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Characteristics and risk factors of an emergency department visit in patients with systemic lupus erythematosus

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Abstract

This study aimed to examine the characteristics of patients with systemic lupus erythematosus (SLE) visiting the emergency department (ED) and the risk factors of an ED visit by these patients. This 4-year retrospective study was performed at a tertiary care center in Japan. We included all 205 patients with SLE who were treated in our outpatient clinic between April 1, 2008 and March 31, 2012 and divided them into two groups: those who visited the ED (the ED-user group) and those who did not (the ED-non-user group). We statistically compared the patient backgrounds and characteristics of the groups and identified the risk factors of an ED visit. Of all the patients, 118 visited the ED during study period and 87 did not. In total, 269 events were identified in the ED-user group. Of these, 91 (33.8%) were cases of infection, 32 (11.9%) were orthopedic problems, 32 (11.9%) were cases of gastrointestinal disease, 31 (11.5%) were cases of neurological disease, and 25 (9.3%) were cardiovascular events. Twenty-four events (8.9%) were due to SLE flares, of which ten (41.7%) were cases of neuropsychiatric lupus (NPSLE). The glucocorticoid dosage and the presence of a psychiatric illness, NPSLE, and lupus nephritis were higher among the ED-user group. Multivariate logistic regression analysis demonstrated high glucocorticoid dosage to be a risk factor of an ED visit. Among SLE patients, infections were the principal reason for visiting the ED. The most common reasons for an ED visit were common diseases rather than flares.

Keywords Systemic lupus erythematosus (SLE) · Emergency department · Infection · Flare · Rheumatologic emergency

Introduction

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease predominantly affecting women, with typical manifestations occurring in multiple organs. Immune system aberrations as well as heritable, hormonal, and environmental factors contribute to organ damage [1]. In addition, patients with SLE suffer from complications or adverse reactions to drugs, resulting in decreased activity of daily life (ADL) and a high prevalence of disabilities [2].

An acute or severe disease condition requires an ED visit. Patients with SLE often receive glucocorticoids and immunosuppressive agents and may visit the ED frequently due to infections [3]. Patients with SLE manifest not only constitutional symptoms such as fever and fatigue but also various organ symptoms in the skin, the kidneys, and the musculoskeletal, central nervous and cardiovascular systems. Differentiating between SLE flares and complications in the ED is important but also occasionally challenging, especially for primary care or emergency physicians, and delays in diagnosis and treatment are an ever-present concern. To the best of our knowledge, there are few studies of ED visits by patients with SLE. The risk of frequent visits to the ED and the reasons for consultation in the ED by patients with SLE have been previously reported [3, 4]. However, no studies describing the characteristics and risk factors of ED visits in detail have been done.

Therefore, we herein investigated the characteristics and risk factors of ED visits by patients with SL in detail and

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determined the proportion of flares among the reasons for the visits.

Patients and methods

We included all patients with SLE who had been treated between April 1, 2008 and March 31, 2012 at Tokyo Metropolitan Tama Medical Center, a tertiary care center in west Tokyo, Japan. Approximately 40,000 patients visit the hospital's ED yearly, and about 8700 of these are conveyed to our hospital by ambulance.

All the patients in the present study met the 1997 American College of Rheumatology (ACR) classification criteria for SLE [5]. We divided all patients with SLE into two groups: those who visited the ED (ED-user group) and those who did not (ED-non-user group). Of 205 patients with SLE who had been treated at our outpatient clinic, 118 patients visited the ED during study period and 87 patients did not.

