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Disease Flare of Systemic Lupus Erythematosus in Patients With Endstage Renal Disease on Dialysis

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ABSTRACT. ***Objective.*** Although systemic lupus erythematosus (SLE) disease activity diminishes after starting dialysis, flares have been documented during dialysis. Hence, we studied the various clinical and therapeutic variables of patients with SLE who had a disease flare while on dialysis.

Methods. The medical records of patients with SLE who received dialysis at 2 tertiary referral hospitals in South Korea were reviewed. The disease activity was analyzed in terms of the nonrenal SLE Disease Activity Index (SLEDAI), and the factors associated with SLE flares were evaluated.

Results. Of the total of 121 patients with SLE on dialysis, 96 (79.3%) were on hemodialysis (HD) and 25 (20.7%) were on peritoneal dialysis (PD). During a median follow-up of 45 months (IQR 23-120) after the initiation of dialysis, 32 (26.4%) patients experienced an SLE flare (HD, n = 25; PD, n = 7). The most common features of SLE flare were hematologic (40.6%; thrombocytopenia [31.2%] and leukopenia [21.8%]) and constitutional manifestations (40.6%). Fever was the most common (34.3%) feature among the constitutional symptoms. Treatments for disease flares were based on corticosteroids, and 11 (34.3%) patients required additional immunosuppressants, including cyclophosphamide and mycophenolate mofetil. Nonrenal SLEDAI score before dialysis initiation (HR 1.24, 95% CI 1.12-1.36; $P = 0.001$) was a significant risk factor for disease flare during dialysis.

Conclusion. More than a quarter of the patients with SLE experienced a disease flare during dialysis, which most commonly had hematologic manifestations, particularly thrombocytopenia. Continued follow-up and appropriate treatments, including immunosuppressants, should be considered for patients with SLE receiving dialysis.

Key Indexing Terms: dialysis, endstage renal disease, immunosuppressant, lupus nephritis, systemic lupus erythematosus

Lupus nephritis (LN) is one of the most serious clinical manifestations with organ involvement of systemic lupus erythematosus (SLE), leading to approximately 10% to 20% of patients progressing to endstage renal disease (ESRD).[1-4] The SLE disease activity in patients with LN generally declines after the initiation of renal replacement therapy (RRT); this is known as the "burn out" phenomenon that possibly occurs because of the suppression of cellular and humoral immunity in the ESRD state and elimination of pathogenic factors of disease by dialysis.[5-8]

However, several studies have shown that SLE flares could occur even during RRT.[9-12] In a previous study, SLE manifestations were frequently found in patients with SLE with ESRD, with hematologic signs as the most commonly observed form.[10,13] Although the development and risk factors of SLE flares while receiving dialysis have been reported previously, there have been few studies on the characteristic details of disease flares and, in particular, on the treatment of patients with SLE undergoing dialysis. In addition, regarding the dialysis modality, limited data with conflicting results are available on the differences in SLE activity between hemodialysis (HD) and peritoneal dialysis (PD) in patients with SLE.[10,12,14,15] Further, considering the risk of possible adverse events (AEs) of immunosuppressive drugs in the kidney failure state, immunosuppressants should be used with caution, thus necessitating further research.

In this regard, we examined the clinical features, risk factors, and treatment details of patients with SLE experiencing a disease flare under RRT.

METHODS

Study population. We retrospectively reviewed the medical records of patients

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who were diagnosed with SLE between January 1995 and December 2020 following the American College of Rheumatology classification criteria at 2 tertiary referral hospitals in South Korea—Asan Medical Center and Ulsan University Hospital.[16] All patients in this study were either clinically or histologically diagnosed with LN and the LN classification based on the International Society of Pathology/Renal Pathology Society 2003 criteria was recorded.[17] This study was performed in accordance with the Declaration of Helsinki and its later amendments. The study protocol was approved by the institutional review boards of Asan Medical Center (Seoul; S2020-3159-0001) and Ulsan University Hospital (Ulsan; 2021-04-021). Informed consent was waived considering the retrospective nature of the study.

