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メタデータ	<p>言語: English</p> <p>出版者: The Fukushima Society of Medical Science</p> <p>公開日: 2015-07-06</p> <p>キーワード (Ja):</p> <p>キーワード (En): Systemic lupus erythematosus, Hemophagocytic syndrome, Autoimmune-associated hemophagocytic syndrome, Primary manifestation</p> <p>作成者: Ono, Atsushi, Kawasaki, Yukihiro, Kanno, Syuto, Ohara, Shinichiro, Sakai, Nobuko, Suyama, Kazuhide, Hosoya, Mitsuaki</p> <p>メールアドレス:</p> <p>所属:</p>
URL	<p>https://fmu.repo.nii.ac.jp/records/2001877</p>

[Case Report]

A CASE OF A CHILD WITH SLE PRESENTING WITH HPS AS A PRIMARY MANIFESTATION

ATSUSHI ONO, YUKIHIKO KAWASAKI, SYUTO KANNO, SHINICHIRO OHARA,
NOBUKO SAKAI, KAZUHIDE SUYAMA and MITSUAKI HOSOYA

Department of Pediatrics, Fukushima Medical University School of Medicine

(Received December 17, 2013, accepted October 22, 2014)

Abstract : The primary manifestations of systemic lupus erythematosus (SLE) are various. One such manifestation is hemophagocytic syndrome (HPS). We here report a child with SLE presenting with HPS as a primary manifestation. In October 2010, an 11-year-old Japanese boy presented with pancytopenia, elevated liver enzymes, hyperferritinemia and hemophagocytosis due to macrophages in the bone marrow, and was diagnosed with HPS. A year later, he was found to have proteinuria and hematuria. Oral aphtha and Raynaud's phenomenon were observed, and the patient showed low serum complement levels and was positive for anti-nuclear antibodies (ANAs). He was subsequently diagnosed with SLE. Moreover, low serum complement levels and ANA positivity were detected in a serum sample preserved at the onset of HPS. The HPS was considered to be a primary manifestation of SLE on the basis of these findings. Based on this case, the presence of an underlying disease, such as SLE, should be investigated in cases of HPS.

Key words : Systemic lupus erythematosus, Hemophagocytic syndrome, Autoimmune-associated hemophagocytic syndrome, Primary manifestation

INTRODUCTION

Systemic lupus erythematosus (SLE) is a multi-systemic disease characterized by widespread inflammatory involvement of the connective tissues. For this reason, many clinical manifestations have been found, with various primary manifestations including musculoskeletal, cutaneous, constitutional, neurologic, and renal involvement as well as lymphadenopathy and Raynaud's phenomenon. One primary manifestation is hemophagocytic syndrome (HPS). HPS is characterized by increased proliferation and activation of benign macrophages with hemophagocytosis. It usually manifests as fever, pancytopenia, hepatosplenomegaly, elevated liver enzymes, and hyperferritinemia. The prevalence of HPS in SLE has been reported to be 0.9-2.4%¹⁾. However, there have been only a few reports on SLE with HPS as a primary manifestation in the literature to date. Moreover, there have been no reports of SLE presenting with HPS only as a primary

manifestation in children. Herein, we describe a case of a child who presented with HPS only as a primary manifestation of SLE.

CASE REPORT

An 11-year-old Japanese boy with eyelid edema and prolonged fever was admitted to hospital in October 2010. Laboratory findings revealed pancytopenia (white blood cell count $1.5 \times 10^3/\mu\text{l}$, red blood cell count $4.16 \times 10^6/\mu\text{l}$, platelet count $92 \times 10^3/\mu\text{l}$) and elevated liver enzymes (aspartate aminotransferase 99 IU/l, alanine aminotransferase 69 IU/l). The result of dermatological and neurological examinations were unremarkable. Multiple cultures of blood, urine and sputum were negative for bacteria. There was no serological evidence of recent infection with Epstein-Barr virus or cytomegalovirus. Bone marrow aspiration was performed and revealed hemophagocytosis due to the presence of macrophages (Fig. 1). Hyperferritinemia (1,146.1 ng/ml)

