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Clinical Characteristics and Treatment Outcomes of Autoimmune-Associated Hemophagocytic Syndrome in Adults

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Objective. **To better define the clinical characteristics and treatment outcomes of autoimmune-associated hemophagocytic syndrome (AAHS) in adults.**

Methods. **Adults with AAHS (defined as pathologic evidence of hemophagocytosis without any obvious cause other than an autoimmune disease) were identified through a review of the literature.**

Results. **Among 116 patients identified, underlying diseases included systemic lupus erythematosus (SLE) in 52.3%, adult-onset Still's disease (AOSD) in 26.7%, and dermatomyositis in 6.9%. Fever, lymphadenopathy, hepatomegaly, and splenomegaly were found in 86.8%, 41.0%, 41.8%, and 45.5% of patients, respectively. Cytopenia, liver dysfunction, and hyperferritinemia developed frequently, and coagulopathy was seen in 50.6% of patients. Normal or low C-reactive protein levels were characteristic of patients with underlying SLE. The most commonly used therapy was corticosteroids, which were initially administered in 95.7% of patients, with 57.7% responding. Patients with corticosteroid-refractory disease were usually treated with cyclosporine, intravenous cyclophosphamide (IV CYC), or intravenous immunoglobulin (IVIG), with IV CYC being highly effective. Treatment with biologic agents resulted in favorable effects in the majority of patients. The mortality rate was 12.9%. Male sex (odds ratio [OR] 6.47, 95% confidence interval [95% CI] 2.06–30.39, $P < 0.01$), dermatomyositis (OR 5.57, 95% CI 1.08–28.65, $P < 0.05$), and anemia (hemoglobin <8 gm/dl; OR 3.74, 95% CI 1.02–13.8, $P < 0.05$) were identified as factors associated with mortality.**

Conclusion. **AAHS is potentially fatal. Corticosteroids are a mainstay of initial treatment. For corticosteroid-refractory disease, IV CYC may be beneficial as compared with cyclosporine or IVIG. Treatment that proceeds directly from corticosteroids to biologic agents is promising.**

Hemophagocytic syndrome, or hemophagocytic lymphohistiocytosis (HLH), is a severe and life-threatening disease, characterized by activation of histiocytes with prominent hemophagocytosis throughout the reticuloendothelial system. Most of the diverse manifestations of HLH, including fever, hepatosplenomegaly, pancytopenia, coagulopathy, and liver dysfunction, are driven by a dysregulated immune response.

Hemophagocytic syndrome can be classified according to underlying etiology into either primary (genetic) or secondary (acquired) hemophagocytic syndrome (1,2). Several genetic diseases predispose patients to hemophagocytic syndrome, including familial HLH (FHLH), immunodeficiency syndromes with albinism (Griscelli syndrome type 2, Chédiak-Higashi syndrome, and Hermansky-Pudlak syndrome type 2), and various primary immunodeficiency syndromes (e.g., X-linked lymphoproliferative disease, X-linked hypogammaglobulinemia, and X-linked severe combined immunodeficiency) (1,2). In these genetic diseases, gene mutations leading to hemophagocytic syndrome were identified, involving mutations in PRF1 (FHLH type 2),

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UNC13D (FHLH type 3), STX11 (FHLH type 4), STXBP (FHLH type 5), RAB27A (Griscelli syndrome type 2), LYST (Chédiak-Higashi syndrome), and AP3B1 (Hermansky-Pudlak syndrome type 2) (3–9). These genes are related to proteins that play important roles in perforin-mediated cytolysis of cytotoxic T lymphocytes (CTLs) and natural killer (NK) cells to target cells (1). An inability of CTLs and NK cells to kill infected cells after an infection like Epstein-Barr virus results in uncontrolled activation and proliferation of CTLs and NK cells with aberrant production of inflammatory cytokines, subsequently leading to the onset of hemophagocytic syndrome.

