Reactive Hemophagocytic Syndrome in Adult Korean Patients with Systemic Lupus Erythematosus: A Case-Control Study and Literature Review

JI-MIN KIM, SEUNG-KI KWOK, JI HYEON JU, HO-YOUN KIM, and SUNG-HWAN PARK

ABSTRACT. ***Objective.*** To determine the characteristics of hemophagocytic syndrome (HPS) in adult Korean patients with systemic lupus erythematosus (SLE).

Methods. We reviewed the medical records of 1033 adult patients with SLE for a recent 14-year period and identified 15 patients who had developed HPS. Forty-two age- and sex-matched patients with SLE admitted for other manifestations were included as disease controls. Features of HPS in these patients were analyzed.

Results. Reactive HPS occurred from some distinct causes during the course of SLE. HPS was associated with SLE in 11 patients (4 at onset of SLE and 7 at SLE flare), infection in 3 patients (2 bacterial infection; 1 viral infection), and drug use (azathioprine) in 1 patient. Common clinical features included fever (93.3%), hepatomegaly (60.0%), and splenomegaly (60.0%). Steroid pulse therapy (46.7%), immunosuppressants (46.7%), and intravenous immunoglobulin (46.7%) were frequently used for treatment of HPS. One patient (6.7%) died. Compared with SLE patients without HPS, those with HPS showed a higher SLEDAI score ($p = 0.003$) and lower levels of plasma leukocytes ($p < 0.001$), hemoglobin ($p = 0.013$), and platelets ($p < 0.001$) as well as a higher serum C-reactive protein level ($p = 0.039$) and a lower serum albumin level ($p = 0.004$).

Conclusion. HPS was observed in 1.5% of adult Korean patients with SLE. The occurrence of HPS was most frequently associated with the SLE disease activity. Profound pancytopenia, a high SLEDAI score, and notable changes in the level of acute-phase reactants can be the characteristics of SLE patients with HPS. (First Release Dec 15 2011; J Rheumatol 2012;39:86–93; doi:10.3899/jrheum.110639)

Key Indexing Terms:
HEMOPHAGOCYTIC SYNDROME
ADULT
TRIGGER FACTOR
SYSTEMIC LUPUS ERYTHEMATOSUS

Hemophagocytic syndrome (HPS) is a rare but potentially life-threatening disorder. The term refers to the characteristic pathologic findings of activated histiocytes engulfing erythrocytes, leukocytes, platelets, and their precursors in bone marrow and other reticuloendothelial systems[1]. Common clinical features of HPS include fever, cytopenia, hepatosplenomegaly, abnormal liver function tests, coagulopathy with hypofibrinogenemia, hyperferritinemia, and high blood triglyceride levels[2]. HPS is divided into primary and secondary HPS[3,4]. The primary (hereditary) form, also called familial hemophagocytic lymphohistiocytosis, is observed mostly in infants and is often caused by genetic mutations such as perforin gene mutations[5]. Secondary (reactive) HPS occurs at all ages and is associated with various clinical conditions including infections, malignancies, autoimmune diseases, and administration of certain drugs[1,4,6,7,8,9,10]. In addition, other miscellaneous conditions have been reported as the cause of reactive HPS[11,12,13,14].

Among the systemic autoimmune diseases, systemic lupus erythematosus (SLE) is most frequently described as the underlying disease for HPS[15,16,17]. Some studies have reported the prevalence of HPS in SLE to be 0.9%–2.4%[15,18]. In the setting of SLE, reactive HPS can be associated either with an active infection, which is often a complication of an immunosuppressive treatment, or with immune dysregulation induced by the disease itself[19]. Although understanding the factors that suggest the presence of HPS may allow an earlier diagnosis and more prompt management, there is a lack of overall information about HPS in patients with SLE.

We reviewed demographic data, laboratory and clinical features, treatments, and outcomes of SLE patients with HPS. We also analyzed the characteristics that might distinguish SLE patients with HPS from those without HPS.

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Accepted for publication September 15, 2011.