Corresponding author : Atsushi Ono E-mail : a-ono@fmu.ac.jp
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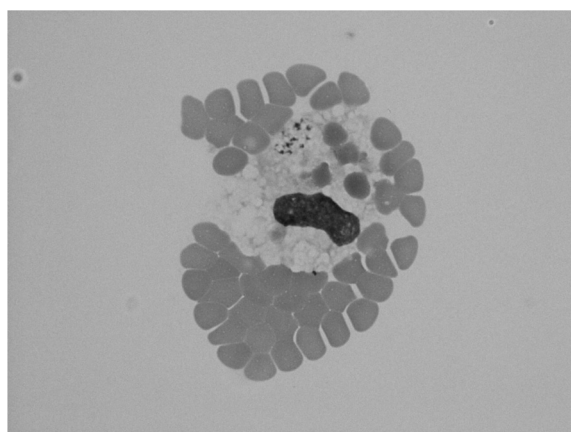


Fig. 1. Hemophagocytic cells in the bone marrow at the onset of SLE. (May-Giemsa stain, $\times 400$) Bone marrow smear shows macrophages phagocytosing red blood cells.

was, however, present and the patient was, therefore, diagnosed with HPS. The course of HPS was unclear at that time, but his fever was reduced a few days later and laboratory findings improved without treatment. He was, therefore, discharged without further examination on the ninth hospital day.

In June 2011, proteinuria and hematuria were detected during a routine school urinary screening program. The boy visited a hospital and received a follow-up examination from a doctor, but urinalysis showed no improvement and immunological findings revealed him to be positive for anti-nuclear antibodies (ANAs) ($\times 160$, speckled pattern) as well as the presence of low serum complement levels (C3 18 mg/dl, CH50 13 U/ml). He fulfilled the criteria for the diagnosis of SLE in children and was sent to our

hospital for treatment in October 2011. On admission, his body temperature was 36.9°C and blood pressure was 126/70 mmHg. Oral aphtha and Raynaud's phenomenon were observed. Pulmonary, cardiac and neurological examinations showed no abnormalities. The results of laboratory examinations at admission are shown in Table 2: white blood cell count $4.7 \times 10^3/\mu\text{l}$, red blood cell count $3.81 \times 10^6/\mu\text{l}$, platelet count $18.6 \times 10^4/\mu\text{l}$, total protein 7.1 g/dl, albumin 4.4 mg/dl, γ -globulin 1.5 g/dl, serum creatine 0.52 mg/dl and C-reactive protein 0.03 mg/dl. Coagulation test revealed a prothrombin time 85.2% of normal, activated partial thromboplastin time 30.2 seconds, fibrinogen 242 mg/dl, D-dimer 0.6 $\mu\text{g}/\text{ml}$, antithrombin III 91% and plasmin inhibitor complex 1.7 $\mu\text{g}/\text{ml}$. Urine examination revealed protein excretion of 0.35g/day, β_2 -microglobulin 0.18 $\mu\text{g}/\text{ml}$, N-acetyl glucosaminidase 6.9 U/l, sediments contained 10–19 erythrocyte, 5–9 leukocytes and granular casts per high-power field. Twenty-four hour creatine clearance was 133.2 ml/min/ 1.73 m^2 . Immunological examination revealed C3 14 mg/dl, C4 12 mg/dl, CH50 8 U/ml, ANA 320 titer, anti-DNA antibody 1.5 IU/ml, anti-S antibody $<0.5 \text{ IU/l}$, anti-SSA antibody 14.0 U/ml, anti-SSB antibody $<0.5 \text{ U/ml}$, anti-U1RNP antibody 39.0 U/ml, anti-Scl70 antibody $<0.5 \text{ U/ml}$, and anti-cardiolipin antibody $<10.0 \text{ U/ml}$. Moreover, we examined a serum sample preserved at the onset of HPS (Table 1). Laboratory findings showed low serum complement levels (C3 20 mg/dl, C4 22 mg/dl, CH50 10 U/ml). He was subsequently diagnosed with SLE on basis of the presence of ANAs, low serum complement levels, proteinuria, and oral aphtha.

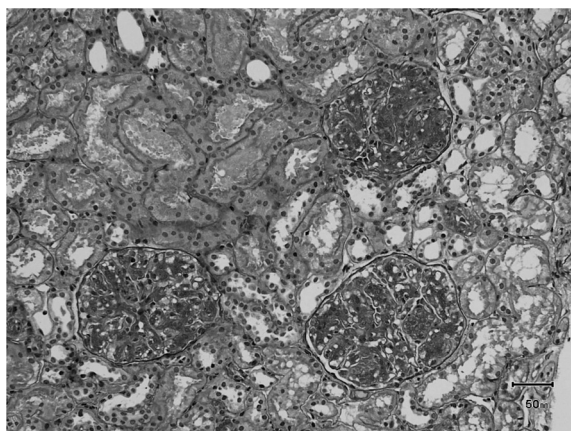
Table 1. The results of laboratory examinations and a serum sample preserved at the onset of HPS