Secondary hemophagocytic syndrome occurs in association with infectious agents, malignant diseases, and autoimmune diseases. Thirty years ago, Hadchouel et al described a severe complication of juvenile rheumatoid arthritis that was induced by macrophage activation secondary to treatment or intercurrent infection (10). This complication was referred to as macrophage activation syndrome (MAS) (11). On the other hand, Wong et al reported reactive hemophagocytosis in the bone marrow of patients with active systemic lupus erythematosus (SLE) (12), with no evidence of an underlying infection or any other causes of hemophagocytic syndrome except for the active SLE. As a result, the occurrence of hemophagocytosis was associated with the activity of SLE itself, and therefore Wong et al proposed the disease entity known as acute lupus hemophagocytic syndrome. In 1995 and 1997, adult cases of hemophagocytosis that developed in association with underlying autoimmune diseases other than SLE were reported (13,14). Since then, various autoimmune diseases have been reported to underlie reactive hemophagocytic syndrome (15–17).

Thus, reactive hemophagocytic syndrome occurring in patients with autoimmune diseases can be separated into hemophagocytic syndrome associated with an active infection, often a complication of immunosuppressive therapy, and hemophagocytic syndrome specifically associated with a flare or activity of an underlying autoimmune disease (17,18). Accordingly, autoimmune-associated hemophagocytic syndrome (AAHS) can be defined as hemophagocytic syndrome occurring specifically in association with a flare or activity of underlying autoimmune disease. A recent study from Japan suggested that the incidence of AAHS is ~10% among all cases of hemophagocytic syndrome (19).

The number of case reports on AAHS is increasing; however, clinical manifestations, treatment efficacy, and outcomes in adults with this syndrome are not well understood. In this study, we extensively investigated the underlying diseases, clinical characteristics, effective treatments, and outcomes of AAHS in adults, through a review of the medical literature.

PATIENTS AND METHODS

Search strategy and criteria for case selection. A systematic literature review was performed using the National Library of Medicine PubMed database. The following medical subject headings were combined for the search: hemophagocytic syndrome, hemophagocytosis, hemophagocytic histiocytosis, or macrophage activation syndrome, and/or the subheadings autoimmune disease, collagen disease, SLE, rheumatoid arthritis, adult-onset Still's disease (AOSD), dermatomyositis, mixed connective tissue disease, or Sjögren's syndrome. We searched for articles included in the PubMed database up until March 2013.

All articles published in English were considered eligible. Articles were subsequently reviewed and were included if the following criteria were met: 1) treatments and outcomes of each case were described clearly, 2) the pathologic examination had been completed, and histiocytic hemophagocytosis in bone marrow or other reticuloendothelial systems (e.g., lymph node) was evident, 3) hemophagocytosis occurred during an active phase or at the onset of an underlying autoimmune disease, 4) patients showed no evidence of any other known underlying cause of reactive hemophagocytic syndrome, such as infections or malignancies, and 5) patients were ≥16 years old at onset of the autoimmune disease and at occurrence of hemophagocytosis. Cases were excluded if the autoimmune diseases occurred before the age of 16 years and persisted into adulthood.

Since validated diagnostic criteria for secondary hemophagocytic syndrome are currently not available, only patients with histologically proven hemophagocytosis were included in this study. SLE was defined according to the 1997 revised criteria for the classification of SLE (20) or the 1982 revised criteria (21). The diagnosis of other autoimmune diseases was made based upon international criteria (22–31).

Data analysis. We collected data regarding underlying disease, age, sex, physical and laboratory findings, treatments, and outcomes (alive or deceased) of each case. Physical findings consisted of the presence or absence of fever, lymphadenopathy, hepatomegaly, and splenomegaly. Laboratory findings, including peripheral blood cell counts, clotting profile (prothrombin time, activated partial thromboplastin time, international normalized ratio, fibrinogen, fibrinogen degradation products, and/or D-dimer levels), serum liver enzyme levels (aspartate aminotransferase [AST], alanine aminotransferase [ALT], and lactate dehydrogenase [LDH]), C-reactive protein (CRP) levels, and serum ferritin levels, were analyzed. Coagulopathy was defined as the presence of hypofibrinogenemia (fibrinogen levels below the lower limit of normal), elevated levels of fibrinogen degradation products, or prolonged prothrombin time or activated partial thromboplastin time. Initial treatment, as well as further therapies if the disease was refractory to initial treatment, was analyzed.

