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Original Article

Prevalence and Risk Factors Associated with Neutropenia in Hospitalized Patients with Systemic Lupus Erythematosus

Min Kyung Chung, In Je Kim, Jisoo Lee
Division of Rheumatology, Department of Internal Medicine, Ewha Womans University School of Medicine, Seoul, Korea

Objective. This study estimated the prevalence and explored possible risk factors associated with neutropenia in hospitalized patients with systemic lupus erythematosus (SLE). **Methods.** This review included 160 admissions of 85 SLE patients between 2006 and 2013. Neutropenia was defined as absolute neutrophil count (ANC) below 1,500/mm^3. The baseline characteristics of the patients were compared between patients who experienced neutropenia and those who did not. Clinical and serological factors related to neutropenia episodes during admission were analyzed. **Results.** Thirty-five (21.9%) neutropenic episodes were found among the 160 admissions. Most of the neutropenic episodes were mild to moderate. Severe neutropenia of ANC $<$ 500/mm^3 occurred in 3.1% of the cases. Patients with neutropenia had higher frequencies of ANA (100.0% vs. 86.8%, p = 0.042) and anti-double stranded DNA (87.5% vs. 60.4%, p = 0.008), and satisfied more SLE classification criteria at the time of diagnosis than those without (5.1 vs. 4.6, p = 0.009). Anemia, leukopenia, thrombocytopenia and low complement levels were frequently accompanied with neutropenia. Chronic kidney disease (odds ratio, 11.17; 95% confidence interval, 1.46 ~ 85.27; p = 0.020) was associated with neutropenia. **Conclusion.** This study demonstrates that neutropenia is frequent in hospitalized patients with SLE, and patients with neutropenia have more hematologic and immunologic abnormalities. Renal damage was more frequent among those presenting with neutropenia. **(J Rheum Dis 2017;24:203-210)**

Key Words. Systemic lupus erythematosus, Neutropenia, Risk factors

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease of unclear etiology that affects multiple organs and shows heterogeneous clinical features [1]. Hematologic manifestations such as hemolytic anemia, leukopenia, lymphopenia, and thrombocytopenia are common and characteristic features associated with SLE patients, which are included as one of criteria for the classification of SLE proposed by the American College of Rheumatology (ACR) [2]. When SLE patients manifest with hematologic abnormalities, it is important to distinguish these abnormalities from SLE disease activity, bone marrow suppression secondary to use of immunosuppressive drugs, and primary hematologic disease such as myelodysplastic syndrome [3,4].

Leukopenia in SLE is defined as leukocyte count below 4,000/mm^3 on two or more occasions according to the ACR criteria [2]. Lymphopenia is a most commonly found leukocyte abnormality, but neutropenia is also frequently observed occurring in about 50% to 60% of patients with active SLE [5]. Most of the neutropenia episodes occurring in patients with SLE are mild, but approximately 5% of patients may experience moderate (500/mm^3 $\leq$ absolute neutrophil count [ANC] $<$ 1,000/mm^3) to severe neutropenia (ANC $<$ 500/mm^3) [6]. The pathogenesis of neutropenia in SLE is not entirely understood, but both humoral and cellular immune responses are known to be involved. Increased peripheral destruction of granulocyte by circulating antineutrophil antibodies [7], increased margination or changes in marginal and splenic pool [8], and decreased granulocytopoiesis in the bone

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Corresponding to : Jisoo Lee, Division of Rheumatology, Department of Internal Medicine, Ewha Womans University School of Medicine, 1071 Anyangcheon-ro, Yangcheon-gu, Seoul 07985, Korea. E-mail : leejisoo@ewha.ac.kr

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marrow [9,10] were suggested as potential mechanisms. Clinically, neutropenia in SLE patients can increase susceptibility to recurrent infection [3,11]. Infection can be detrimental in the immunocompromised patients, thus neutropenia occurring in the SLE patients require high level of vigilance. Infection is currently one of the leading causes of mortality in patients with SLE in spite of the improvement of overall survival rate [12,13]. It is crucial to understand the risk factors associated with neutropenia in SLE patients, but there is a paucity of clinical data regarding neutropenia in patients with SLE. Although many studies deal with hematologic abnormalities in SLE [14], only one previous study showed clinical data focusing on neutropenia reporting risk factors associated with neutropenia in 33 SLE patients with moderate and severe neutropenia [6]. They reported that concomitant medications including immunosuppressants, history of thrombocytopenia and central nervous systemic manifestation as risk factors of developing neutropenia in SLE. Therefore, we investigated the clinical, serologic characteristics of SLE patients with neutropenic episodes during admissions to determine the risk factors associated with neutropenia in hospitalized patients with SLE.