Patient data collection. We gathered information on age, sex, BMI, duration of SLE, and duration from diagnosis of LN to ESRD. The laboratory data at the time of dialysis initiation (baseline), including immunological parameters, such as anti-dsDNA and complement levels, are presented in Table 1 and Table 2. Serology data, including antinuclear antibody and antiphospholipid antibody (aPL) levels, were also collected prior to starting dialysis. The dialysis modality and complications related to dialysis were also investigated; dialysis-related complications included vascular access obstruction and continuous ambulatory PD (CAPD) peritonitis. The diagnosis of CAPD peritonitis was made clinically in accordance with the International Society of Peritoneal Dialysis guidelines.[18]

The disease activity was analyzed using the nonrenal SLE Disease Activity Index (SLEDAI) scores obtained before and after dialysis, and the information on corticosteroid (CS) use was collected. Low-dose, medium-dose, and high-dose CS were defined as < 7.5 mg, 7.5 mg to 30 mg, and > 30 mg prednisone equivalent per day; CS pulse therapy was defined as > 250 mg of prednisone equivalent per day.[19] Disease flare was defined as new onset or worsening clinical symptoms, signs, and/or laboratory measurements as assessed by increases in the SLEDAI score by ≥ 3.[20] To exclude other causes that may mimic disease flare, we classified the patients as SLE flare only when the patients' symptoms were improved after new administration or an increase in the CS dose. Clinical characteristics and medications, including immunosuppressive drugs at the time of disease flare, were assessed. AEs such as cytopenia and infection related to medication were collected.

Statistical analysis. Continuous values are expressed as means with SDs for parametric data or as medians with IQRs for nonparametric data. Differences were assessed using *t* test for continuous variables and chi-square test and Fisher exact tests for categorical variables. Cox proportional hazards regression analysis with clinical variables were analyzed to identify the risk factors associated with SLE flare. HRs were reported with their respective 95% CIs and *P* values > 0.05 were considered statistically significant.

RESULTS

Baseline characteristics of patients with SLE with ESRD undergoing dialysis. A total of 121 patients with SLE on RRT were analyzed. The clinical and laboratory data of the patients at baseline (time of RRT initiation) are summarized in Table 1. Of the patients, 95 (78.5%) were women, and the median age was 40 years (IQR 31-50); 44 (36.4%) and 10 (8.3%) patients had hypertension and diabetes, respectively. The median disease duration of SLE was 95 months (IQR 22-149) and the median interval from diagnosis of LN to ESRD was 76 months (IQR 11-128). The mean estimated glomerular filtration rate at the time of dialysis initiation was 7.29 mL/min/1.73m² (SD 4.96).

Prior to RRT, 79 (65.3%) patients received CS; the most commonly used immunosuppressant was mycophenolate mofetil (MMF; n = 28, 23.1%) followed by tacrolimus (TAC; n = 24, 19.8%). After the initiation of RRT, all patients discontinued

Table 1. Baseline characteristics of patients with SLE with ESRD on dialysis.