Response to treatment was defined as improvement in the clinical and laboratory features present at the onset of hemophagocytosis (e.g., fever, cytopenia, and hyperferritinemia). If treatment was described as effective, we considered the patient as having responded to treatment.

Statistical analysis. Univariate and multivariate analyses of clinical and laboratory data were performed to identify prognostic variables. Statistical analysis was performed using SPSS software, version 18 (IBM). Data are presented as the mean ± SD unless otherwise specified. Univariate analysis was performed to compare patient mortality using Student's unpaired *t*-test or chi-square test, as appropriate. Multivariate logistic regression analysis was then performed using the forced entry method. Age, sex, and all comparisons of clinical variables with a *P* value of less than 0.05 by univariate analysis were entered into the model. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated. *P* values less than 0.05 were considered significant.

RESULTS

Underlying diseases and clinical characteristics. A search of the literature yielded 56 reports (Supplementary Table 1, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.38672/abstract), and a total of 116 cases were considered relevant for the review. Among these cases, underlying diseases included SLE (52.3%), AOSD (26.7%), dermatomyositis (6.9%), rheumatoid arthritis (4.3%), Evans' syndrome (3.4%), sarcoidosis (1.7%), systemic sclerosis (0.9%), mixed connective tissue disease (0.9%), vasculitis syndrome (0.9%), Sjögren's syndrome (0.9%), and ankylosing spondylitis (0.9%).

This study included 28 men and 88 women (male:female ratio 1:3) (Table 1). The mean ± SD age was 41.6 ± 18.7 years. Fever, lymphadenopathy, hepatomegaly, and splenomegaly were found in 86.8%, 41.0%, 41.8%, and 45.5% of patients, respectively. Mean ± SD white blood cell (WBC) counts, hemoglobin (Hgb) levels, and platelet counts in peripheral blood are shown in Table 1. Leukocytopenia (WBC count $<4 \times 10^9$/liter), anemia (Hgb <11.5 gm/dl), and thrombocytopenia (platelet count $<100 \times 10^9$/liter) were found in 78.3%, 88.3%, and 65.2% of patients, respectively. Coagulopathy was present in 50.6% of patients. Mean serum levels of AST, ALT, and LDH were elevated. The mean ± SD CRP level was 7.7 ± 10.2 mg/dl, and the ferritin level was 15,334.1 ± 35,181 μg/liter. The median ferritin level was 2,949 μg/liter. Twenty-two percent of patients had normal or low levels of serum ferritin (<500 μg/liter).

Differences in clinical characteristics between patients with underlying SLE and patients with AOSD. Age, sex, and physical and laboratory findings were compared between patients with underlying SLE and patients with underlying AOSD (Table 1). Patients with underlying SLE were significantly younger than those

Table 1. Clinical characteristics of the adults with AAHS*

	Total (n = 116)†	Underlying SLE (n = 61)	Underlying AOSD (n = 31)	*P*‡
Age, mean ± SD (range) years	41.6 ± 18.7 (16–86)	34.4 ± 14.2	43.4 ± 17.4	0.014
Male:female ratio	1:3	1:4.1	1:4.2	
Physical findings				
Fever, no./total no. (%)§	99/114 (86.8)	56/60 (93.3)	30/31 (96.8)	NS
Lymphadenopathy, no./total no. (%)	32/78 (41)	16/40 (40)	13/24 (54.2)	NS
Hepatomegaly, no./total no. (%)	28/67 (41.8)	12/29 (41.3)	10/20 (50)	NS
Splenomegaly, no./total no. (%)	40/88 (45.5)	15/43 (34.9)	16/25 (64)	NS
Laboratory findings				
WBC count, mean ± SD (range) $\times 10^9$/liter	4.1 ± 6.08 (0.1–41.1)	2.2 ± 1.2	6.8 ± 6.6	0.002
Hgb, mean ± SD (range) gm/dl	8.9 ± 2 (4.8–14.1)	8.7 ± 1.8	9.6 ± 1.9	NS
Platelet count, mean ± SD (range) $\times 10^9$/liter	98.1 ± 96.8 (2–560)	81.9 ± 52.2	141.9 ± 142	NS
Coagulopathy, no./total no. (%)¶	40/79 (50.6)	24/35 (68.6)	12/27 (44.4)	NS
AST, mean ± SD (range) IU/liter	264.2 ± 548 (9–3,420)	211.3 ± 341	423.4 ± 757.9	NS
ALT, mean ± SD (range) IU/liter	183.6 ± 351 (6–2,126)	96.1 ± 117	315.9 ± 402	0.029
LDH, mean ± SD (range) IU/liter	1,251 ± 1,592 (115–10,586)	1,012 ± 974	1,923.1 ± 1,721	NS
CRP, mean ± SD (range) mg/dl	7.7 ± 10.2 (0.2–39.3)	2.8 ± 4.0	14.9 ± 12.6	0.00002
Ferritin, mean ± SD (range) μg/liter	15,334.1 ± 35,181 (16–210,000)	5,849.5 ± 10,472	40,136.4 ± 64,069.7	0.003