MATERIALS AND METHODS

Patients and data collection

We identified 85 SLE patients who fulfilled the 1997 ACR classification criteria for SLE [2] and were hospitalized at the Rheumatology Division of Ewha Womans University Mokdong Hospital between January 2006 and December 2013. Admissions due to cancer chemotherapy or hematologic malignancy which can cause neutropenia independently from SLE were excluded from the study. Of these 85 patients, 160 admissions occurred. The medical records of each admission were retrospectively reviewed to identify admissions with neutropenia. Neutropenia was defined as ANC less than 1,500/mm^3. Demographics, clinical, and laboratory data were collected from medical chart using a standardized format. Demographic data included sex and age of SLE diagnosis and admission. Clinical data included clinical manifestations and the autoantibody profiles at the time of SLE diagnosis and comorbidities, concomitant medication, and disease activity measurement at the time of admission. Laboratory tests including complete blood count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), complement (C)3, C4, anti-double stranded (anti-ds)DNA were collected at the time of admission. Disease activity was assessed using SLE disease activity index (SLEDAI) [15]. Duration of neutropenia, use of granulocyte-colony stimulating factor (G-CSF), accompanied neutropenic fever, and bone marrow biopsy findings were reviewed when available. Neutropenic fever was defined as having fever over 38°C with ANC below 500/mm^3 or 1,000/mm^3 with predicted to $\leq$500/mm^3 [16]. Chronic kidney disease was defined as estimated glomerular filtration rate $<$60 mL/min/1.73 m^2 for 3 months or more [17]. The present study was approved by the Institutional Review Board of Ewha Womans University Mokdong Hospital (no. 2015-05-029-001).

Statistical analysis

All statistical analyses were conducted using PASW Statistics 18.0 (IBM Co., Armonk, NY, USA). Continuous variables were expressed as median±standard deviation while categorical data were shown as number of sample and percentage values (%). Comparing 2 groups of patients who had or had not experienced neutropenia, Mann-Whitney test was applied for continuous variables, and χ^2 test for categorical variables. Risk factors associated with development of neutropenia in SLE patients were analyzed by comparing admissions with and without neutropenia episode using generalized estimating equation (GEE) which can evaluate effects of independent variables in dichotomous outcomes, and were expressed as odds ratio (OR) and 95% confidence interval (CI). The fact that a SLE patient could contribute to more than one admission related to each other made GEE necessary. Factors associated with neutropenia with a p-value of less than 0.2 in the univariate analysis were entered in multivariate model, and a p-value of less than 0.05 was considered to indicate statistical significance in the final analysis.

RESULTS

Initial disease characteristics of SLE patients at the time of SLE diagnosis according to the presence of neutropenia during admission

To assess the disease characteristics which might predispose for development of neutropenia during admission, clinical and serologic characteristics at the time of SLE diagnosis was compared between 32 SLE patients who developed neutropenia during hospitalization and 53 patients who did not (Table 1). Age at diagnosis and sex of

Table 1. Initial characteristics of SLE patients at the time of SLE diagnosis according to the presence of neutropenia during hospitalization (n=85)

Variable	With neutropenia (n=32)	Without neutropenia (n=53)	p-value
Female	31 (96.9)	47 (88.7)	0.247
Age at diagnosis (yr)	32.8±11.7	31.1±11.7	0.253
SLE criteria satisfaction	5.1±1.1	4.6±1.3	0.009*
Manifestation at diagnosis			
Malar rash	11 (34.4)	19 (35.8)	0.890
Discoid rash	6 (18.8)	11 (20.8)	0.050
Photosensitivity	9 (28.1)	11 (20.8)	0.602
Oral ulcer	12 (37.5)	13 (24.5)	0.203
Arthritis	14 (43.8)	31 (58.5)	0.187
Serositis	5 (15.6)	6 (11.3)	0.740
Hematologic	23 (71.9)	29 (54.7)	0.116
Renal	10 (31.3)	9 (17.0)	0.126
Neuropsychiatric	2 (6.3)	2 (3.8)	0.630
Autoantibody†			
ANA	32 (100)	46 (86.8)	0.042*
Anti-dsDNA	28 (87.5)	32 (60.4)	0.008*
Anti-Sm	7 (21.9)	10 (18.9)	0.737
Anti-RNP	11 (34.4)	11 (20.8)	0.165
Anti-SSA/Ro	15 (46.9)	15 (28.3)	0.083
Anti-SSB/La	6 (18.8)	9 (17.0)	0.836
Lupus anticoagulant	16 (50.0)	20 (37.7)	0.268
Anticardiolipin antibody	14 (43.8)	22 (41.5)	0.839