Blood count			Serum chemistry			Immunological data		Urinalysis	
WBC	1,500	$/\mu\text{l}$	TP	6.8	g/dl	HBs-Ag	negative	pH	6.0
RBC	4.16×10^6	$/\mu\text{l}$	Alb	3.3	g/dl	HCV-Ab	negative	SG	1.005
Hb	11.3	g/dl	AST	99	IU/l			U-pro	(–)
Ht	34.7	%	ALT	69	IU/l	EBV-VCA-IgG	10.8	U-bld	(–)
Plt	92×10^3	$/\mu\text{l}$	LDH	779	IU/l	EBV-VCA-IgM	0.1	U-glu	(–)
			ALP	263	IU/l	EBV-EBNA	3.3	U-ket	(–)
Coagulation test			BUN	7.9	mg/dl			RBC	$<1 \text{ /HPF}$
			Cre	0.60	mg/dl	CMV-IgG	7.5	WBC	$<1 \text{ /HPF}$
PT	81	%				CMV-IgM	0.42		
PT-INR	1.19		Na	136	mmol/l				
APTT	36.5	sec	K	3.7	mmol/l				
Fib	377	mg/dl	Cl	103	mmol/l				
			CRP	0.10	mg/dl				
FDP	5.2	$\mu\text{l}/\text{ml}$	FT	1,146.1	ng/ml				

Preserved serum sample		
C3	20	mg/dl
C4	22	mg/dl
CH50	10	CH50/ml
ANA	1 : 320	

Table 2. The results of laboratory examinations at the times of admission to our hospital

Blood count			Serum chemistry			Immunological data			Urinalysis	
WBC	4,700	/ μ l	TP	7.1	g/dl	IgG	1608	mg/dl	pH	6.0
RBC	3.81×10^6	/ μ l	Alb	4.4	g/dl	IgA	231	mg/dl	SG	1.025
Hb	<u>10.9</u>	g/dl	AST	22	IU/l	IgM	125	mg/dl	RBC	<u>10-19</u> /HPF
Ht	32.6	%	ALT	15	IU/l				WBC	5-9 /HPF
Plt	186×10^3	/ μ l	LDH	189	IU/l	C3	<u>14</u>	mg/dl	Cast	granular, hyaline
Coagulation test			ALP	532	IU/l	C4	<u>12</u>	mg/dl		
			CHE	288	IU/l	CH50	<u>8</u>	CH50/ml	Urinary protein	
			GGT	14	IU/l				<u>64</u>	mg/dl
PT	85.2	%	BUN	11	mg/dl	ANA	<u>1 : 320</u>		<u>0.35</u>	g/day
PT-INR	1.05		Cre	0.52	mg/dl	dsDNA-Ab	1.5	IU/ml	U-pro/cre	<u>0.52</u>
APTT	30.2	sec	UA	4.7	mg/dl	Sm-Ab	<0.5	U/ml	B2-MG	0.18 μ g/ml
Fib	242	mg/dl	Na	141	mmol/l	Sc170-Ab	<0.5	U/ml	NAG	6.9 U/l
TT	63	%	K	4.1	mmol/l	U1-RNP-Ab	<u>39.0</u>	U/ml	24hCCr	
DD	0.6	μ g/ml	Cl	105	mmol/l	SSA-Ab	<u>14.0</u>	U/ml	133.2 ml/min/1.73 m ²	
ATIII	91	%	Ca	9.1	mg/dl	SSB-Ab	<0.5	U/ml		
PIC	1.17	μ g/ml	P	4.1	mg/dl	CL-Ab	<10.0	U/ml		
			CRP	0.03	mg/dl					
			TG	54	mg/dl	RF	2	IU/ml		
			TC	141	mg/dl	ASO	238	IU/ml		
			LDL-C	84	mg/dl					
			HDL-C	40	mg/dl					

Fig. 2. ISN/RPS classification IV-G(A). (Periodic acid-Schiff stain, $\times 200$)