* NS = not significant; WBC = white blood cell; Hgb = hemoglobin; AST = aspartate aminotransferase; ALT = alanine aminotransferase; LDH = lactate dehydrogenase; CRP = C-reactive protein.
† Includes the 61 patients with underlying systemic lupus erythematosus (SLE), the 31 with underlying adult-onset Still's disease (AOSD), and the 24 with other autoimmune diseases underlying autoimmune-associated hemophagocytic syndrome (AAHS).
‡ Underlying SLE versus underlying AOSD.
§ Body temperature ≥37.5°C.
¶ Hypofibrinogenemia, increased fibrinogen degradation products, or prolonged prothrombin time or activated partial thromboplastin time.

Table 2. Treatment of AAHS in adults*

	Total (n = 116)†	Underlying SLE (n = 61)	Underlying AOSD (n = 31)
Treatment, no. (%)‡			
Corticosteroids	114 (98.3)	61 (100)	30 (96.8)
Prednisolone	79 (68.1)	50 (82.0)	21 (70.0)
IV MP	71 (61.2)	38 (62.3)	17 (56.7)
IVIG	28 (24.1)	12 (19.7)	8 (25.8)
Cyclosporine	24 (20.7)	13 (21.3)	8 (25.8)
IV CYC	17 (14.7)	11 (18.0)	3 (9.7)
G-CSF	8 (6.9)	2 (3.3)	2 (6.5)
Plasma exchange	5 (4.3)	3 (4.9)	2 (6.5)
Tacrolimus	5 (4.3)	2 (3.3)	1 (3.2)
Methotrexate	4 (3.4)	1 (1.6)	3 (9.7)
Etoposide	3 (2.6)	1 (1.6)	1 (3.2)
Vincristine	3 (2.6)	1 (1.6)	1 (3.2)
Splenectomy	2 (1.7)	1 (1.6)	0 (0)
Leukapheresis	1 (0.9)	0 (0)	0 (0)
CHOP	1 (0.9)	0 (0)	1 (3.2)
Biologic agents			
Infliximab	2 (1.7)	1 (1.6)	1 (3.2)
Etanercept	3 (2.6)	2 (3.3)	1 (3.2)
Rituximab	3 (2.6)	3 (4.9)	0 (0)
Tocilizumab	1 (0.9)	0 (0)	1 (3.2)
Effects of treatment, no. of responders/total no. (%)			
Initial therapy			
Corticosteroids	64/111 (57.7)	32/59 (54.2)	18/30 (60)
Corticosteroids alone	46/87 (52.9)	28/53 (52.8)	11/20 (55)
Corticosteroids + other agents§	18/24 (75)¶	4/6 (66.7)	7/10 (70)
IVIG	1/4 (25)	0/2 (0)	1/1 (100)
Cyclosporine	1/1 (100)		
Overall response to initial therapy	66/116 (56.9)	32/61 (52.4)	19/31 (61.3)
Therapy for corticosteroid-refractory disease#			
Cyclosporine	5/14 (35.7)	2/10 (20)	2/3 (66.7)
IV CYC	11/12 (91.6)**	5/6 (83.3)**	5/5 (100)
IVIG	1/12 (8.3)	0/7 (0)	0/1 (0)