We classified the reason for the ED visits as infection, orthopedic problems or gastrointestinal, neurological, cardiovascular, allergic or endocrine disease. We further distinguished between SLE flares and complications based on a chart review. A board-certified rheumatologist retrospectively reviewed all the patients' electronic medical records and defined SLE flares as follows: (1) new symptoms characteristic of SLE that were unexplained by other diseases or (2) worsening of pre-existing symptoms attributable to SLE. In addition, we categorized arthralgia and arthritis due to SLE as arthritis with typical symptoms of SLE, which are migratory, symmetrical and polyarticular arthritis with a predilection for the knee, wrists, and fingers. We obtained information on demographic characteristics [age, sex, disease duration (years)], comorbidities (diabetes mellitus, hypertension, dyslipidemia, psychiatric illness, preexisting lung disease, and preexisting cardiovascular disease), the admission in intensive care unit (ICU) and the presence of neuropsychiatric lupus (NPSLE), lupus nephritis or osteonecrosis. We also extracted the data on treatments, including current treatments with glucocorticoids, intravenous cyclophosphamide pulse (IVCY), azathioprine, cyclosporine, tacrolimus or mizoribine, and past treatments with IVCY or glucocorticoid pulse therapy. Laboratory data, including serum creatinine, estimated glomerular filtration rate (eGFR), complement 3 (C3), C4, and anti-double-stranded DNA (anti-dsDNA) antibody were obtained at the time of the patients' last outpatient visit before their ED visit. We obtained the data of non-ED-use group from the data in 2010. We statistically compared the patient backgrounds and characteristics of the two groups and identified the risk factors of an ED visit. The institutional ethical review board approval at Tokyo Metropolitan Tama Medical Center was obtained for this retrospective data analysis.

Statistical analysis

Normally distributed numerical data were presented using the mean ± standard deviation (SD) and non-normally distributed numerical data were presented using the median and interquartile range (IQR). Differences between the ED-user group and ED-non-user group were examined using the Chi square test or Fisher's exact test for categorical data and the Student's *t* test and Mann–Whitney *U* test for continuous variables without normal distribution. Kolmogorov–Smirnov test was performed to measure normality of data distribution. A logistic regression analysis was performed to identify the risk factors of an ED visit. A two-sided *P* value of < 0.05 was considered statistically significant. All analyses were conducted using SPSS version 23 software (IBM Inc., Chicago, IL, USA).

Results

Patient's characteristics in ED-user and ED non-user

The patient characteristics of both groups are shown in Table 1. Of the 205 patients with SLE who had been treated at our outpatient clinic, 118 patients visited the ED (ED-user group) and 87 patients did not (ED-non-user group). The mean age was 48.4 ± 16.5 and 48.7 ± 14.5 years old in the two groups, respectively. The proportion of females was 89.0% and 92.0%, and the median disease duration was 8.0 [0–16.5] and 8.0 [1–22] years, respectively. There was no difference in age, sex, disease duration or comorbidities such as diabetes mellitus, hypertension, dyslipidemia, psychiatric illness, preexisting lung disease or preexisting cardiovascular disease between the two groups.

Reasons for visiting the ED

In total, 269 events were identified in the ER-user group ($n = 118$). The reasons for the ED visits are shown in Table 2. Of these events, 91 (33.8%) were cases of infection, 32 (11.9%) were orthopedic problems, 32 (11.9%) were cases of gastrointestinal disease, 31 (11.5%) were cases of neurological diseases, and 25 (9.3%) were cardiovascular events. Among the 91 events due to infections, pneumonia, and upper respiratory tract infections were the most common ($n = 22$), and urinary tract infections ($n = 20$) and gastroenteritis ($n = 20$) were the second most common. Among the 32 events related to orthopedic problems, arthralgia and arthritis unrelated to SLE flares were the most common. Falls were the second most common orthopedic problem. Among the eight events related to falls, 5 (63%) resulted

Table 1 Characteristics of emergency department (ED)-user and ED-non-user in patients with systemic lupus erythematosus