We recognized that the HPS was a primary manifestation of SLE. Renal biopsy was performed on the seventh hospital day (Fig. 2). Light microscopy revealed diffuse medial mesangial proliferation in all glomeruli. Electron microscopy also showed the presence of electron-dense deposits in the subendothelial and paramesangial regions. Immunofluorescence staining revealed mesangial deposits of C1q, C3, C4 and fibrinogen. Therefore, we diagnosed lupus nephritis associated with category IV-G(A) (ISN/RPS classification) lesions. The clinical course after admission is shown in Table 3. After

biopsy, a first course of methylprednisolone pulse therapy (1,000 mg/day for 3 days) was initiated, followed by prednisolone (60 mg/day). Urinary protein levels were gradually reduced but no increase in serum complement level was observed. Therefore, a second and third course of methylprednisolone pulse therapy was administered together with mizoribine (150 mg/day). Mizoribine was not effective, and was changed to tacrolimus (2~3 mg/day) about two months after the start of mizoribine administration. The C3 level was slowly elevated and the prednisolone dose was tapered. Finally, although C4 and CH50 levels remained low, his urinary protein levels did not increase again. As of May 2013, the patient was being treated with 5 mg/day of PSL without flare-up, and he demonstrated normal complement and ANA levels.

DISCUSSION

SLE is a chronic autoimmune disease, characterized by multi-systemic involvement, with a broad spectrum of clinical and laboratory manifestations. SLE presents with many primary manifestations, including fever, butterfly rash, arthritis, abnormal urine, and Raynaud's phenomenon. Although HPS has been described as one primary manifestation of SLE, it has been related to SLE flare up or other dis-

Table 3. The clinical course after admission to our hospital. PSL; prednisolone, mPSL; methylprednisolone, MZB; mizoribine, Tac; tacrolimus

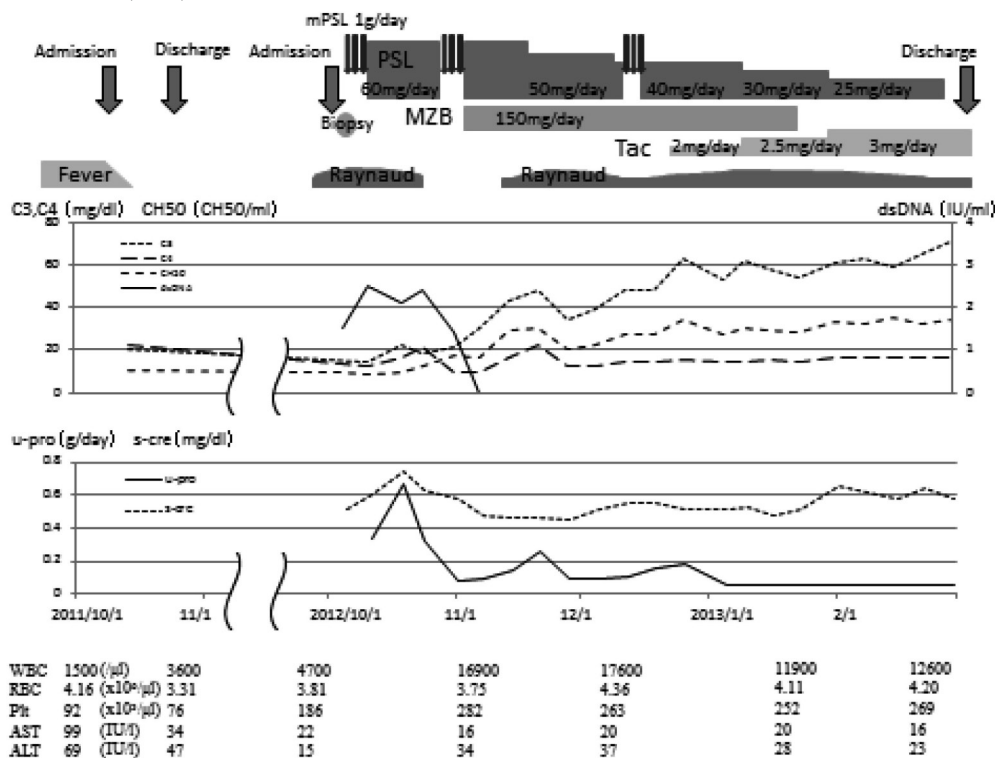


Table 4. Classification of HPS

1. Primary HPS
 - Familial hemophagocytic lymphohistiocytosis (FHL)
2. Secondary or reactive HPS
 - a. Infection associated hemophagocytic syndrome (IAHS)
 - Virus-associated hemophagocytic syndrome (VAHS)
 - Bacteria-associated hemophagocytic syndrome (BAHS)
 - Other : e.g., fungal, malaria, leishmaniasis, histoplasmosis, toxoplasmosis, tsutsugamushi disease
 - b. Malignancy-associated hemophagocytic syndrome (MAHS)
 - Lymphoma-associated hemophagocytic syndrome (LAHS)
 - Other : e.g., multiple myeloma, acute leukemia, mycosis fungoidosis, melanoma, hepatocellular carcinoma
 - c. **Autoimmune-associated hemophagocytic syndrome (AAHS)**
 - d. Other
 - Drug-associated
 - Miscellaneous underlying disease : e.g. Kawasaki disease, Kikuchi's disease, Chediak-Higashi disease