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MATERIALS AND METHODS

Cases and controls. We retrospectively reviewed the medical records of 1033 adult Korean patients with SLE who were treated at the rheumatology department of Seoul St. Mary's Hospital between January 1997 and June 2010. All patients satisfied the 1982 revised criteria for the classification of SLE[20]. Among them, we found 15 patients with HPS. The diagnosis of HPS was made in cases of otherwise unexplained cytopenia that affected at least 2 cell lines and abnormally activated hemophagocytic histiocytes identified in bone marrow, liver, spleen, or lymph node biopsies[7,10]. Forty-two patients with SLE matched for age and sex were included as disease controls. They were randomly chosen among patients with SLE who were admitted for other manifestations at the same time that SLE patients with HPS were admitted.

Methods. All medical records of these patients were reviewed and the following conditions were evaluated: demographic data such as age, sex, disease duration, potential trigger factors for HPS onset, various clinical features and laboratory findings, treatment modalities for HPS management, and outcomes. Disseminated intravascular coagulation (DIC) was defined as a DIC score ≥ 5 according to the scoring system of the International Society on Thrombosis and Hemostasis[21]. Terms for steroid doses came from the recommendations for the standardized nomenclature for glucocorticoid dosages and glucocorticoid treatment regimens as published in 2002[22]: (1) pulse therapy ≥ 250 mg prednisone equivalent a day for 1 or a few days; (2) high dose (> 30 mg), but ≤ 100 mg prednisone equivalent a day; and (3) medium dose > 7.5 mg, but ≤ 30 mg prednisone equivalent a day. SLE disease activity was evaluated using the SLE Disease Activity Index (SLEDAI) score[23].

Statistical analysis. Comparisons of descriptive data between groups were performed by Student t test or Mann-Whitney U test. Categorical data were compared using the chi-square or Fisher's exact test. A p value < 0.05 was considered statistically significant.

Systematic review. We completed our study with a systematic review of the published cases of HPS that occurred in the course of SLE. We searched the Medline database using the terms "hemophagocytic syndrome," "hemophagocytic lymphohistiocytosis," "hemophagocytosis," or "macrophage activation syndrome," combined with "lupus," between 2006 and 2010. The search was limited to well described adult cases. A manual search of all the references in the articles supplemented this screening.

RESULTS

Demographic and clinical features of HPS. Fifteen (1.5%) out of 1033 patients with SLE recruited for our study were diagnosed with HPS. The demographic and clinical data of 15 patients with HPS in the course of SLE are presented in Table 1. Age at the time of HPS diagnosis ranged from 17 to 50 years (mean 28.9 ± 9.9 yrs). The patients with HPS included 13 women and 2 men. The mean duration of SLE was 69.9 ± 88.9 months (range 0–270 mo). All of the patients were hospitalized for > 9 days because of HPS (mean duration of hospitalization 36.7 ± 30.3 days). It took an average of 15.8 ± 15.2 days to get pathological confirmation from the first day of admission.

All patients except 1 presented fever at the time of admission. The afebrile patient was admitted to our hospital only with general weakness. Hepatomegaly was observed in 9 patients (60%) and splenomegaly in 9 patients (60%); the 2 conditions did not necessarily occur in the same patient. Six patients showed the enlargement of superficial lymph nodes. Neuropsychiatric symptoms such as depressive mood, psychosis, and seizure were noted in 3 patients (20%). Most patients were diagnosed as having HPS from bone marrow analysis. Only 1 patient revealed excessive hemophagocytosis in spleen and liver and not in bone marrow.

Table 1 also shows the SLE manifestations that each patient had ever had before the onset of HPS. Among our 15 patients, 7 had lupus nephritis and 4 had neuropsychiatric lupus. Six patients, on the other hand, had only mild symptoms such as cutaneous or articular manifestations of SLE.