* Dosages of cyclosporine ranged from 2 mg/kg/day to 5 mg/kg/day, and dosages of intravenous cyclophosphamide (IV CYC) ranged from 0.5 gm to 1 gm per pulse. IV MP = IV methylprednisolone; G-CSF = granulocyte colony-stimulating factor; CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone.
† Includes the 61 patients with underlying systemic lupus erythematosus (SLE), the 31 with underlying adult-onset Still's disease (AOSD), and the 24 with other autoimmune diseases underlying autoimmune-associated hemophagocytic syndrome (AAHS).
‡ Includes initial therapy and therapy for refractory disease.
§ Includes cyclosporine, tacrolimus, IV CYC, or methotrexate.
¶ $P < 0.05$ versus corticosteroids alone.
# The most frequently used treatments were evaluated.
** $P < 0.01$ versus cyclosporine or IV immunoglobulin (IVIG).

with underlying AOSD (mean ± SD age 34.4 ± 14.2 years versus 43.4 ± 17.4 years; $P = 0.014$).

The ratio of men to women revealed no significant difference between the 2 groups (1:4.1 among patients with SLE and 1:4.2 among patients with AOSD). There was no significant difference in frequencies of fever, lymphadenopathy, hepatomegaly, or splenomegaly between the 2 groups. The mean WBC count and levels of ALT, CRP, and ferritin were significantly lower in patients with underlying SLE than in those with underlying AOSD (WBC count mean ± SD 2.2 ± 1.2 versus 6.8 ± 6.6 $\times 10^9$/liter [$P = 0.002$], ALT 96.1 ± 117 versus 315.9 ± 402 IU/liter [$P = 0.029$], CRP 2.8 ± 4.0 versus 14.9 ± 12.6 mg/dl [$P = 0.00002$], and ferritin 5,849.5 ± 10,472 versus 40,136.4 ± 64,069.7 μg/liter [$P = 0.003$]). There was no significant difference in the percentage of patients who experienced coagulopathy between the SLE and AOSD groups (68.6% versus 44.4%). The proportion of the patients who had normal or low levels of CRP (≤0.3 mg/dl) was greater in those with SLE than in those with AOSD (27.5% versus 3.4%; $P < 0.05$). Fifty percent of patients with underlying SLE had a CRP level of <1.0 mg/dl, as compared with 6.8% of those with underlying AOSD ($P < 0.01$). Moreover, low levels of ferritin (<500 μg/liter) were found in 23.9% of patients with underlying SLE, but low

Table 3. Clinical characteristics and treatment outcomes*

	Patients still living (n = 101)	Patients deceased (n = 15)
Age, mean ± SD years	40.9 ± 17.7	45.8 ± 24.9
Male sex, no. (%)	19 (18.8)	9 (60.0)†
Physical findings		
Fever, no./total no. (%)‡	85/99 (85.9)	14/15 (93.3)
Lymphadenopathy, no./total no. (%)	27/69 (39.1)	5/9 (55.6)
Hepatomegaly, no./total no. (%)	20/55 (36.4)	8/12 (66.7)
Splenomegaly, no./total no. (%)	34/77 (44.2)	6/11 (54.5)
Laboratory findings		
WBC count, mean ± SD $\times 10^9$/liter	3.7 ± 5	7.2 ± 11.8
Hgb, mean ± SD gm/dl	9 ± 2	8.8 ± 2.3
Platelet count, mean ± SD $\times 10^9$/liter	130.6 ± 131.7	83.3 ± 104
Coagulopathy, no./total no. (%)§	33/69 (47.8)	7/10 (70)
AST, mean ± SD IU/liter	224.8 ± 448.2	571.2 ± 1034
ALT, mean ± SD IU/liter	164.1 ± 318.9	302.7 ± 514.9
LDH, mean ± SD IU/liter	1,196 ± 1,571	1,714 ± 1,784
CRP, mean ± SD mg/dl	7.5 ± 10.4	9.3 ± 8.1
Ferritin, mean ± SD μg/liter	12,963 ± 27,982	32,133 ± 66,866