	ED-user ($n=118$)	ED-non-user ($n=87$)	P
Age (years)	48.4 ± 16.5	48.7 ± 14.5	0.90
Female	105 (89.0%)	80 (92.0%)	0.479
Disease duration (years)	8.0 [0–16.5]	8.0 [1–22]	0.223
Welfare benefits	11 (9.3%)	3 (3.4%)	0.099
Diabetes mellitus	12 (10.2%)	3 (3.4%)	0.068
$HbA1_c$ (%)	7.21 ± 1.24	6.27 ± 0.15	0.219
Hypertension	47 (39.8%)	30 (34.5%)	0.435
Dyslipidemia	33 (28.0%)	25 (28.7%)	0.904
Preexisting lung disease[a]	12 (10.2%)	4 (4.6%)	0.142
Preexisting cardiovascular disease[b]	12 (10.2%)	5 (5.7%)	0.256
Psychiatric illness	17 (14.4%)	3 (3.4%)	0.009*
NPSLE	23 (19.5%)	6 (6.9%)	0.011*
Lupus nephritis	48 (40.7%)	22 (25.3%)	0.022*
Osteonecrosis	16 (13.6%)	6 (6.9%)	0.128
Creatinine (mg/dl)	0.84 ± 0.92	0.70 ± 0.35	0.189
eGFR (ml/min/1.73 m^2)	81.2 ± 32.9	82.4 ± 26.7	0.765
Anti-dsDNA antibody	41/116 (35.3%)	27/84 (32.1%)	0.637
Hypocomplementemia	66/109 (60.6%)	44/84 (52.4%)	0.256
C3 (mg/dl)	85.6 ± 25.5	89.3 ± 19.7	0.269
C4 (mg/dl)	18.3 ± 8.7	18.5 ± 7.4	0.887

NPSLE neuropsychiatric lupus

*P value < 0.05 were considered significant

[a]Preexisting lung diseases: interstitial lung disease, old tuberculosis, asthma, bronchiectasis, nontuberculous mycobacteriosis, and chronic obstructive pulmonary disease

[b]Preexisting cardiovascular diseases: old myocardial infarction, chronic heart failure, and stable angina pectoris

in fractures. Gastrointestinal diseases were also the second most common problem ($n=32$). Among the 32 events related to gastrointestinal diseases, 16 were cases of nonspecific abdominal pain, and six were cases of gastrointestinal bleeding.

There were 25 cases of cardiovascular disease, including life-threatening emergencies such as acute coronary syndrome ($n=6$), subarachnoid hemorrhage ($n=3$), cerebral infarction ($n=1$), cerebral hemorrhage ($n=1$), pulmonary embolism ($n=1$), and aortic dissection ($n=1$).

Of these events, 94 (34.9%) culminated in admission to our hospital. Among 118 patients who visited the ED, 16 patients (13.6%) were admitted in ICU and 3 patients (2.5%) died from severe clostridium difficile infection, perforation of sigmoid colon, and septic shock. The median number of ED visits in a patient with SLE during this study period was twice (range 1–10).

ED visits due to SLE flare

ED visits due to SLE flares are shown in Table 2. Of 269 events, 24 (8.9%) were SLE flares; of these, ten (41.7%) were cases of NPSLE, including disturbance of consciousness, aseptic meningitis, seizure, and visual field abnormality. Other events due to SLE flares were arthritis ($n=4$), pleuritis ($n=4$), fever ($n=2$), rash ($n=2$), nephrotic syndrome due to lupus nephritis ($n=1$), and scleritis ($n=1$). There were no patients who were accompanied by infections.

Risk factors of ED visits

The ED-user group had more cases of psychiatric illness than the ED-non-user group, at 17 (14.4%) and 3 (3.4%) cases, respectively ($P=0.009$). The number of patients with NPSLE and lupus nephritis was significantly greater in the ED-user group, at 23 (19.5%) vs 6 (6.9%) patients ($P=0.011$) and 48 (40.7%) vs 22 (25.3%) patients ($P=0.022$), respectively. The characteristics of the medications in the ED-user and ED-non-user groups are shown in Table 3. Significantly more patients received glucocorticoids in the ED-user group than in the ED-non-user group (91.5% vs 78.2%, respectively). The median glucocorticoid dosage in the ED-user and ED-non-user groups was 7.5 mg [5.0–10.0] and 5.0 mg [2.0–8.0], respectively (prednisolone equivalent, $P<0.0001$). The two groups did not differ in terms of past treatments with glucocorticoid