Trigger factors for HPS onset. Possible trigger factors for HPS are described in Table 1. SLE-associated HPS occurred in 11 of our 15 patients (73.3%). Among 11 patients with SLE-associated HPS, HPS and SLE were diagnosed simultaneously in 4 patients. The other 7 patients experienced a flare of SLE just before or almost simultaneously with the development of HPS. Among those 7 patients, 1 (Patient 5) had stopped taking drugs for more than 3 months because of poor compliance. No medication change was associated with Patient 7, but the patient was known to be under stress due to job and family problems before the SLE flare. Patient 8 was in the 12th week of pregnancy without any changes to her medication for at least 6 months. We could not determine any medication change or environmental changes in the other patients before the SLE flare. No evidence of infection was found in these 11 patients with SLE-associated HPS. Active infection triggered HPS in 3 patients (20%). Bacterial infection was identified in 2 patients. *Bacillus* species was isolated in both urine and blood in 1 patient. Another patient, who was under antibiotic therapy in a local clinic for 1 month before admission to our hospital, had a urinary tract infection caused by extended-spectrum ß-lactamase-producing *Escherichia coli*. Viral infection was diagnosed in Patient 14, who had a positive result for IgM antibody to Epstein-Barr viral capsid antigen. A specific drug (azathioprine) was suspected as a possible trigger factor in Patient 11, who developed HPS on the fifth day of readministration after transient discontinuation of the drug owing to mild symptoms of upper respiratory tract infection.

Laboratory characteristics of HPS. Table 2 shows the laboratory findings of 15 patients with HPS. Leukopenia or anemia were found in 13 patients (86.7%). Yet all patients showed thrombocytopenia ranging from 16,000 to 121,000/mm^3. An elevated erythrocyte sedimentation rate (ESR) was observed in 12 patients (80%) and the level of C-reactive protein (CRP) was elevated in all but 1 patient. The transaminase levels were high in 14 patients (93.3%). All patients presented with hypoalbuminemia, hyper-lactate dehydrogenase (LDH)-nemia and hyperferritinemia. DIC was diagnosed in 6 patients (54.5%) out of the 11 whose data were available. Anti-dsDNA antibodies were present in 10 patients (66.7%).

Treatment and outcome of HPS. The treatments and outcomes of 15 patients with SLE and HPS are illustrated in Table 3. Steroid therapy was given to all patients for the treatment of HPS although the dosage or the type of steroid differed. Doses of steroids equivalent to > 30 mg/day of prednisone were administered to 12 patients, including 7 who received methyl-

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Table 1. Demographic and clinical characteristics of 15 patients with HPS and SLE.

Patient	Age, Sex	SLE Duration, mo	Time from Admission to Pathologic Confirmation, days	Days in Hospital	Fever	Hepato-megaly	Spleno-megaly	Lymph-adenopathy	Neuro-psychiatric Symptom	Site of Pathologic Confirmation	Trigger Factor	Cumulative SLE Manifestations
1	48, F	244	14	17	+	+	–	NA	–	Bone marrow	Infection	Malar rash, arthritis, nephritis, CNS lupus (seizure), cytopenias, anti-dsDNA Ab, ANA
2	27, F	125	8	30	+	+	+	NA	–	Bone marrow	SLE flare	Malar rash, photosensitivity, arthritis, nephritis, cytopenias, anti-dsDNA Ab, aPL, ANA
3	23, F	0	6	24	+	+	+	NA	–	Bone marrow	SLE onset	Arthritis, cytopenias, anti-dsDNA Ab, ANA
4	18, F	0	2	16	+	+	+	+	–	Bone marrow	SLE onset	Malar rash, oral ulcer, serositis (pleuritis), nephritis, CNS lupus (psychosis), cytopenias, anti-dsDNA Ab, aPL, ANA
5	31, M	7	12	25	+	–	–	+	Depression	Bone marrow	SLE flare	Discoid rash, photosensitivity, anti-dsDNA Ab, aPL, ANA
6	31, F	0	8	10	+	–	–	+	NA	Bone marrow	SLE onset	Malar rash, serositis (pleuritis, pericarditis), cytopenias, ANA
7	24, F	24	9	41	+	–	+	–	Psychosis, seizure	Bone marrow	SLE flare	Malar rash, oral ulcer, arthritis, serositis (pleuritis), nephritis, CNS lupus (psychosis, seizure), cytopenias, anti-dsDNA Ab, ANA
8	29, F	118	43	53	+	+	+	–	–	Spleen, liver	SLE flare	Malar rash, discoid rash, photosensitivity, oral ulcer, arthritis, cytopenias, anti-dsDNA Ab, aPL, ANA
9	17, F	16	5	118	+	+	+	+	Seizure	Bone marrow	SLE flare	Malar rash, CNS lupus (psychosis), cytopenias, anti-dsDNA Ab, aPL, ANA
10	37, F	51	25	32	–	+	–	–	–	Bone marrow	SLE flare	Malar rash, discoid rash, photosensitivity, nephritis, cytopenias, anti-dsDNA Ab, anti-Smith Ab, ANA
11	23, M	97	54	65	+	–	+	–	–	Bone marrow	Drug	Nephritis, cytopenias, anti-dsDNA Ab, aPL, ANA
12	25, F	1	28	78	+	+	+	–	–	Bone marrow	SLE flare	Malar rash, discoid rash, photosensitivity, arthritis, cytopenias, anti-dsDNA Ab, ANA
13	19, F	0	4	11	+	+	+	+	–	Bone marrow	SLE onset	Photosensitivity, cytopenias, anti-dsDNA Ab, anti-Smith Ab, ANA
14	31, F	96	9	14	+	–	–	+	–	Bone marrow	Infection	Arthritis, nephritis, cytopenias, anti-dsDNA Ab, anti-Smith Ab, ANA
15	50, F	270	10	17	+	–	–	–	–	Bone marrow	Infection	Malar rash, discoid rash, photosensitivity, oral ulcer, anti-dsDNA Ab, ANA