Values are presented as number (%) or mean±standard deviation. SLE: systemic lupus erythematosus, ANA: antinuclear antibodies, Anti-dsDNA: anti-double stranded deoxyribonucleic acid, Anti-Sm: anti-Smith, Anti-RNP: anti-ribonucleoprotein. *Represents statistical significance of $p<0.05$. †Autoantibody positivity at diagnosis.

the patients were similar between the 2 groups. However, patients who developed neutropenia satisfied more number of 1997 ACR classification criteria for SLE than those who did not develop neutropenia (5.1±1.1 vs. 4.6±1.3, p=0.009). Patients who developed neutropenia showed higher frequency of ANA and anti-dsDNA positivity at the time of the SLE diagnosis. ANA was detected in all patients who developed neutropenia while it was detected in 86.8% in those who did not develop neutropenia (p=0.042). Anti-dsDNA was also more commonly observed in SLE patients who developed neutropenia than in those who did not (87.5% vs. 60.4%, p=0.008). Patients who developed neutropenia had tendency to have anti-SSA/Ro positivity (46.9% vs. 28.3%, p=0.083).

Prevalence and characteristics of neutropenia in hospitalized patients with SLE

Thirty-five (21.9%) neutropenic episodes were found among 160 admissions. Characteristics of neutropenia associated in SLE were shown in Table 2. Most of the neutropenic episodes were mild ($1,000/mm^3 \leq ANC < 1,500/mm^3$) to moderate ($500/mm^3 \leq ANC < 1,000/mm^3$) occurring in 17 (48.6%) and 13 (37.1%) of neutropenic admissions respectively. Severe neutropenia of ANC $<500/mm^3$ occurred only in 5 (14.3%) admissions. Overall average of neutrophil count was $934/mm^3$. When cause of admission was compared between mild, moderate, and severe neutropenia groups, although SLE flare was the most common cause of admission, infection as a cause of admission appeared to increase with severity of neutropenia (5.9% in mild neutropenia vs. 15.4% in moderate neutropenia vs. 40% in severe neutropenia). On average, neutropenia lasted for a duration of 8 days, and remained for the longest period of 12 days in admissions with severe neutropenia. Most of neutropenia improved without using G-CSF except for 2 admissions with severe neutropenia. No death occurred as a consequence of neutropenia. Neutropenic fever occurred in 10 (28.6%) admissions with neutropenia, and was accompanied more frequently in admissions with severe neutropenia. A bone marrow biopsy was performed in 2 cases with findings of slightly decreased cellularity in one case, and

Table 2. Characteristics of admissions with neutropenia in patients with SLE

Variable	Total (n=35)	Neutropenia		
		Mild* (n=17)	Moderate† (n=13)	Severe‡ (n=5)
Cause of admission				
Infection	5 (14.3)	1 (5.9)	2 (15.4)	2 (40.0)
SLE flare	27 (77.1)	13 (76.5)	11 (84.6)	3 (60.0)
Others§	3 (8.6)	3 (17.6)	0 (0.0)	0 (0.0)
Neutropenia duration (d)	7.9±4.4	7.5±4.6	7.0±2.4	12.4±5.8
Use of G-CSF	2 (5.7)	0 (0)	0 (0)	2 (40.0)
Neutropenic fever	10 (28.6)	0 (0)	6 (46.2)	4 (80.0)

Values are presented as number (%) or mean±standard deviation. SLE: systemic lupus erythematosus, G-CSF: granulocyte-colony stimulating factor, ANC: absolute neutrophil count. *ANC≥1,000/mm^3~<1,500/mm^3, †ANC≥500/mm^3~<1,000/mm^3, ‡ANC<500/mm^3. §Peripheral neuropathy, allergic rhinitis, deep vein thrombosis.

