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CASE REPORT

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A case report: a pediatric patient with acute lupus hemophagocytic syndrome; differences from reactive hemophagocytosis caused by hypercytokinemia

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Abstract We report the youngest known girl with acute lupus hemophagocytic syndrome (ALHS) at the onset of her illness. We investigated the pathogenesis of ALHS by assessment of factors thought to influence the onset, such as cytokines, Th1/Th2 balance, immune complexes, and autoantibodies. A girl 8 years and 10 months old with systemic lupus erythematosus (SLE) had high fever, pancytopenia, and hemophagocytosis in the bone marrow. We diagnosed SLE complicated by ALHS. Treatment with predonisolone (2 mg/kg/day) was started, and her clinical features improved. Th2 dominance of the Th1/Th2 balance, hypocomplementemia, and high levels of anti-ds-DNA antibody, PAIgG, and immune complexes were seen, but no hypercytokinenemia, hyperferritinemia, or hypertriglyceridemia. ALHS at the onset of SLE, excluding that caused by infections, could be a form of reactive hemophagocytosis caused by excessive production of autoantibodies and immune complexes. High-dose steroid therapy is effective without need for immunosuppressive drugs. Our patient showed hypocomplementemia along with high levels of anti-dsDNA antibody, anticardiolipin antibody, platelet-associated IgG (PAIgG), and immune complexes. The autoimmune-associated hemophagocytic syndrome (AAHS) is thought to involve an autoantibody-mediated mechanism or an immune complex-mediated mechanism. On the basis of our data, ALHS could simultaneously involve both these mechanisms. We demonstrated that there was no hypercytokinemia and no hyperferritinemia in ALHS associated with Th2 dominance. Autoantibodies and immune complexes may cause histiocytic hemophagocytosis in ALHS. High-dose steroids and high-dose immunoglobulin are effective but immunosuppressive drugs are not needed.

Key words Acute lupus hemophagocytic syndrome (ALHS) · Hypercytokinemia · Immune complex · Th1/Th2 balance

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Introduction

Pancytopenia and hemophagocytosis in the bone marrow are occasionally found during the course of systemic lupus erythematosus (SLE). Because this hemophagocytic syndrome is not associated with infection, it is called the acute lupus hemophagocytic syndrome (ALHS).[1,2] No previous studies have assessed the pathogenesis of ALHS with respect to the cytokine profile, Th1/Th2 balance, autoantibodies, and immune complex levels. Here we report the profile of these pathogenic factors in the youngest girl with ALHS to be documented in the literature.

Case report

A girl aged 8 years and 10 months suffered from a continuous high fever, 38.5°–39.0°C, for 20 days. Her fever showed no response to any antibiotic. She had not taken any nonsteroidel antiinflammatory medications (NSAIDs). She gradually developed weight loss and fatigue and was admitted to our hospital for further examination. There was no family history of rheumatic disease. She also had no past history of severe infections or immune deficiency. She had no butterfly rash, photosensitivity, cervical lymphadenopathy, arthritis, edema, or hepatomegaly. On admission, there was slight splenomegaly and small ecchymoses and petechiae on the chest and buttocks. She showed pancytopenia, hematuria, proteinuria, and telescoped urine sediment (Table 1). Pleurisy was revealed by a chest X-ray film. There was no evidence of a coronary aneurysm or pericardial effusion on echocardiography. Because antinuclear antibody was strongly positive and hypocomplementemia was present, we made a diagnosis of SLE according to ACR

(1997) criteria (positive antinuclear antibody, positive anti-dsDNA antibody, pancytopenia, pleurisy, and proteinuria).

We carried out bone marrow aspiration on hospital day 2 to rule out malignant disease because of her severe thrombocytopenia. Histiocytes accounted for 2.8% of all bone marrow cells, and active hemophagocytosis of erythroblasts and platelets was seen (Fig. 1). The nucleated cell count was 7–10 $\times$ 10^4/μl, the megakaryocyte count was within normal limits (but there was a decrease in the production of platelets), and the M/E ratio was 70.8/6.4 with maturation arrest of the myeloid series. We started the patient on oral prednisolone at a dose of 60 mg/day (2 mg/kg) on hospital day 4. After 4 weeks, the hematological and urine findings became normal and the patient's general condition also improved. We could not perform renal biopsy because permission was refused by the parents.