	N = 121
Age, yrs	40 (31-50)
Female	95 (78.5)
BMI, kg/m²	21.6 ± 3.6
Disease duration of SLE, months	95 (22-149)
Disease duration from LN onset to ESRD, months	76 (11-128)
SLEDAI at time of dialysis initiation	11.1 (8.0-15.0)
Nonrenal SLEDAI at the time of dialysis initiation	3.4 (2.0-5.0)
Comorbidities	
Hypertension	44 (36.4)
Diabetes mellitus	10 (8.3)
Atrial fibrillation	4 (3.3)
Laboratory data at the time of dialysis initiation	
Uric acid, mg/dL	9.47 ± 5.32
Albumin, g/dL	2.93 ± 0.65
Creatinine, mg/dL	8.74 ± 3.67
eGFR, mL/min/1.73m²	7.29 ± 4.96
ESR, mm/h	33 (10-50)
CRP, mg/dL	0.5 (0.1-2.8)
C3, mg/dL	58.9 ± 27.5
C4, mg/dL	18.0 ± 11.1
Anti-dsDNA antibody, IU/mL	12.2 (4.1-47.9)
Medications taken 1 yr prior to the initiation of dialysis	
HCQ	23 (19.0)
CS	79 (65.3)
MMF	28 (23.1)
TAC	24 (19.8)
CYC	22 (18.2)
AZA	9 (7.4)
RTX	4 (3.3)
History of SLE activity 1 yr prior to dialysis initiation	
Constitutional	
Fever[a]	12 (9.9)
Hematologic	
Leukopenia, < 1000 cells/mL[a]	20 (16.5)
Hemolytic anemia[a]	1 (0.8)
Thrombocytopenia, < 100 K/mL[a]	15 (12.4)
Positive aPL[b]	47 (38.8)
Dialysis modality	
Hemodialysis	96 (79.3)
Conversion to peritoneal dialysis	8 (8.3)
Peritoneal dialysis	25 (20.7)
Conversion to hemodialysis	4 (16.0)

Data are median (IQR), mean ± SD, or n (%). [a] Fever: temperature > 38.3 °C; hemolytic anemia: evidence of hemolysis, such as reticulocytosis, low haptoglobin, elevated indirect bilirubin, elevated lactate dehydrogenase and positive Coomb (direct antiglobulin) test; persistent leukopenia: < 1000 WBC in tests performed continuously at intervals of 1 month or more; persistent thrombocytopenia: < 100,0000/mm³ platelet in tests performed continuously at intervals of 1 month or more. [b] Anticardiolipin antibody of IgG and/or IgM isotype in serum or plasma present in titers > 40 IgG; anti-β_2 glycoprotein I antibody of IgG and/or IgM isotype in serum or plasma in titers > 99th percentile; presence of lupus anticoagulant. aPL: antiphospholipid antibody; AZA: azathioprine; CRP: C-reactive protein; CS: corticosteroid; CYC: cyclophosphamide; eGFR: estimated glomerular filtration rate; ESR erythrocyte sedimentation rate; ESRD: endstage renal disease; HCQ: hydroxychloroquine; LN: lupus nephritis; MMF: mycophenolate mofetil; RTX: rituximab; SLE: systemic lupus erythematosus; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; TAC: tacrolimus; WBC: white blood cells.

Table 2. Comparison of baseline characteristics in patients with SLE according to dialysis modality.

	Hemodialysis, n = 96	Peritoneal Dialysis, n = 25	*P*
Baseline characteristics			
Age, yrs	41.7 ± 12.8	38.9 ± 11.7	0.30
Female	75 (78.1)	20 (80.0)	0.93
BMI, kg/m^2	21.5 ± 3.6	21.9 ± 3.5	0.65
Disease duration of SLE, months	92 (29-169)	88 (3-122)	0.14
Disease duration from LN onset to ESRD, months	79 (13-135)	60 (3-98)	0.05
Disease activity			
Nonrenal SLEDAI			
At the initiation of dialysis	3.5 (2.0-5.0)	2.0 (1.7-4.0)	0.30
At 1 yr after the initiation of dialysis	0.5 (0-1.0)	0.0 (0-0.5)	0.59
Paired *t* test (before and after dialysis)	< 0.01	< 0.01	
Cumulative amount of steroid, g			
During 1 yr prior to the initiation of dialysis	2.5 (1.2-5.3)	5.9 (1.9-8.9)	0.42
During 1 yr after the initiation of dialysis	3.5 (1.4-4.1)	4.1 (2.4-4.9)	0.76
Paired *t* test (before and after dialysis)	0.03	0.90	
Patients with disease flare during additional follow-up	25 (26.0)	7 (28.0)	0.73

Data are median (IQR), mean ± SD, or n (%). ESRD: endstage renal disease; LN: lupus nephritis; SLE: systemic lupus erythematosus; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index.

immunosuppressive drugs. Of the 23 (19.0%) patients who received hydroxychloroquine (HCQ), 5 (4.1%) continued receiving HCQ after dialysis. In terms of dialysis modality, 96 (79.3%) patients underwent HD, whereas 25 (20.7%) were on PD.