eases, including infections^{2,3)}. Common clinical features of HPS include fever, pancytopenia, hepatosplenomegaly, elevated liver enzymes, and hyperferritinemia. HPS was first described in 1939 by Scott and Robb-Smith, and it is now classified as shown in Table 4. The prevalence of HPS in SLE has been reported to be 0.9-2.4%¹⁾. Among these patients, the proportion with HPS as a primary manifestation has been variously reported to be 25-

100%.

SLE, among the various systemic autoimmune diseases, is most frequently described as the underlying disease for HPS. However, only a few incidents of SLE with HPS have been reported in the literature to date. Moreover, there have been no reports of SLE with HPS as a primary manifestation in children. In a review of literature published between January 2000 and September 2012 through

Table 5. Cases of adults with SLE presenting with HPS as a primary manifestation

Author [Ref]	Number of Patients	Age (Sex : Number)	Treatment	Prognosis (Number)
Lloyd MS [8]	1	61yo (F : 1)	IVIg, CPM	Recovered
Dhote R [9]	6	17~62yo (F : 6)	NA	NA
Mootsikapun P [10]	1	36yo (F : 1)	Steroid	Recovered
Hagiwara K [11]	1	38yo (F : 1)	Steroid, IVIg	Recovered
Qian J [12]	2	25yo and 29yo (F : 2)	Steroid, IVIg, Transfusion	Recovered
Yoshida S [13]	1	33yo (F : 1)	Steroid, Tac	Recovered
Tabata R [14]	2	78yo and 82yo (M : 2)	Steroid	Recovered (1), Died (1)
Taki H [15]	1	21yo (M : 1)	Steroid	Recovered
Carvalheiras G [16]	1	40yo (F : 1)	Steroid	Recovered
Botelho C [17]	1	36yo (F : 1)	Steroid, CPM	Recovered
Kim JM [1]	4	19~31yo (F : 4)	Steroid, CPM, AZA, IVIg, PA	Recovered

M ; Male, F ; Female

Steroid ; PSL or PSL and mPSL, CPM ; cyclophosphamide, Tac ; tacrolimus, PA ; plasmapheresis, NA ; not available

MEDLINE, we detected 21 cases in which patients with SLE presented with HPS as a primary manifestation (Table 5), and all of these patients were adults. Several others cases of SLE with HPS, together with related SLE flare-ups or infection, have been reported. Our patient was diagnosed as having SLE with HPS as a primary manifestation on the basis of low complement levels and a positive ANA titer at the onset of HPS, as well as the presence of proteinuria and oral aphtha.

The precise mechanisms of the development of reactive HPS in SLE patients remain unclear. However, there have been some reports suggesting that not only autoantibodies or immune-complexes but also cytokines might contribute to the development of SLE-associated HPS⁴⁻⁶⁾. Moreover significant correlations between several cytokines and SLE activity has been reported⁷⁾. Based on the above, we suggest that the high cytokine activity induced by SLE might lead to the pathogenesis of HPS.

In SLE-associated HPS, not only fever and pancytopenia but also symptoms suggestive of SLE, such as skin rash, Raynaud phenomenon, pericarditis or polyarthritis, are often present. SLE-associated HPS shows a good response to immunosuppressant therapy, and the outcome of SLE-associated HPS is better than that of the other underlying disorders associated HPS. In our case, fever was present at the onset of HPS, but there were no other significant clinical features such as symptoms suggestive of SLE. Viral culture and cultivation assay were negative, and no abnormal laboratory findings were observed apart from pancytopenia, hyperferritinemia and elevated liver enzymes. Fever and pancytopenia improved without

treatment, and the progress of SLE has been good to date.

In conclusion, we reported a case of a child with SLE presenting with HPS as a primary manifestation. It is necessary to take the underlying disease, including SLE, into consideration when treating both adult and pediatric HPS patients.

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