Table 1. Laboratory findings on admission: hematological, biochemical, and immunological tests

WBC/μl	1400
RBC/10^4/μl	3.23
Hb, g/dl	9.2
Platelets, 10^4/μl	1.8
PT, s	12.8
PT%	66
INR	1.31
APTT, s	57.1
Fibrinogen, mg/dl	191
FDP, μg/ml	14.6
D-D dimer μlg/ml	3.6
GOT (AST), IU/l	64
GPT (ALT), IU/l	50
LDH, IU/l	293
CK, IU/l	35
CRP, mg/dl	0.06
IgG, mg/dl	1910
IgA, mg/dl	225
IgM, mg/dl	168
C_3, mg/dl	21
C_4, mg/dl	3
CH_{50}, U/ml	13
T-Cho, mg/dl	150
HDL-Cho, mg/dl	24
LDL-Cho, mg/dl	318
Triglyceride, mg/dl	120
Ferritin, ng/ml	200
ANA (FANA), dils	640
Anti ds-DNA (ELISA), IU/ml	400
Anti ss-DNA (ELISA), IU/ml	800
Anti RNP (ELISA), Index	11.4
ESR, mm/h	31
anti-CL IgG (ELISA), U/ml	60.9
anti-CL β_2GPI (ELISA), U/ml	3.9
anti-Sm (ELISA), Index	0.2
U-NAG, U/l	6.6
U-β_2 MG	531
U-Prot, g/day	2.03
U-RBC/HPF	100
U-hyaline casts/LPF	10
U-red cell casts/LPF	10
U-white cell casts/LPF	10

PAIgG, platelet-associated immunoglobulin G; WBC, white blood cell count; RBC, red blood cell count; PT, prothrombin time; APTT, activated partial thromboplastin time; CRP, C-reactive protein; BUN, blood urea nitrogen

References values: anti-dsDNA (ELISA) IU/ml; <12.0; anti-ssDNA (ELISA) IU/ml, <25.0; anti-RNP (ELISA) Index, <15.0; anti-CL IgG (ELISA) U/ml, <10.0; anti-CL β_2 GPI (ELISA) U/ml, <3.5; anti-Sm (ELISA) Index, <15.0; U-NAG U/l, <7.0; U-β_2MG, <250

The hematological, biochemical, and rheumatological findings on admission are summarized in Table 1. The white cell count was 1400/μl and the platelet count was 1.8 $\times$ 10^4/μl. There was no hypertriglyceridemia or hyperferritinemia. Antinuclear antibody (Hep-2 cell; FANA) was 640 dils and anti-dsDNA antibody was 400 IU. The levels of interferon (INF)-γ, tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-4, Il-6, and IL-8 were normal or slightly elevated. The neopterin level was high and immune complexes (C1q and anti-C3d antibody) were extremely high. Platelet-associated IgG (PAIgG) was also positive (Table 2). The Coombs test and anti-leukocyte antibodies were not examined. Th2 dominance was seen in the acute phase, but Th1 dominance was seen during the recovery phase on assessment of the Th1/Th2 balance (Table 3).

The patient was negative for EB virus DNA and parvovirus B19 by the polymerase chain reaction (PCR). Serum antibody tests for cytomegalovirus IgM (EIA, <0.8) ×0.6, IgG (EIA, <2.0) ×226 suggested no evidence of recent infection. Serum antibody tests for EB virus anti-VCA IgM (EIA, <1.0) ×0.8, anti-VCA IgG (EIA, <1.0) ×8.4, EBNA IgG (EIA, <1.0) ×14.6, and EA-DR IgG