Comparison between HD vs PD groups. We compared the baseline characteristics between patients who underwent HD and those who started PD (Table 2). There were no significant differences in age or sex between the 2 groups. However, the PD group had a shorter duration of LN compared with the HD group (median [IQR] 79 [13-135] months in HD vs 60 [3-98] months in PD; $P = 0.05$).

To analyze the changes in disease activity after dialysis, we compared the nonrenal SLEDAI value before and after 1 year of dialysis (Table 2). The nonrenal SLEDAI values at the time of dialysis initiation were 3.5 (IQR 2.0-5.0) in the HD group and 2.0 (IQR 1.7-4.0) in the PD group ($P = 0.30$). Both groups showed significant decreases in disease activity, with the HD group showing a nonrenal SLEDAI value of 0.5 (IQR 0-1.0; $P < 0.01$) and the PD group showing a value of 0 (IQR 0-0.5; $P < 0.01$) after 1 year of dialysis. Interestingly, when we compared the cumulative CS dose before and after dialysis, the cumulative dose used for 1 year after dialysis had significantly increased in the HD group (2.5 [IQR 1.2-5.3] to 3.5 [IQR 1.4-4.1]; $P = 0.03$); in contrast, the PD group did not show a significant change in the cumulative CS dose after dialysis (5.9 [IQR 1.9-8.9] to 4.1 [IQR 2.4-4.9]; $P = 0.90$).

In terms of dialysis-related complications, arteriovenous fistula (AVF) obstruction (n = 10) and AVF infection (n = 4) were the most common findings in the HD group. Seven of the 10 patients who experienced AVF obstruction were positive for aPL. These patients, except 1 (n = 6), received anticoagulation therapy with warfarin. Eight (8.3%) out of 96 patients in the HD group were switched to PD during follow-up, mainly because of AVF obstruction (Table 1). In the PD group, the most common complication was CAPD peritonitis (11/25, 44.0%), and 4 (16%) patients were switched to HD because of recurrent peritonitis (n = 1), volume overload (n=1), or peritoneal adhesion (n = 2).

Characteristics of patients with a nonrenal flare of SLE during follow-up. Next, we examined the development of SLE flare during a median follow-up of 45 months (IQR 23-120) after starting RRT. Of the total patients, 32 (26.4%) experienced disease flare with an incidence rate of 0.04 episodes/patient-year. SLE flare was observed at a median of 17 (IQR 8.0-36.0) months after the initiation of dialysis, and the value of nonrenal SLEDAI at the time of disease flare was 7.5 (5.0-12.0). The incidence rate of disease flare was 26.0% (25/96) in the HD group and 28.0% (7/25) in the PD group ($P = 0.73$; Table 2). Further, when we analyzed the features of SLE flare, there were no significant differences between the HD group and the PD group in terms of the indicators of disease activity, including nonrenal SLEDAI, complement level, and anti-dsDNA levels (Table 3). The most common features in SLE flare were hematologic (40.6%) and constitutional (40.6%) manifestations, followed by neurologic manifestations (28.0%). Thrombocytopenia (31.2%) was the most common finding among the hematologic manifestations, followed by leukopenia (21.8%). Fever was the most common (34.3%) symptom among the constitutional manifestations. Seizure was the most common (12.5%) neurologic manifestation, followed by headache (9.3%). When comparing the disease flare episodes between the HD and PD groups, there were no significant differences in disease manifestation except for the higher proportion of musculoskeletal presentation in the PD group (1/7, 14.2%) than in the HD group (1/25, 4.0%; $P = 0.02$).