Table 2 Reasons of emergency department visits in patients with systemic lupus erythematosus

Reasons	$n=269$
Infections Urinary tract infection 20, gastroenteritis 20, upper respiratory tract infection 14, pneumonia 8, cellulitis 5, abscess 4, herpes zoster 3, influenza 2, empyema 2, others 13 (*Mycobacterium avium* infection 1, septic shock 1, infected arterial aneurysm 1, vertebral osteomyelitis 1 etc.)	91
Orthopedic problems Arthralgia/arthritis 12, fall 8 (fracture 5), lumbago 7, others 5 (osteonecrosis of femoral head 1 etc.)	32
Gastrointestinal diseases Abdominal pain 16, gastrointestinal bleeding/peptic ulcer diseases 6, appetite loss 2, nausea 2, others 6 (appendicitis 1, diverticular perforation of sigmoid colon 1, etc.)	32
Neurological diseases Headache 15, dizziness and vertigo 9, syncope 3, others 4 (seizure 1, etc.)	31
Cardiovascular diseases Acute coronary syndrome 6, palpitation 5, subarachnoid hemorrhage 3, arrhythmia 3, heart failure 2, others 6 (cerebral infarction 1, cerebral hemorrhage 1, pulmonary embolism 1, aortic dissection 1, etc.)	25
Allergy diseases Drug eruption 3, asthma 2, urticaria 2	7
Endocrine diseases Hyperglycemia 2, hypoglycemia 2, hypercalcemia 1	5
Others Trauma and injury 8, generalized pain 5, overdose 3, eczema 2, others 4 (suicide attempt 1, etc.)	22
ER visits due to SLE flare NPSLE 10 (disturbance in consciousness 4, aseptic meningitis 3, seizure 2, visual field abnormality 1) arthritis 4, pleuritis 4, nephrotic syndrome (lupus nephritis) 1, fever 2, rash 2, scleritis 1	24 (8.9%)

NPSLE neuropsychiatric lupus

Table 3 Comparison of drug uses in emergency department (ED)-user and ED-non-user

	ED-user ($n=118$)	ED-non-user ($n=87$)	*P*
Glucocorticoids	108 (91.5%)	68 (78.2%)	0.007*
Prednisolone equivalent (mg/day)	7.5 [5.0–10.0]	5.0 [2.0–8.0]	< 0.0001*
PSL = 0	10 (8.5%)	19 (21.8%)	
0 < PSL ≤ 5	29 (24.6%)	33 (37.9%)	
5 < PSL ≤ 10	50 (42.4%)	26 (30.0%)	
10 < PSL	29 (24.6%)	9 (10.3%)	
Cumulative dosage of glucocorticoids in the past 3 months (mg/90 days)	652.5 [428–878]	450 [203–698]	< 0.0001*
Duration of glucocorticoids (years)	8.0 [0–16]	8.0 [1–20]	0.221
Immunosuppressive drugs	43 (36.4%)	35 (40.2%)	0.575
IVCY	5 (4.2%)	1 (1.1%)	0.244
Azathioprine	12 (10.2%)	15 (17.2%)	0.139
Cyclosporine	2 (1.7%)	4 (4.6%)	0.405
Tacrolimus	11 (9.3%)	7 (8.0%)	0.75
Bredinin	13 (11.9%)	8 (9.2%)	0.671

PSL prednisolone, *IVCY* intravenous cyclophosphamide pulse

*P value < 0.05 were considered significant

pulse therapy or IVCY nor in the use of immunosuppressive drugs, including IVCY, azathioprine, cyclosporine, tacrolimus or mizoribine.

The multivariate logistic regression analysis of risk factors of an ED visit is shown in Table 4. An increase in the glucocorticoid dosage was a risk factor of an ED visit.