HPS: hemophagocytic syndrome; SLE: systemic lupus erythematosus; NA: not available; CNS: central nervous system; anti-dsDNA Ab: anti-double-stranded DNA antibody; ANA: antinuclear antibody; aPL: antiphospholipid antibody.

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Table 2. Laboratory data at the time of HPS.

Patient	Leukocyte /mm^3, n: 4000–10000	ANC /mm^3, n: 2000–7500	Hg, g/dl, n: 12–16	Platelet /mm^3, n: 150000–450000	ESR, mm/h, n: 0–20	CRP, mg/dl, n: 0.1–0.47	AST, U/l, n: 14–40	ALT, U/l, n: 9–45	Albumin, g/dl, n: 3.5–5.2	LDH, U/l, n: 200–400	TG, mg/dl, n: 40–200	Ferritin, µg/l, n: 10–140	Fibrinogen, mg/dl, n: 160–350	D-dimer, µg/ml, n < 1.3	FDP, µg/ml, n < 5	C3, mg/dl, n: 90–180	C4, mg/dl, n: 10–40	Anti-dsDNA Ab*, IU/ml, n < 7
1	4020	3095.4	6.4	47000	30	16.15	435	150	2.6	2383	44	1210	211	2.81	7.04	49.8	9.09	NA
2	2710	1447.1	8.1	16000	42	12.3	66	31	3.2	1076	142	3030	345	36	84.57	116	20.6	6.1
3	1660	280.5	8.7	77000	26	11.24	110	121	3.2	751	NA	1060	643	NA	91.82	108	26.6	10.84
4	1530	639.5	9.1	95000	11	0.82	126	134	3	829	640	NA	NA	NA	NA	33.5	6.75	126.1
5	1650	770.6	14.2	72000	19	1.73	232	676	3.29	2538	270	4890	143	6.63	17.08	57.8	10	NA
6	6310	3823.9	7.4	44000	16	5.98	152	116	2.77	2130	424	4520	230	3.23	5.5	88.3	23.4	0.76
7	940	19.7	6.8	81000	24	8.01	686	824	2.2	3751	112	16500	500	17	80	35	8	791.23
8	1340	750.4	6.9	29000	53	14.43	112	187	2.5	1861	92	2890	125	15.38	54.52	71.4	17.2	5.86
9	2550	1428.0	8.6	50000	60	41.9	824	565	3	2558	308	1770	187	2.51	40	55	5.5	NA
10	1000	250.0	9.5	129000	23	2.23	633	219	2.3	3236	223	2254	289	16.88	47.14	20.7	5.13	29.68
11	1150	0.0	15.4	121000	29	0.35	12	16	2.6	565	264	517	448	2.5	3.67	48.9	8.54	5.64
12	1000	300.0	6.7	55000	29	9.06	124	39	2.7	1934	222	6750	178	NA	46	13.8	7.4	NA
13	1010	429.3	9.2	80000	24	0.89	73	46	3.3	1561	175	1100	317	17	5.31	15	4.2	25.8
14	1060	629.6	10.2	99000	55	1.08	165	161	2.7	1578	NA	1620	NA	NA	NA	29	9.5	26.62
15	1270	549.9	10	43000	51	8.38	216	164	2.9	1454	175	9400	209	11.39	42.45	146	15.1	3.09