Table 3. Laboratory data and disease manifestation in patients who experienced SLE flare on renal replacement therapy according to dialysis modality.

	Total, n = 32	Hemodialysis, n = 25	Peritoneal Dialysis, n = 7	*P*
Duration of dialysis, months	17 (8-36)	19 (11-36)	10 (7-25)	0.66
Laboratory data				
Uric acid, mg/dL	7.0 ± 2.9	6.6 ± 2.5	8.1 ± 3.9	0.12
Albumin, g/dL	2.7 ± 0.7	2.8 ± 0.6	2.6 ± 0.8	0.93
Nonrenal SLEDAI	7.5 (5.0-12.0)	6.5 (5.0-13.2)	10.5 (8.5-11.2)	0.83
ESR, mm/h	41.3 ± 28.1	49.1 ± 30.1	26.8 ± 17.4	0.19
CRP, mg/dL	1.1 (0.4-4.0)	1.1 (0.4-4.4)	1.1 (0.2-3.4)	0.64
C3, mg/dL	52.8 ± 27.0	49.0 ± 28.2	59.4 ± 21.1	0.44
C4, mg/dL	14.0 ± 10.6	12.3 ± 10.6	17.7 ± 9.4	0.14
Anti-dsDNA, IU/mL	28 (8-147)	29 (5-224)	22 (10-59)	0.35
Disease manifestation				
Cardiac[a]	2 (6.2)	2 (8.0)	0 (0.0)	0.99
Constitutional[b]	13 (40.6)	10 (40.0)	3 (42.8)	0.99
Fever	11 (34.3)	9 (36.0)	2 (28.5)	0.77
Myalgia	3 (9.3)	2 (8.0)	1 (14.2)	0.76
Gastrointestinal[c]	5 (15.6)	5 (20.0)	0 (0.0)	0.34
Hematologic[d]	13 (40.6)	9 (36.0)	4 (57.1)	0.42
Leukopenia, < 1000 cells/mL	7 (21.8)	4 (16.0)	3 (42.8)	0.07
Thrombocytopenia, < 100 K/mL	10 (31.2)	7 (28.0)	3 (42.8)	0.31
Musculoskeletal[e]	2 (6.2)	1 (4.0)	1 (14.2)	0.019
Neurologic[f]	9 (28.0)	5 (20.0)	4 (57.1)	0.37
Headache	3 (9.3)	1 (4.0)	2 (28.5)	0.23
Cognitive dysfunction	1 (3.1)	1 (4.0)	0 (0.0)	0.32
Seizure	4 (12.5)	2 (8.0)	2 (28.5)	0.32
Cerebrovascular event	1 (3.1)	1 (4.0)	0 (0.0)	0.32
Pulmonary[g]	5 (15.6)	5 (20.0)	0 (0.0)	0.89
Skin[h]	4 (12.5)	3 (12.0)	1 (14.2)	0.95

Data are median (IQR), mean ± SD, or n (%). [a] Pericarditis, myocarditis. [b] Fever, myalgia, fatigue, weight loss. [c] Enteritis. [d] Anemia, thrombocytopenia, leukopenia. [e] Arthritis. [f] Seizure, psychosis, headache, cognitive dysfunction. [g] Pleurisy. [h] Malar rash, alopecia, photosensitivity. CRP: C-reactive protein; ESR erythrocyte sedimentation rate; ESRD: endstage renal disease; LN: lupus nephritis; SLE: systemic lupus erythematosus; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index.