Discussion

Our study found that patients with SLE visited the ED for various reasons, with infection being the principal reason. The most common reasons for an ED visit in patients with

Table 4 Multivariate logistic analysis to predict emergency department visits in patients with systemic lupus erythematosus

	Odds ratio	95% CI	95% CI	*P*
Age (years)	1.005	0.985	1.025	0.657
Duration of disease (years)				
< 5	Reference			
5 ≤	1.007	0.524	1.936	0.984
Dosage of glucocorticoid (mg prednisolone/day)				
PSL = 0	Reference			
0 < PSL ≤ 5	1.550	0.603	3.984	0.363
5 < PSL ≤ 10	3.101	1.227	7.840	0.017*
10 < PSL	4.098	1.310	12.822	0.015*
Lupus nephritis	1.571	0.808	3.054	0.183
NPSLE	2.044	0.735	5.685	0.171

PSL prednisolone, *NPSLE* neuropsychiatric lupus

**P* value < 0.05 were considered significant

SLE were common diseases rather than flares. The use of glucocorticoids was the biggest risk factor of an ED visit, and the risk increased as the dosage of glucocorticoids increased.

Patients with SLE often receive glucocorticoids and immunosuppressive agents and require visiting the ED due to infections, including opportunistic infections. Patients with SLE typically present not only with constitutional symptoms, but also various symptoms in multiple organs. In clinical practice, differentiating between SLE flares and complications is clinically extremely important but may be challenging, especially for primary care or emergency physicians, as well as, occasionally, for rheumatologists. As a result, delays in diagnosis and treatment are an urgent concern.

A report on consultations during ED visits in patients with SLE showed that the reasons for ED consultation were fever, arthralgia, abdominal pain, upper respiratory infection, and chest pain [4]. Forty-nine of 180 patients (32.7%) were hospitalized. These results were consistent with our findings in terms of infections, orthopedic problems, and gastrointestinal diseases being the most common reasons for an ED visit. Moreover, the rate of hospitalization in this study was roughly equivalent to our findings (34.9%). However, it was unclear whether the reasons for the ED visits were SLE flares or complications such as infections. Whether or not symptoms such as fever are due to flares is a major diagnostic problem in lupus patients in the ED. The present study is the first report to describe in detail the characteristics and proportion of flares in patients with SLE who visit the ED.

In our study, as shown in Table 2, the principal reason for an ED visit was infections. Patients with SLE are highly susceptible to infections due to effects of immunosuppressive therapy and the abnormalities of the immune system that the disease itself causes. Infections remain an important cause of mortality and morbidity in patients with SLE. Moreover, infections are also one of the leading causes of hospitalization in SLE patients [6, 7]. According to previous reports, 11–45% of SLE patients experienced a severe infection [8–11]. Chen et al. reported that 1321 (34.6%) of 3815 hospitalized patients with SLE received the diagnosis of infection. Bacterial infections were predominant (50.6%) and were followed by viral (36.4%) and fungal infections (12.5%). The lung and upper respiratory tract were the most common infection sites, followed by the urinary tract, skin, and soft tissue [12]. Tektonidou et al. also reported that pneumonia was the most common, serious infection among hospitalized adults with SLE [7]. Moreover, Iliopoulos et al. reported that common infections, as well as opportunistic pathogens, are frequently encountered among patients with SLE [8]. These results were consistent with our own observations. Most of the infections encountered in the present study were common infections although we also encountered opportunistic infections, including *Pneumocystis jirovecii* pneumonia and disseminated *Mycobacterium avium* complex infections.

In our study, ED visits due to SLE flares comprised only 8.9% of the total number of visits. This result showed that most of the patients with SLE visited the ED due to a common disease rather than SLE flares. We tend to suspect lupus flares when febrile SLE patients visit the ED. The initial clinical presentation of patients with SLE is very similar to that of the acute, febrile phase of an infection. It is important to distinguish between lupus flares and infections, as the treatments for the conditions are completely different. However, differentiating between the two conditions may not be easy in clinical practice, and the two processes may coexist in the same patient. A combination of immunosuppressive therapy and antibiotic therapy may be considered in these patients. Our findings suggest that it is necessary to consider complications such as infections before considering the possibility of lupus flares when we see SLE patients in the ED.