* WBC = white blood cell; Hgb = hemoglobin; AST = aspartate aminotransferase; ALT = alanine aminotransferase; LDH = lactate dehydrogenase; CRP = C-reactive protein.
† $P < 0.01$ versus patients still living.
‡ Body temperature ≥37.5°C.
§ Hypofibrinogenemia, increased fibrinogen degradation products, or prolonged prothrombin time or activated partial thromboplastin time.

ferritin levels were not found in patients with underlying AOSD ($P < 0.05$). High levels of ferritin (>5,000 μg/liter) were observed in 79.7% of patients with underlying AOSD, as compared with 28.3% of those with underlying SLE ($P < 0.01$). The median ferritin level was 1,683 μg/liter in patients with underlying SLE and 14,879 μg/liter in those with underlying AOSD.

In addition, analysis of bone marrow in SLE patients with low ferritin levels showed "active phagocytosis of trilineage hematopoietic cells, including megakaryocytes, erythroblasts, and granulocytes," "histiocytic hemophagocytosis," "massive infiltration of hemophagocytosis," "marked hemophagocytosis," and "prominent hemophagocytosis" (Supplementary Table 1, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.38672/abstract and refs. 13, 19, 22, 28, and 34), indicating that hemophagocytosis was evident in these cases. Clinical findings in SLE patients with low levels of ferritin were then compared to findings in patients with high ferritin levels (Supplementary Table 2), and differences in serum liver enzyme and CRP levels were found. Serum levels of AST, LDH, and CRP were significantly higher in patients with high ferritin levels than in those with low ferritin levels. A slight elevation of serum AST, LDH, and CRP levels was characteristic of patients with low levels of ferritin.

Treatments. Therapies provided to the 116 patients are listed in Table 2. Overall, 114 of 116 patients (98.3%) received corticosteroids. Prednisolone and intravenous methylprednisolone were administered in 68.1% and 61.2% of patients, respectively. Intravenous immunoglobulin G (IVIG), cyclosporine, and intravenous cyclophosphamide (IV CYC) were given in 24.1%, 20.7%, and 14.7% of patients, respectively. Patients received cyclosporine at dosages ranging from 2 mg/kg/day to 5 mg/kg/day, and IV CYC at doses ranging from 0.5 gm to 1 gm per pulse. A small number of patients were treated with biologic agents, including infliximab, etanercept, rituximab, and tocilizumab. The frequency of corticosteroid usage did not differ significantly between patients with SLE or AOSD (100% and 96.8%, respectively), and no other significant differences were found in treatments between the 2 groups (Table 2).

As the initial therapy, the most commonly used treatment was corticosteroids. Corticosteroids were initially administered in 111 of 116 patients (95.7%) either alone or in combination with other immunosuppressants, and 57.7% of the patients responded to the treatment. A greater response rate was seen in patients treated with corticosteroids in combination with other immunosuppressants as compared with patients treated with corticosteroids alone (75.0% versus 52.9%, respectively; $P < 0.05$). Other initial therapies included IVIG in 4 patients

Table 4. Factors associated with mortality, as determined by multivariate analysis*