* The titer was measured using Farr assay. HPS: hemophagocytic syndrome; n: normal; ANC: absolute neutrophil count; Hg: hemoglobin; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; AST: aspartate aminotransferase; ALT: alanine aminotransferase; LDH: lactate dehydrogenase; TG: triglyceride; FDP: fibrinogen degradation product; anti-dsDNA antibody: anti-double-stranded DNA antibody; NA: not available.

Table 3. Treatment and outcome of 15 patients with HPS and SLE.

Patient	Treatment	ICU	MV Therapy	Outcome
1	High-dose MP + IVIG	+	+	Died
2	MP pulse + CSA + IVIG	–	–	Survived
3	Medium-dose PD + IVIG	–	–	Survived
4	MP pulse + CPP pulse + AZA + plasmapheresis	–	–	Survived
5	MP pulse	–	–	Survived
6	Medium-dose PD	–	–	Survived
7	High-dose DX + CSA + IVIG	+	–	Survived
8	High-dose DX + CSA + IVIG + splenectomy	+	–	Survived
9	MP pulse + CSA + IVIG	+	+	Survived
10	High-dose MP	–	–	Survived
11	AZA stop + MP pulse	–	–	Survived
12	MP pulse + CPP pulse + IVIG	–	–	Survived
13	MP pulse	–	–	Survived
14	High-dose DX	–	–	Survived
15	Medium-dose PD + CSA	–	–	Survived

HPS: hemophagocytic syndrome; SLE: systemic lupus erythematosus; ICU: intensive care unit; MV: mechanical ventilator; MP: methylprednisolone; IVIG: intravenous immunoglobulin; CSA: cyclosporine A; PD: prednisolone; CPP: cyclophosphamide; AZA: azathioprine; DX: dexamethasone.

prednisolone pulse therapy. The other 3 patients (Patients 3, 6, and 15) received medium-dose steroid therapy (15 mg/day prednisolone). In addition to steroid therapy, immunosuppressants were added for 7 patients (46.7%); cyclosporine A in 5 (Patients 2, 7, 8, 9, and 15), intravenous cyclophosphamide in 2 (Patients 4 and 12), and azathioprine in 1 (Patient 4). On the other hand, Patient 11, who was diagnosed as having drug-induced HPS, recovered after he stopped taking the causative immunosuppressive drug (azathioprine). Intravenous immunoglobulin (IVIG) was used in 7 patients (46.7%). Splenectomy was performed in Patient 8, who was resistant to medical therapy. Plasmapheresis was used in 1 patient (Patient 4) in combination with other medical treatments, including steroid and immunosuppressive drugs. We had confidence that Patient 6 had no evidence of infection at the time of admission and she was the only patient who did not receive antibiotic therapy.

Four patients needed the intensive care unit because of

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their respiratory or hemodynamic problems. Two patients (Patients 1 and 9) required mechanical ventilation. Fourteen patients recovered from HPS, but 1 died of diffuse pulmonary alveolar hemorrhage.