Diffuse alveolar hemorrhage (DAH), transverse myelitis, NPSLE, and catastrophic antiphospholipid syndrome (CAPS) are well-known, life-threatening, critical conditions in patients with SLE and are associated with a high mortality rate [13]. However, DAH [14–19] and transverse myelitis [20, 21] occur in approximately 1.4–2.9% and 1.0–3.2% of patients with SLE, respectively, while CAPS occurs in fewer than 1% of patients with APS [22]. As our study showed, these critical, devastating conditions are relatively rare, and most patients with SLE visit the ED due to a common disease. Indeed, common conditions can be overlooked in SLE patients with a fever or arthralgia by physicians too focused on finding an SLE-related condition. Moreover, in our study, patients with SLE occasionally visited the ED due

to a common life-threatening emergency such as acute coronary syndrome, subarachnoid hemorrhage, cerebral infarction, cerebral hemorrhage, pulmonary embolism or aortic dissection. Both life-threatening conditions and common diseases should be suspected and tested for first at every ED visit as is normally done in clinical practice regardless of whether or not the patient has SLE. The differential diagnosis of SLE-related conditions should only then be performed.

Multivariate logistic analysis demonstrated that a higher glucocorticoid dosage was the biggest risk factor of an ED visit. It is well-known that glucocorticoids produce a wide spectrum of adverse effects in a dose- and time-dependent manner. Glucocorticoids are responsible for increasing the risk of severe infections [8, 23], with higher dosages being associated with a correspondingly higher risk of infection [12]. Rua-Figueroa et al. also reported that a dose–response relationship was found between glucocorticoids and the bacteremia risk in SLE patients [24]. Therefore, the dosage of glucocorticoids should be reduced, and steroid-sparing agents such as immunosuppressive drugs and hydroxychloroquine (HCQ) should be substituted to decrease the risk of an ED visit.

There are several limitations to this study. First, because it was a retrospective, single-center study, we were unable to obtain the SLE Disease Activity Index (SLEDAI)-2K score [25] or the British Isles Lupus Assessment Group (BILAG) index score [26], which are normally used to assess disease activity in SLE patients. SLEDAI-2 K or BILAG were developed and validated as clinical indices for the SLE management. However, in our study, a board-certified rheumatologist reviewed the electronic medical records of all SLE patients who visited our ED during the stated period, the reason for their visit, and the patient outcomes in detail, confirming that the reasons for their ED visit corresponded with the occurrence of SLE flares in each patient. As a result, our definition of SLE flare did not deviate from the previously cited definition.

Second, HCQ was not approved for use in Japan during the study period. HCQ is an important medication for treating SLE and is widely used in more than 70 countries. In addition, HCQ has been shown to prevent SLE flares [27] and reduce the risk of infection [28]. If HCQ had been used in Japan, it might have decreased the rate of ED visits by preventing flares and infections. In 2015, HCQ was finally approved for use in Japan. Therefore, we need to confirm our findings with a larger patient cohort using HCQ as one of the available treatment options.

In conclusion, among SLE patients, infections were the principal reason for visiting the ED. Higher glucocorticoid dosage was found to be biggest risk factor for an ED visit. In addition, ED visits due to SLE flares comprised only 8.9% of the total visits to the ED. These results showed that the most common reasons for an ED visit in patients with SLE were common diseases rather than SLE flares. Therefore, when we see patients with SLE in the ED, we should first determine if a common disease such as an infection is present before considering the differential diagnoses of SLE-related conditions.

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Author contributions YN designed the study, collected the date, drafted and revised the manuscript. NY participated in designing the study, interpreted the date. KS participated interpreted the data and revised the manuscript. SS designed the study and interpreted the data. All the authors read and approved the final manuscript.

Compliance with ethical standards

Conflict of interest All authors declare that there are no conflicts of interest.

Ethical standards All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent This study was approved by the Institutional Review Board (IRB) of Tokyo Metropolitan Tama Medical Center (30–46), and the patient's written informed consent was waived by the approving IRB, as this was a retrospective study.

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