Table 3. Comparison of clinical characteristics of admissions with and without neutropenia in patients with SLE

Variable	With neutropenia (n=35)	Without neutropenia (n=125)	p-value
Age at admission (yr)	36.7±11.8	36.9±11.2	0.971
Disease duration (yr)	5.3±8.1	4.9±5.0	0.690
Cause of admission			
Infection	5 (14.3)	21 (16.8)	0.714
SLE	27 (77.1)	95 (76.0)	0.741
Others†	3 (8.6)	9 (7.2)	0.978
Comorbidities			
DM	1 (2.9)	3 (2.4)	0.839
Hypertension	4 (11.4)	13 (10.4)	0.904
Chronic kidney disease	7 (20.0)	2 (1.6)	0.004*
Sjögren's syndrome	3 (8.6)	4 (3.2)	0.234
Medication in use			
Glucocorticoid	20 (57.1)	95 (76.0)	0.050
Dose of glucocorticoid (mg)	6.79±8.03	8.32±9.01	0.319
Hydroxychloroquine	13 (37.1)	60 (48.0)	0.153
Cyclophosphamide	2 (5.7)	1 (0.8)	0.104
Azathioprine	6 (17.1)	20 (16.0)	0.827
MMF	1 (2.9)	5 (4.0)	0.763
Mizoribine	3 (8.6)	7 (5.6)	0.383
SLEDAI	11.3±6.4	10.2±7.5	0.576
Hemoglobin (mg/dL)	10.3±1.9	11.2±2.1	0.029*
Leukocyte (/mm^3)	2,029.4±6,668.2	6,534.2±3,337.1	0.001*
Platelet (×10^3/mm^3)	149.0±71.9	190.9±93.1	0.029*
ESR (mm/h)	21.23±16.81	24.47±19.92	0.250
CRP (mg/dL)	2.13±5.62	2.95±4.77	0.535
Decreased C3	29 (82.9)	68 (54.4)	0.005*
Decreased C4	19 (54.3)	35 (28.0)	0.012*
Rise in anti-dsDNA titer	27 (77.1)	79 (63.2)	0.207
Presence of proteinuria‡	9 (25.7)	28 (22.4)	0.766

Values are presented as number (%) or mean±standard deviation. SLE: systemic lupus erythematosus, DM: diabetes mellitus, MMF: mycophenolate mofetil, SLEDAI: systemic lupus erythematosus disease activity index, ESR: erythrocyte sediment rate, CRP: C-reactive protein, C: complement, Anti-dsDNA: anti-double stranded deoxyribonucleic acid. *Represents statistical significance of $p<0.05$, using generalized estimating equation analysis. †Myocardial infarction, peripheral neuropathy, allergic rhinitis, drug fever, hemarthrosis, compression fracture, deep vein thrombosis, gastrointestinal bleeding, gastric spasm. ‡Proteinuria>0.5 g/d.

myelofibrosis in another suggesting primary bone marrow abnormality rather than peripheral destruction.

Clinical characteristics of admissions with and without neutropenia in patients with SLE

Clinical and laboratory characteristics of 35 admissions with neutropenia and 125 admissions without neutropenia were analyzed (Table 3). Mean age and disease duration at the time of admission were similar between the 2 groups. Infectious causes included pneumonia, upper respiratory infection, cellulitis, enterocolitis, meningitis, and parotitis. Other causes of admission included myocardial infarction, peripheral neuropathy, allergic rhinitis, drug fever, hemarthrosis, compression fracture, deep vein thrombosis, gastrointestinal bleeding, and gastric spasm. Among comorbidities, chronic kidney disease was more frequently accompanied in admissions with neutropenia than those without (p=0.004). Medications in use at the time of admission were not significantly different, except that glucocorticoid was employed more frequently in admissions without neutropenia. Disease activity measured by SLEDAI was not significantly different between the 2 groups. Hemoglobin, leukocyte counts, platelet counts were significantly lower in neutropenic group than in non-neutropenic group. Lower level of C3 and C4 were more frequently accompanied in admissions

Table 4. Risk factors associated with neutropenia during hospitalization in patients with SLE in univariate and multivariate analysis