Table 2. Inflammatory and immunological markers

Marker	Value	Reference value
INF-γ (EIA)	0.2 IU/ml	<0.1 IU/ml
TNF-α (EIA)	ND	<5 pg/ml
IL-1β (EIA)	17 pg/ml	<10 pg/ml
IL-4 (EIA)	17.2 pg/ml	<6.0 pg/ml
IL-6 (EIA)	6.1 pg/ml	<4.0 pg/ml
IL-8 (EIA)	13.7 pg/ml	<20.0 pg/ml
IC (C_1q)	30.4 μg/ml	<3.0 μg/ml
IC (anti C_3d antibody)	20.6 μg/ml	<13 μg/ml
PAIgG	142.4 ng/10^7 cells	9.0–25.0 ng/10^7 cells
neopterin	43 pmol/ml	2.0–8.0 pmol/ml
2–5 AS	57 pmol/dl	<100 pmol/dl
PMN elastase	370 μg/l	16–54 μg/l

ND, not detected; IC, immune complex; 2–5 AS, 2′–5′ oligoadenylate synthetase; PMN elastase, polymorphonuclear elastase

Table 3. Th1/Th2 balance

	Th1/Th2 (CD4) ratio (%)	Th1: IFNγ+/IL-4- (%)	TH2: INFγ−/IL-4+ (%)	Th0: INFγ+/IL-4+ (%)	Th0: INFγ−/IL-4- (%)
Th1/Th2 (CD4) (active phase)	4.70	11.80	2.50	2.00	83.70
Th1/Th2 (CD4) (recovery phase)	11.60	11.60	1.60	0.30	87.10

(EIA, <1.0) ×3.8 revealed a postinfection pattern. The procalcitonin level was 0.5(<0.3) ng/ml.

Discussion

Acute lupus hemophagocytic syndrome (ALHS) presents with pancytopenia and hemophagocytosis during the active phase of SLE.[1] The differential diagnosis includes bacteria-associated hemophagocytic syndrome (BAHS), virus-associated hemophagocytic syndrome (VAHS), macrophage activation syndrome (MAS), and autoimmune-associated hemophagocytic syndrome (AAHS). These disorders are recognized to be reactive hemophagocytic syndromes, and ALHS shares many similarities with the features of AAHS. The disorders underlying AAHS include mixed connective tissue disease, scleroderma, and other autoimmune diseases. AAHS is treated with immunosuppressants and steroids[3] whereas steroids and high-dose gamma globulin are more effective for ALHS.[2] Both AAHS and ALHS patients have autoantibodies to autologous blood cells, and both hemophagocytic syndromes are associated with normal to slightly elevated serum ferritin levels. ALHS occurs in the active period of SLE or at the time of relapse.

Infection should be excluded before making a diagnosis of ALHS. MAS occurs in patients with the systemic-onset type of juvenile rheumatoid arthritis (JRA). Infection or NSAID may act as a trigger to induce hypercytokinemia (including TNF-α) during the course of systemic-onset JRA, but autoantibodies and immune complexes are not involved in MAS. Cyclosporin A and steroids are effective for MAS, in which the activation of macrophages is understood to be caused by hypercytokinemia resulting from T-cell dysfunction. Wong et al. first reported six patients with ALHS among 250 with SLE.[1] One of these six ALHS patients was a 12-year-old girl. Reactive hemophagocytic syndrome in SLE can be caused by SLE itself or can be secondary to infection in patients with or without immunosuppressive therapy. Primary ALHS at the onset of SLE before the start of therapy has only been reported in three patients, including our case (see Table 3). Two patients had nephrotic syndrome, and one patient died. Two of three patients showed severe hypocomplementemia. Our patient is the youngest to be reported in the literature, and this case has provided some useful data on the mechanism of ALHS.