In addition, we examined the treatment details, including AEs of the 32 patients who experienced an SLE flare while receiving dialysis. Table 4 shows the detailed data, including AEs of treatments in each patient. All patients who had a disease flare had received CS-based treatment; 15 (46.8%) patients received high-dose CS, 9 (28.1%) patients received CS pulse therapy, and 8 (25.0%) patients received medium-dose CS. Of the total patients with an SLE flare, 11 (34.3%) patients required treatments with additional immunosuppressants, including cyclophosphamide (CYC; n = 1), cyclosporine (n = 3), TAC (n = 2), MMF (n = 2), rituximab (n = 3) and intravenous Ig (n = 1). In these patients, immunosuppressive drugs were administered to control clinical symptoms after extensive inspection to exclude other causes, including infection. In terms of the AEs related to immunosuppressants, 1 patient developed pneumonia after the use of high-dose CS for 24 days but improved after antibiotic treatment. A total of 6 patients developed cytopenia while receiving immunosuppressive drugs, but the condition improved without significant sequelae after drug discontinuation. No one showed liver enzyme elevation, and there were no cases of life-threatening severe AEs.

Finally, we performed Cox proportional regression analysis to identify the risk factors for disease flare during RRT in patients with LN ESRD (Table 5). Nonrenal SLEDAI score at the time of RRT initiation (HR 1.24, 95% CI 1.12-1.36; $P = 0.001$) was significantly associated with the development of SLE flare, whereas the dialysis modality did show a significant association. The cumulative amount of CS during the 1 year prior to dialysis initiation (HR 1.04, 95% CI 0.995-1.09; $P = 0.09$) also increased the risk of flare, albeit without statistical significance.

DISCUSSION

In the present study, we analyzed the data of 121 patients with LN ESRD treated at tertiary referral hospitals and found that as many as 26.4% of patients (n = 32) experienced an SLE flare during RRT, which commonly had hematologic and constitutional manifestations. Approximately one-third of the patients required additional immunosuppressive drugs to manage the SLE flare, but significant medication-related AEs were not observed. In the analysis for risk related to the SLE flare, nonrenal SLE activity before RRT initiation was a significant factor in developing a SLE flare under RRT.

It has been reported that while the prevalence of SLE disease flares decreases over time with dialysis, if a disease flare occurs, it tends to occur within 1 year of starting dialysis.[21,22] When we compared the nonrenal SLEDAI values 1 year before and after dialysis, we found a significant decrease in the values regardless of dialysis modality. Most patients maintained a quiescent state,

Table 4. Clinical characteristics and treatment details of patients who experienced SLE flares while on renal replacement therapy.