Variable	Univariate			Multivariate		
	Odds ratio	95% CI	p-value	Odds ratio	95% CI	p-value
Age at admission	0.99	0.96～1.04	0.971	-	-	-
Disease duration	1.02	0.94～1.09	0.690	-	-	-
Cause of admission						
Infection	0.84	0.32～2.18	0.714	-	-	-
SLE	1.16	0.49～2.71	0.741	-	-	-
Others†	0.98	0.27～3.63	0.978	-	-	-
Comorbidities						
DM	1.27	0.12～13.04	0.839	-	-	-
Hypertension	0.91	0.21～4.02	0.904	-	-	-
Chronic kidney disease	16.38	2.44～109.85	0.004*	11.17	1.46～85.27	0.020*
Sjögren's syndrome	3.14	0.48～20.67	0.234	-	-	-
Medication in use						
Glucocorticoid	0.44	0.19～1.00	0.050	0.51	0.18～1.48	0.217
Dose of glucocorticoid	0.98	0.93～1.03	0.319	-	-	-
Hydroxychloroquine	0.56	0.25～1.24	0.153	0.70	0.22～2.24	0.543
Cyclophosphamide	5.76	0.70～47.72	0.104	5.57	0.89～34.96	0.067
Azathioprine	1.12	0.41～3.09	0.827	-	-	-
MMF	0.78	0.16～3.90	0.763	-	-	-
Mizoribine	1.61	0.55～4.73	0.383	-	-	-
SLEDAI	1.01	0.97～1.06	0.576	-	-	-
Hemoglobin	0.82	0.68～0.98	0.029*	1.00	0.82～1.22	0.995
Leukocyte	0.99	0.995～0.998	0.001*	-	-	-
Platelet	0.82	0.68～0.98	0.029*	1.00	0.99～1.00	0.183
ESR	0.99	0.97～1.01	0.250	-	-	-
CRP	0.97	0.86～1.08	0.535	-	-	-
Decreased C3	3.70	1.49～9.18	0.005*	2.130	0.69～6.60	0.190
Decreased C4	2.90	1.26～6.65	0.012*	1.635	0.52～5.17	0.402
Increased anti-dsDNA	1.75	0.73～4.15	0.207	-	-	-
Presence of proteinuria‡	1.14	0.48～2.69	0.766	-	-	-

SLE: systemic lupus erythematosus, CI: confidence interval, DM: diabetes mellitus, MMF: mycophenolate mofetil, SLEDAI: systemic lupus erythematosus disease activity index, ESR: erythrocyte sediment rate, CRP: C-reactive protein, C: complement, Anti-dsDNA: anti-double stranded deoxyribonucleic acid, -: not applicable. *Represents statistical significance of $p<0.05$, using generalized estimating equation analysis. †Myocardial infarction, peripheral neuropathy, allergic rhinitis, drug fever, hemarthrosis, compression fracture, deep vein thrombosis, gastrointestinal bleeding, gastric spasm. ‡Proteinuria > 0.5 g/d.

with neutropenia than in those without. There was no significant difference in ESR, CRP, and rise in anti-dsDNA titer between neutropenic and non-neutropenic admissions.

Risk factors associated with neutropenia during hospitalization in patients with SLE

Following variables were associated with the development of neutropenia in the univariate analysis; concomitant chronic kidney disease (OR, 16.38; 95% CI, 2.44～109.85, p=0.004), low platelet count (OR, 0.99; 95% CI, 0.99～1.00, p=0.006), decrease of C3 (OR, 3.70; 95% CI, 1.49～9.18, p=0.005), and decrease of C4 (OR, 2.90; 95% CI, 1.26～6.65, p=0.012). Glucocorticoid use decreased the likelihood of developing neutropenia (OR, 0.44; 95% CI, 0.19～1.00, p=0.050). Multivariate analysis using generalized estimating equation revealed accompanied chronic renal failure (OR, 11.17; 95% CI, 1.46～85.27, p=0.020) as an independent risk factor for developing neutropenia in SLE patients (Table 4).

DISCUSSION

In this study, we found that neutropenia is a frequent event during hospitalization occurring in 22% of admissions experienced by SLE patients. Hematologic and immunologic abnormalities were more frequently accompanied during admissions associated with neutropenia. Co-existence of chronic kidney disease appeared to increase the risk of developing neutropenia during admission.