Comparison of the SLE patients with and without HPS. The results comparing SLE patients with HPS and those without HPS are described in Table 4. Both groups had a statistically similar distribution of age and sex. There was also no significant difference in the duration of SLE between the groups. The SLEDAI scores were higher in SLE patients with HPS ($p = 0.003$). There were also significant differences in the severity of leukopenia, anemia, and thrombocytopenia between the groups ($p < 0.001$, $p = 0.013$, and $p < 0.001$, respectively). The level of CRP and LDH was higher in the HPS group ($p = 0.039$ and $p < 0.001$), although the level of ESR was comparable between the groups. Hypoalbuminemia was more prominent in the HPS group ($p = 0.004$). The complement level showed no difference between the groups.

DISCUSSION

Reactive HPS has rarely been described in connection with SLE. A few previous studies reported the prevalence and characteristics of HPS in the course of several overall systemic diseases[7,17]. HPS occurring in patients with SLE has most often been reported in the form of case reports. As shown in Table 5, our Medline search identified 42 adult HPS cases with SLE from 2006 to 2010[11,17,18,24,25,26,27,28,29,30,31,32,33,34,35]. Those 42 patients consisted of 13 whites and 29 Asians. The demographic and clinical features of the literature cases did not differ from our cases, except for the frequency of using steroid pulse therapy (Table 6). There were 33 female and 9 male patients. The average age of the patients was 34.2 ± 14.4 years. Thirty-six patients (85.7%) had developed HPS associated only with SLE. Both SLE and infection (cytomegalovirus) caused the HPS at the same time in 1 patient (2.4%). Active infection was suggested as a sole trigger factor in 4 patients (9.5%; influenza B virus, cytomegalovirus, parvovirus B19, and *Enterococcus faecalis* in 1 patient each). Pregnancy was associated with the development of HPS in 1 patient (2.4%). All 42 patients in the literature and our 15 cases received steroid treatments, although steroid pulse therapy was used more frequently in the literature cases than in ours ($p = 0.045$). The frequency of using immunosuppressive agents did not differ between the groups ($p = 0.358$). Cyclosporine A was administered most frequently to the patients in both groups (5 patients among our 15 cases, 9 patients among the 42 literature cases). The second most common drug treatment was intravenous cyclophosphamide (2 patients among our 15, 6 patients among the 42 literature cases). IVIG was used as often as immunosuppressive drugs for the treatment of HPS in both groups. The overall mortality did not differ between the 2 groups.

Diagnosis of reactive HPS remains difficult in adult patients, although Henter, *et al* published revised diagnostic guidelines for hemophagocytic lymphohistiocytosis in 2004[36]. Some studies asserted that reactive HPS in adults is distinct from HPS in children and that we should be prudent in adopting guidelines for adult patients[37]. Tsuda described a different frequency of hepatosplenomegaly, rash, and neurologic involvement, which were all more common in children[38]. Hypertriglyceridemia has been described as rare in adults[39]. Accordingly, we adopted definitions that could be accepted universally in the study of reactive HPS with autoimmune diseases in adult patients[17,40]. But more intensive and extensive studies of adults with HPS will be needed in order to create differentiated HPS guidelines for adults.

One afebrile patient (Patient 10) may seem to be a distinctive case. We raised that patient's dosage of prednisolone from

Table 4. Characteristics of SLE patients with and without HPS. Values are mean ± SD.

Characteristics	SLE with HPS, N = 15	SLE without HPS, N = 42	p*
Age, yrs	28.9 ± 9.9	29.1 ± 10.8	0.949
Women:men	13:2	36:6	1.000
SLE duration, yrs	5.9 ± 7.5	4.7 ± 3.9	0.571
SLEDAI	14.5 ± 8.4	8.3 ± 5.9	0.003
Leukocyte/mm^3, n: 4000-10000	1946.7 ± 1477.4	6228.8 ± 2711.8	< 0.001
Hemoglobin, g/dl, n: 12-16	9.2 ± 2.6	11.0 ± 2.2	0.013
Platelet/mm^3, n: 150,000-450,000)	692,000.0 ± 32,698.2	190,452.4 ± 85,464.9	< 0.001
ESR, mm/h, n: 0-20	32.8 ± 15.4	33.6 ± 27.0	0.910
CRP, mg/dl, n: 0.1–0.47	9.0 ± 10.6	2.5 ± 5.7	0.039
Albumin, g/dl, n: 3.5-5.2	2.8 ± 0.3	3.3 ± 0.5	0.004
LDH, U/l, n: 200-400	1880.3 ± 913.4	625.3 ± 678.5	< 0.001
C3, mg/dl, n: 90-180	59.2 ± 39.6	62.5 ± 25.0	0.771
C4, mg/dl, n: 10-40	11.8 ± 7.1	12.3 ± 7.6	0.837