Patient/ Sex/ Age, yrs	Dialysis Modality	Duration of RRT, months	Disease Manifestations	Dose of IS Therapy, mg/d	Initial CS Dose[a], mg/d	Complications
1/F/36	HD	27	C (Libman-Sacks vegetation), N (cognitive dysfunction)	CYC (750)	56.3	NA
2/F/37	HD	25	G (enteritis)	NA	67.5	NA
3/F/45	HD	4	Co (myalgia)	NA	60	NA
4/F/53	HD	53	Co (fever), P (pleural effusion)	NA	50	Pneumonia, cytopenia
5/M/52	HD	73	P (pleural effusion)	NA	20	NA
6/F/65	HD	102	G (enteritis), H (thrombocytopenia, anemia, leukopenia, aplastic anemia)	CSA (300)	75	Cytopenia
7/F/48	HD	23	G (enteritis)	NA	62.5	NA
8/F/41	HD	182	N (cerebrovascular disease)	RTX (500)	312.5	NA
9/F/48	HD	5	H (hemolytic anemia)	NA	75	NA
10/F/31	HD	19	G (enteritis), N (seizure)	NA	625	NA
11/F/46	HD	3	Co (fever), H (thrombocytopenia)	NA	75	NA
12/M/33	HD	27	Co (myalgia, fever, general weakness), H (anemia, leukopenia, thrombocytopenia)	RTX (500)	125	NA
13/F/25	HD	36	P (diffuse alveolar hemorrhage)	NA	1250	NA
14/F/28	HD	35	C (pericardial effusion), Co (fever), M (arthritis)	NA	30	NA
15/F/23	HD	2	H (TTP)	TAC (6)	312.5	NA
16/M/36	HD	8	Co (fever, general weakness), S (malar rash)	MMF (1000)	30	Cytopenia
17/F/29	HD	11	Co (fever), N (seizure), S (malar rash)	NA	1581	NA
18/F/35	HD	18	H (catastrophic APS)	NA	625	NA
19/F/49	HD	58	Co (fever), S (Raynaud phenomenon)	RTX (500)	312	NA
20/M/30	HD	13	Co (fever), H (anemia, leukopenia, thrombocytopenia)	CSA (150)	18	Cytopenia
21/F/36	HD	12	G (enteritis), N (headache)	NA	26	NA
22/F/49	HD	16	P (pleural effusion)	NA	20	NA
23/M/37	HD	39	Co (fever), H (thrombocytopenia, anemia)	NA	312.5	NA
24/F/55	HD	11	H (leukopenia, thrombocytopenia)	NA	125	NA
25/F/21	HD	3	H (thrombocytopenia), P (pleural effusion)	CSA (250), MMF (1440)	36	NA
26/F/28	PD	12	Co (fever, general weakness), N (headache), S (malar rash)	NA	15	NA
27/F/47	PD	6	N (headache)	NA	50	NA
28/F/38	PD	38	H (thrombocytopenia), N (seizure)	NA	1250	Cytopenia
29/F/60	PD	8	Co (fever), H (leukopenia, thrombocytopenia)	NA	40	NA
30/F/37	PD	99	H (thrombocytopenia, leukopenia)	TAC (5)	60	NA
31/F/55	PD	10	N (seizure)	NA	75	NA
32/F/46	PD	5	Co (myalgia), H (leukopenia), M (arthritis)	IVIG	20	Cytopenia

[a] CS dose is represented as prednisone equivalent. APS: antiphospholipid syndrome; C: cardiac; Co: constitutional; CS: corticosteroid; CSA: cyclosporine A; CYC: cyclophosphamide; G: gastrointestinal; H: hematologic; HD: hemodialysis; IS: immunosuppressive; IVIG: intravenous immunoglobulin; M: musculoskeletal; MMF: mycophenolate mofetil; N: neurologic; NA: not applicable; P: pulmonary; PD: peritoneal dialysis; RTX: rituximab; RRT: renal replacement therapy; S: skin; SLE: systemic lupus erythematosus; TAC: tacrolimus; TTP: thrombotic thrombocytopenic purpura.

Table 5. Multivariable analysis of factors associated with SLE flare under dialysis.

	HR	95% CI	*P*
Nonrenal SLEDAI at the initiation of dialysis	1.24	1.12-1.36	0.001
Hematologic manifestation prior to dialysis	1.26	0.69-2.83	0.15
Cumulative amount of steroid during 1 yr prior to the initiation of dialysis	1.04	0.995-1.09	0.09
Dialysis modality: HD	0.77	0.26-2.24	0.63

HD: hemodialysis; HR: hazard ratio; SLE: systemic lupus erythematosus; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index.

but 32 (26.4%) patients showed a disease flare at a median of 17 (IQR 8.0-36.0) months after the initiation of dialysis, which is equivalent to 0.04 episodes/patient-year of prevalence and similar to the results from previous studies.[11] In a study conducted in South Korea, patients receiving HD showed a disease flare rate of 29% (9/28).[12] In addition, a systematic review found that the disease flare rate varied from 10% to 80%, depending on the study.[12,22] Although it is generally accepted that dialysis

can reduce SLE disease activity by removing immune complexes, dialysis cannot completely prevent disease flares.[23] Therefore, even after starting dialysis, regular follow-up of disease activity in patients with SLE is necessary.