Our results suggest that neutropenia is a frequent event occurring in the disease course of patients with SLE, and the prevalence was similar with that of the previous reports [4,14,18,19]. While there is no universal cut-off level in defining neutropenia in SLE patients, neutropenia is reported in 20% to 40% of the SLE patients during their disease course [4,18], especially in 25.4% at the onset of their disease [14]. In this study, we observed that neutropenia occurred in 21.9% of admissions of SLE patients which is compatible with other studies. Most of neutropenia are reported to be mild while moderate to severe neutropenia with ANC $< 1,000/mm^3$ is described in only 0.8% to 4% of patients [14,19]. Severe neutropenia defined as ANC below $500/mm^3$ occurred in 3.1% of admissions in our study.

Limited studies have been explored the risk factors for developing neutropenia in patients with SLE. Both internal and external factors were reported to contribute to the development of neutropenia. Intrinsic factors such as thrombocytopenia, lupus activity in central nervous system, and circulating autoantibodies and extrinsic factors such as use of immunosuppressive drugs and concomitant infections were reported as risk factors for neutropenia in SLE patients [6,10,20-22]. Antineutrophil antibodies were shown to be directly involved in the peripheral destruction of neutrophils in SLE patients [7,23,24]. In patients with Sjögren's syndrome, frequency of anti-SSA/Ro and anti-SSB/La positivity were shown to be higher in patients with neutropenia than those without [25]. Our findings that SLE patients with neutropenia were more likely to be seropositive with ANA or anti-dsDNA at the time of the diagnosis, increased tendency for developing neutropenia in patients with anti-SSA/Ro positivity, and hypocomplementemia accompanying admissions with neutropenia support the role of circulating autoantibodies in development of neutropenia. In our study, use of immunosuppressive drugs did not increase the risk of neutropenia development. However, low hemoglobin, platelet, and leukocyte count detected at the admissions were shown to be associated with neutropenia in our study suggesting that primary bone marrow abnormalities might contribute to development of neutropenia [9,26]. Chronic kidney disease that might reflect lupus nephritis was revealed as an independent risk factor for neutropenia in SLE patients in this study. Reasons for association of neutropenia with kidney damage is not fully understood. It was hypothesized in a previous review article that a proportion of neutrophils which infiltrate the kidney may undergo active apoptosis causing neutropenia and organ damage to occur simultaneously [1].

Generally, the rate of infection is inversely associated with neutrophil counts [27]. In spite of the improvements in short and medium term survival rate of SLE patients [12], infection is still considered to be the most common cause of mortality and a poor prognostic factor [28]. Although a clear association between increased infection risk and the cut off value of neutropenia is uncertain, serious infection was reported to be associated with moderate to severe neutropenia of ANC $< 1,000/mm^3$ [6]. Admission caused by infection was not significantly high in neutropenic group compared with non-neutropenic group in this study. However, when we subgroup the admissions according to the severity of neutropenia, the rate of infection-induced admission was 5.9% in mild

neutropenia, 15.4% in moderated neutropenia, and 40% in severe neutropenia, which showed tendency of positive relationship between infection-induced admission rate and severity of neutropenia (p=0.071). G-CSF was used in 2 cases with severe neutropenia in this study. Although there are reports of flare in disease activity associated with G-CSF use in SLE [29,30], there was no disease flare or fatal side effects in those 2 patients treated with G-CSF in this study.

This study has some limitations. Since this is a study performed by retrospective review of medical records, some of the clinical data were missing. In addition, this study included relatively small number of cases with neutropenia since the study was performed in a single center during limited period of 8 years. In particular, this small number of cases might have made a large 95% CI in the correlation between neutropenia and chronic kidney disease, thus making insufficient power to detect differences between groups. Lastly, we included only hospitalized patients, so exclusion of patients treated without hospitalization may have brought bias toward patients with more complicated medical state. Despite the limitations, the results of our study delineating the prevalence and risk factors of neutropenia in patients with SLE may contribute significantly to the clinical management of SLE since there is limited information available for this common and potentially critical problem of neutropenia encountered in the patients with SLE.

CONCLUSION

This study implicates that neutropenia in SLE patients may be promoted by activation of autoimmunity, and may occur in the process of hematologic abnormalities. SLE patients with renal damage should be closely monitored for development of neutropenia. Prospective study including large cohort of patients is required to further define the prevalence and risk factors associated with neutropenia in patients with SLE.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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