* SLE patients with HPS versus SLE patients without HPS. SLE: systemic lupus erythematosus; HPS: hemophagocytic syndrome; n: normal; SLEDAI: SLE Disease Activity Index; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; LDH: lactate dehydrogenase.

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Table 5. Previous reports of adult SLE patients with HPS.

Report	No. Reported Cases	Sex (No.)	Race	Trigger Factor	Outcome
Botelho[24]	1	F	White	SLE onset	Survived
Horai[25]	1	M	Asian	Infection (influenza B virus)	Survived
Kamiya[26]	1	F	Asian	SLE onset	Survived
Taki[27]	1	M	Asian	SLE onset	Survived
Carvalheiras[28]	1	F	White	SLE onset	Survived
Tabata[29]	2	M (2)	Asian	SLE* (2)	Survived (1), died (1)
Takahashi[30]	1	F	Asian	SLE onset	Survived
Kwon[31]	1	M	Asian	SLE onset + infection (CMV)	Survived
Fukaya[17]	18	F (15), M (3)	Asian	SLE (16), infection [2; CMV (1), *E. faecalis* (1)]	Survived (16), died (2)
Pérard[11]	1	F	White	Pregnancy	Survived
Qian[32]	2	F (2)	Asian	SLE onset (2)	Survived (2)
Sakai[33]	1	F	Asian	Infection (parvovirus B19)	Survived
Hagiwara[34]	1	F	Asian	SLE onset	Survived
Lambotte[18]	9	F (8), M (1)	White	SLE onset (8), SLE flare (1)	Survived (9)
Romanou[35]	1	F	White	SLE flare	Survived

* Trigger factor described as "SLE" when specific mention about onset or flare did not exist in the literature. SLE: systemic lupus erythematosus; HPS: hemophagocytic syndrome; CMV: cytomegalovirus.

Table 6. Comparison between 15 cases in our study and 42 other cases in the literature.

Characteristics	Our Study	Literature Cases	p
Women:men	13:2	33:9	0.709
Age, yrs	28.9 ± 9.9	34.2 ± 14.4	0.189
SLE-associated HPS	11/15	37*/42	0.223
Infection-associated HPS	3/15	5†/42	0.422
Use of steroids	15/15	42/42	1.000
Steroid pulse therapy	7/15	33/42	0.045
Use of immunosuppressive agents	8/15	15/42	0.358
Use of IVIG	7/15	9/42	0.113
Died	1/15	3/42	1.000

* These 37 include patients with HPS whose triggering factors were both SLE and infection as well as only SLE. † Five include patients with HPS whose triggering factors were both SLE and infection as well as only infection. SLE: systemic lupus erythematosus; HPS: hemophagocytic syndrome; IVIG: intravenous immunoglobulin.

25 mg/day to 40 mg/day when we noted mild leukopenia, thrombocytopenia, and abnormal levels of liver enzymes, under the assumption that she was experiencing an SLE flare. During the hospitalization, her body temperature was 37.8°C. Her fever might have been partially masked by a prompt dose of steroids. But profound cytopenia, high ferritin and triglyceride levels, hepatomegaly, and remarkable hemophagocytosis in the bone marrow were clinically sufficient to diagnose HPS and treat the patient with high-dose steroids despite the absence of high fever. This case made us reconsider the development of HPS, although fever is not prominent in steroid-treated patients with other features of HPS.

A notable finding in our study was that the onset or flare of SLE frequently caused the HPS. Adult-onset Still's disease is the only other known disease that could be caused by the underlying disease itself[7,40]. In patients with other systemic diseases, infection was almost always present with occurrence of HPS[7]. This finding suggests that treatment decisions for HPS patients with SLE should differ from decisions made for patients with other systemic diseases.