A previous study reported that the incidence of SLE flare is strongly related to nonrenal SLEDAI and hematologic manifestation before the initiation of RRT.[10] Our present findings support this idea, as nonrenal SLEDAI at the time of dialysis initiation had a significant HR (1.24, 95% CI 1.12-1.36; $P = 0.001$) for the risk of a future SLE flare under ESRD. Hematologic manifestation before dialysis increased the risk of disease flare during dialysis, although the value was not statistically significant. However, cytopenia such as thrombocytopenia and anemia can be observed as one of the features related to the ESRD condition itself. Thus, it is important to recognize that hematologic manifestations should be differentiated from other causes under RRT. In our analysis, we attempted to determine the SLE flare more precisely by defining it as a case only when clinical features were improved after the initiation of CS or after increases in the dose thereof.

Considering that the risk of infection caused by immunosuppressive treatment is relatively higher in patients receiving dialysis,[24] there is a tendency to avoid using immunosuppressants other than CS in patients on dialysis. Despite being the most important agent in treating SLE, HCQ was not routinely prescribed in patients with ESRD, considering the potential risks of toxicity.[25] In addition, the pharmacokinetics of immunosuppressants such as CYC and MMF are difficult to predict, and the accumulation of metabolites can cause severe myelotoxicity.[26-29] In the present study, we found that all patients with a disease flare had received CS-based treatment regardless of dialysis modality, and 11 (34.3%) patients needed additional immunosuppressants to control disease flare. The most common complication (n = 6) was cytopenia when using immunosuppressive agents, but this improved after the causative drug was withdrawn.[30] Further, none of the patients who received immunosuppressants experienced severe AEs that led to irreversible morbidity or mortality. As there have not been many studies on the treatment of flares in patients receiving dialysis, our current findings provide valuable information in treating patients experiencing SLE flare on dialysis.

The choice of dialysis modality in patients with SLE is one of the most important clinical considerations. It has been reported that compared to patients undergoing PD as a result of other renal diseases, patients with LN are more susceptible to developing peritonitis while on PD.[31-32] In our study, the prevalence of PD-associated peritonitis was particularly high at 44%; such a high rate of peritonitis in patients with SLE may be related to the consecutive use of steroids before the initiation of dialysis, which are not administered to patients with other types of chronic kidney disease.[32] When we compared the risk of SLE flare between HD and PD, there was no significant difference between the 2 groups, and the modality of dialysis was not significantly associated with the risk of SLE flare. Intriguingly, when we compared the difference in the use of CS before and after dialysis, we found that the cumulative CS dose significantly increased after dialysis in the HD group. In addition, a previous study has shown a higher risk of vascular access thrombosis in patients with SLE with aPLs.[33] It was noted that 10 patients had AVF obstruction and that 7 of them were aPL-positive. Further studies are needed to determine the risk of thrombosis formation in AVF in the presence of aPLs and the effect of anticoagulants in these patients.

There are some limitations to our study. First, we retrospectively collected the patients' data, which can cause selection bias. Second, an SLE flare was difficult to distinguish from various other situations such as infection, insufficient dialysis, and ESRD itself. To overcome this limitation, we studied the SLE flare after the exclusion of other causes that may mimic a disease flare, and defined it as a symptom that improved after an increase in CS. Additionally, the differences according to the different time periods should be considered since the data of our patients were derived from a relatively long time period. Finally, our findings may have limited generalizability because of the small number of patients.

In the present study, while the SLE disease activity of patients with ESRD decreased after dialysis initiation, disease flare occurred in approximately one-quarter of the patients during RRT. Hematologic abnormalities were the most commonly observed manifestations, and all of the patients with a flare had received CS as treatment, of whom one-third needed additional immunosuppressants. Nonrenal SLE activity before RRT was an essential factor in the risk of SLE flare after RRT. Collectively, our results indicate that careful follow-up is required to detect SLE flare even after RRT initiation, particularly in patients who had high nonrenal SLE activity prior to dialysis.

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