Bacterial culture and serum procalciton were negative.[4] Cytomegalovirus (IgM), EB virus (PCR), and parvovirus B19 (PCR) were all negative, and our patient was not on immunosuppressive therapy. Therefore, this case fits the strict definition of ALHS. Our patient showed Th2 dominance in the active phase and Th1 dominance in the recovery phase when the Th1/Th2 balance was investigated. Th1 dominance is seen in patients with hypercytokinemia (INF-γ and IL-12) that causes BAHS, VAHS, and MAS.[5] However, the levels of INF-γ, TNF-α, and IL-β (which are related to BAHS, VAHS, and MAS) were not significantly elevated in our patient. Neopterin was increased as a result

Table 4. Profile of three untreated patients with ALHS at the onset of SLE

	Sex, Age	WBC/μl	RBC $\times 10^4$/μl	Hb, g/l	Platelets $\times 10^4$/μl	ANA	dsDNA	C_3, mg/dl	C_4, mg/l	CH_{50}	Therapy	Outcome
Wong et al.[1]	Female, 12 years	1800	ND	9	6.4	1280, homogeneous and speckled	Positive	25	5	ND	High-dose steroid therapy (1–2 mg/kg) and methylprednisolone pulse therapy	Alive
Papo et al.[2]	Female, 20 years	6000	ND	7	1.3	ND	ND	150	ND	ND	High-dose steroid, IVIG, and cyclophosphamide	Dead
Our case	Female, 8 years 10 months	1400	323	9.2	1.3	640 dils	400 IU	21	3	13	High-dose steroid therapy (2 mg/kg)	Alive

ANA, antinuclear antibody; dsDNA, anti-double-stranded DNA antibody; C_3, complement component 3 (normal range, 60–130 mg/dl); C_4, complement component 4 (normal range, 14–19 mg/dl); ND, not described

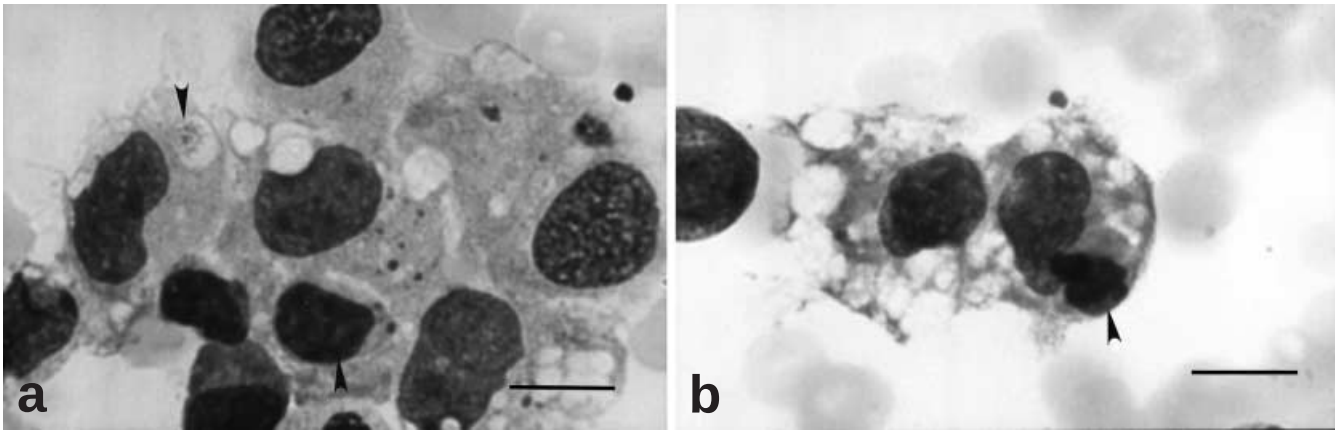

Fig. 1. Smear of the bone marrow aspirate smear with Wright-Giemsa stain, showing stimulated histiocytes phagocytosing platelets (**a**) and erythroblasts (**a**,**b**). *Bar* 10 μm

of the overproduction of macrophages and monocytes to remove autoantibody-bound blood cells and immune complexes. Because ALHS differs from other types of hemophagocytosis such as BAHS, VAHS, and MAS, which are caused by hypercytokinemia resulting from T-cell dysfunction, high-dose steroids with or without high-dose gammaglobulin therapy is a more reasonable regimen for ALHS than cyclosporine A or etopside because suppression of the production of autoantibodies and immune complexes is more important.

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