Our data showed that SLEDAI scores of patients with HPS were higher than those of patients without HPS. The constituents of the SLEDAI score include leukopenia and thrombocytopenia, both of which can be manifestations of HPS. So we subtracted the scores of leukopenia and thrombocytopenia from the SLEDAI scores of patients with HPS and then compared the scores with those of patients without HPS. The corrected SLEDAI scores of SLE patients with HPS were significantly higher than the scores of those without HPS ($p = 0.031$). These findings suggest that a high SLEDAI score may be important when making assumptions about the development of HPS in patients with SLE.

The hematologic involvement of SLE can cause cytopenia, a condition that may lead clinicians to hesitate before evaluating a patient for HPS. That is also why the time from admission to HPS diagnosis varied from 2 to 54 days in our series. But it has been reported that only 1 or 2 cell lines are usually affected, and the patients have only mild pancytopenia[15]. Our results support the previous reports; clinicians should have doubts about the development of HPS in an SLE patient with longstanding, profound pancytopenia. One of the interesting findings is that all our patients with HPS had thrombocytopenia to a greater or lesser degree. It seems that thrombocytopenia is a more prominent feature of HPS in patients with SLE than leukopenia or anemia. We need further investigations and reviews of more cases to confirm this.

Slightly exaggerated hemophagocytosis can be a physio-

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logic process that might occur in conditions including hemolytic and aplastic anemia, graft versus host disease, and after transfusions and cytotoxic treatments[37]. Despite various limitations, morphological evidence of hemophagocytosis is still considered the "gold standard" in the diagnosis of HPS[37]. Pathologic evidence of hemophagocytosis is usually obtained with bone marrow specimens[41]. Most of our patients' diagnoses were confirmed with bone marrow studies, with 1 exception. That patient (Patient 8) had no abnormal findings in bone marrow biopsy, and hemophagocytosis was confirmed later through splenectomy. A negative bone marrow biopsy cannot always rule out HPS. In addition, histological hemophagocytosis is not always a pathognomonic finding in the diagnosis of HPS unless patients have no symptoms or signs of HPS.

HPS results from uncontrolled T lymphocyte activation that leads to macrophage activation and an increment of some cytokines. In the liver, increased inflammatory cytokines such as tumor necrosis factor-α[42], interleukin 1 (IL-1)[42], IL-6[43], IL-18[44], and interferon-γ[45] enhance the synthesis of acute-phase proteins, but they reduce the synthesis of albumin in the patients with HPS[46,47]. In our series, hypoalbuminemia and hyper-CRP-nemia were more remarkable in SLE patients with HPS than in those without HPS. Both albumin and CRP belong to the acute-phase reactants, a class of proteins whose plasma concentrations decrease or increase in response to inflammation[48]. Our study indicated that on average, HPS causes a more potent inflammatory condition than does infection and SLE flare, because the control group (SLE patients without HPS) included SLE patients who had undergone various infections and/or a flare of SLE including cutaneous vasculitis, mesenteric vasculitis, or thrombotic thrombocytopenic purpura. But this may be because our SLE patients with HPS almost always had combined conditions such as HPS with infection or HPS with an SLE flare.

It is common to administer antibiotics to febrile patients with SLE. This is because fever caused by disease activity can be diagnosed only after exclusion of infection by a thorough evaluation, although both infection and SLE disease activity have been reported to be the most common causes of fever in patients with SLE[49,50]. Similarly, it is difficult and time-consuming to identify the causative factors for HPS that mainly consist of SLE and infection. That situation may lead to the prescription of antibiotics for most of these patients and a delay in increasing the dosages of steroids or in adding the proper immunosuppressive agents.

HPS was observed in 1.5% of our adult Korean patients with SLE. The development of HPS was most frequently associated with SLE disease activity. Profound pancytopenia and a high SLEDAI score as well as remarkable changes of the level of acute-phase reactants were the characteristics of HPS patients with SLE. For prompt and appropriate therapy, physicians should be aware of the symptoms of HPS and understand the distinctions in laboratory and clinical findings between a flare of SLE and the occurrence of HPS.

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