% confidence intervals. Hosmer-Lemeshow test was used to evaluate the goodness of fit of the predictive model. P<0.05 was considered to indicate a statistically significant difference. Statistical analyses were performed using Stata software version 10.1 (StataCorp LP).

Results

A total of 84 patients met the study criteria; of those, 36 patients (42.86%) developed neutropenia. Regarding baseline characteristics and clinical manifestations, there were two significant factors between these two groups: Disease duration and BILAG (Table I). Those with neutropenia had a shorter duration of SLE (2.4 vs. 4.8 years; P=0.003), whereas the BILAG score was significantly higher in the neutropenia

Table III. Treatments of patients with systemic lupus erythematosus categorized by presence of neutropenia.

Treatment	No neutropenia (n=48)	Neutropenia (n=36)	P-value
Prednisolone	24 (50.00)	18 (50.00)	0.999
Prednisolone dose, mg[a]	5 (1.4-12.5)	17.5 (5.0-30.0)	0.075
Hydroxychloroquine	37 (77.08)	25 (69.44)	0.461
Azathioprine	22 (45.83)	17 (47.22)	0.999
CSA	2 (4.17)	0	0.504
MMF	12 (25.00)	8 (22.22)	0.802
Methotrexate	18 (37.50)	11 (30.56)	0.644
CYC	2 (4.17)	0	0.504
Dapsone	6 (12.50)	4 (11.11)	0.999

Data are presented as number (%), or as [a]median (1st-3rd quartile range). CSA, cyclosporine; MMF, mycophenolate mofetil; CYC, cyclophosphamide.

Table IV. Factors associated with neutropenia in patients with systemic lupus erythematosus.

Factor	Unadjusted odds ratio (95% confidence interval)	Adjusted odds ratio (95% confidence interval)
Disease duration	0.77 (0.64, 0.94)	0.70 (0.54, 0.92)[b]
Herpes zoster infection	5.55 (1.07, 28.58)	8.46 (1.30, 54.80)[b]
BILAG	1.08 (1.01, 1.62)	1.02 (0.94, 1.10)
Neurological flare	2.69 (0.87, 8.28)	3.92 (0.80, 19.13)
AIHA flare	2.39 (0.99, 5.81)	1.06 (0.34, 3.28)
ITP flare	2.50 (0.89, 6.98)	1.46 (0.39, 5.44)
Lymphopenia[a]	2.17 (0.88, 5.31)	2.30 (0.76, 6.89)

[a]Defined by lymphocyte count of <1,500 cells (4); [b]significant factors. BILAG, British Isles Lupus Assessment Group; AIHA, autoimmune hemolytic anemia; ITP, idiopathic thrombocytopenic purpura.

group than that in the non-neutropenia group (1 vs. 2; P<0.001). Regarding previous infections, only herpes viral infection and tuberculosis were documented. Only herpes zoster virus infection was found at a significantly higher rate in those with neutropenia than those in the non-neutropenia group (19.44 vs. 4.17%; P=0.034). Comorbidities, first-presenting symptoms or presentation after follow-up were comparable between the two groups.

Laboratory results and treatments of the patients in the neutropenia and non-neutropenia groups were comparable except for the total white blood cell, absolute neutrophil and lymphocyte counts (Tables II and III). Those with neutropenia had significantly lower absolute neutrophil counts than those without neutropenia (1,630 vs. 3,624 cells; P<0.001). Seven factors were put in the predictive model for neutropenia (Table IV). Two factors were revealed to be independently associated with the presence of neutropenia: Disease duration and herpes zoster infection. The first factor was negatively related with neutropenia, with an adjusted odds ratio of 0.70 (95% confidence interval, 0.54, 0.92), whereas herpes zoster infection was an independent risk factor for neutropenia with an adjusted odds ratio of 8.46 (95% confidence interval, 1.30, 54.80) (Table IV). The Hosmer-Lemeshow χ^2 of the model was 13.45 (P=0.097) indicating a goodness of fit of the model.

Discussion

The present study identified additional independent predictors for neutropenia in patients with SLE: Disease duration and herpes zoster infection. Although previous studies have reported that central nervous system involvement, thrombocytopenia or lymphopenia are significant predictors for neutropenia in patients with SLE (8,9), these factors were not significant in the present study. These findings may be due to stronger predictors in the multivariate logistic regression model.

Disease duration was negatively associated with neutropenia by 30% per 1 year of SLE duration. These data indicated that patients with SLE may develop neutropenia in the earlier years after diagnosis. These findings were similar with a previous study, which reported a non-significant shorter disease duration in those with neutropenia compared with those without neutropenia (2.2 vs. 3.1 years; P=0.22) (8). Unfortunately, disease duration was not included in the predictive model in the previous study (8). Unlike

the previous study, the present study reported significantly different disease durations between those with and without neutropenia (P=0.007); the disease duration in the present study was comparable with the previous study at 2.4 years in the neutropenia group. These findings may be explained by more severe disease, as the neutropenia group had more proportions of organ flare, such as neuropsychiatric flare, thrombocytopenic flare or autoimmune hemolytic anemia in the present study. A study in children with SLE revealed that those with a shorter duration of SLE had a higher rate of neuropsychiatric involvement than those with a longer duration of SLE (21 vs. 7%; P=0.007) leading to a higher mortality rate (15 vs. 6%; P=0.028) (12). It may be concluded that patients with SLE with multiple organ lupus flare may present with neutropenia faster than those without, which could lead to higher mortality.

Varicella-zoster virus is an infectious pathogen that can cause neutropenia. A previous study compared clinical differences between 122 patients with superficial skin infection and 97 patients with herpes zoster infection. That study demonstrated that neutrophil counts were significantly lower in patients with herpes zoster infection than those with superficial skin infection (4.12 vs. 5.68 $x10^9$/l; P<0.05) (13). Another study in adult patients with SLE reported that high glucocorticoid doses increased the risk of herpes zoster infection by 2% (P=0.03), whereas a study of children with SLE reported similar findings (14,15). Prednisolone use and cyclophosphamide use had adjusted odds ratios of 6.723 (P=0.002) and 4.060 (P<0.0001), respectively, for herpes zoster infection (14). The previous study in children patients also found that a disease duration of <1 year was associated with herpes zoster infection by 2.893 times (P<0.0001) (14).

There are some limitations in the present study. First, some occult infections may not be detected as data regarding infections were collected from the medical records of the patients, and information regarding some related conditions or laboratory tests for infections were not collected. Second, some data may be missing due to retrospective data collection. Finally, some serological tests were not performed routinely resulting in low numbers of people had positive results on the tests, such as anti-Sm or anti-Ro.

In conclusion, the present study revealed that short duration of disease and herpes zoster infection were predictors of neutropenia in patients with SLE. Neutropenia may occur in patients with SLE within 2.4 years of diagnosis.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author upon reasonable request.

Authors' contributions

WT conceived and designed the study. WT, CL, and PP confirm the authenticity of all the raw data. WT, CL, PP and KS analyzed and/or interpretated the data. WT drafted the article. WT, CL, PP and KS critically revised the article for important intellectual content. KS performed statistical analysis. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Institutional Review Board at the Srinakharinwirot University (approval no. ID002/63; Nonthaburi, Thailand).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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