	No. of patients still living (n = 101)	No. of patients deceased (n = 15)	Mortality rate, %	*P* (OR [95% CI])
Age, years				NS
<60	80	11	12.1	
≥60	21	4	16	
Sex				<0.01 (6.47 [2.06–30.39])
Male	19	9	32.1	
Female	82	6	6.8	
Underlying disease				
SLE	55	6	9.8	NS
AOSD	28	3	9.7	NS
Dermatomyositis	4	4	50	<0.05 (5.57 [1.08–28.65])
Rheumatoid arthritis	5	0	0	NS
Evans' syndrome	4	0	0	NS
Sarcoidosis	1	1	50	NS
Systemic sclerosis	0	1	100	NS
Mixed connective tissue disease	1	0	0	NS
Vasculitis syndrome	1	0	0	NS
Sjögren's syndrome	1	0	0	NS
Ankylosing spondylitis	1	0	0	NS
Physical findings†				
Body temperature				NS
<37.5°C	14	1	6.7	
≥37.5°C	85	14	14.1	
Lymphadenopathy				NS
Present	27	5	15.6	
Absent	42	4	8.7	
Hepatomegaly				NS
Present	20	8	28.6	
Absent	35	4	10.3	
Splenomegaly				NS
Present	34	6	15	
Absent	43	5	10.4	
Laboratory findings†				
WBC count, $\times 10^9$/liter				NS
<2	33	5	13.2	
≥2	61	6	9	
Hgb, gm/dl				<0.05 (3.74 [1.02–13.80])
<8	28	8	22.2	
≥8	66	5	7	
Platelet count, $\times 10^9$/liter				NS
<50	24	6	20	
≥50	76	9	10.6	
Coagulopathy				NS
Present	33	7	17.5	
Absent	36	3	7.7	
AST, IU/liter				NS
<100	44	6	12	
≥100	34	4	10.5	
ALT, IU/liter				NS
<100	35	6	14.6	
≥100	20	3	13	
LDH, IU/liter				NS
<500	23	2	8	
≥500	54	7	11.5	
CRP, mg/dl				NS
<2	33	1	2.9	
≥2	44	6	12	
<10	56	3	5.1	
≥10	21	4	16	
Ferritin, μg/liter				NS
<500	20	2	9.1	
≥500	65	10	13.3	
<10,000	60	9	13	
≥10,000	25	3	10.7	

* OR = odds ratio; 95% CI = 95% confidence interval; NS = not significant; SLE = systemic lupus erythematosus; AOSD = adult-onset Still's disease; WBC = white blood cell; Hgb = hemoglobin; AST = aspartate aminotransferase; ALT = alanine aminotransferase; LDH = lactate dehydrogenase; CRP = C-reactive protein.

† Data not available on all patients.

(3.4%) and cyclosporine in one patient (0.9%). One of the 4 patients (25%) responded to initial therapy with IVIG. The overall rate of response to initial therapy was 56.9%.

Among patients who did not to respond to initial corticosteroid treatment, cyclosporine, IV CYC, or IVIG were the most common treatments. IV CYC was beneficial in 91.6% of patients. The response rate in patients receiving IV CYC was significantly higher than that in patients receiving cyclosporine (91.6% versus 35.7%; $P < 0.01$) or IVIG (91.6% versus 8.3%; $P < 0.01$).

To ascertain whether there were differences in the effects of treatment between patients with underlying SLE and patients with underlying AOSD, we compared the treatment response rate between the 2 groups. The rate of response to initial corticosteroid treatment was similar between the 2 groups (54.2% versus 60.0%), and the overall rate of response to initial treatment did not differ significantly (52.4% versus 61.3%) (Table 2). Among patients with corticosteroid-refractory disease in both the group with underlying SLE and the group with underlying AOSD, IV CYC was effective. Five of 6 patients (83.3%) with underlying SLE and 5 of 5 patients (100%) with underlying AOSD responded to IV CYC. Among SLE patients with refractory disease, the effects of IV CYC were significantly superior to the effects of cyclosporine (83.3% versus 20%; $P < 0.01$) and IVIG (83.3% versus 0%; $P < 0.01$). In patients with underlying AOSD, the response rate among those who received IV CYC was high as compared with those who received cyclosporine (100% versus 66.7%) or IVIG (100% versus 0%), although statistical analysis did not show significant differences.

Biologic agents were administered to some patients who had treatment-refractory disease. Infliximab or etanercept was given to 3 patients with underlying SLE, and all of those patients improved. Rituximab was beneficial in 2 of 3 patients with underlying SLE. A patient with underlying AOSD, who at one point had infliximab-refractory disease, was successfully treated with etanercept. Tocilizumab was effective in another patient with underlying AOSD.

Treatment outcomes and factors associated with mortality. Of 116 cases, 15 patients (12.9%) died. Among the 15 deaths, 6 (40%) occurred in patients with underlying SLE, 4 (26.7%) occurred in patients with underlying dermatomyositis, 3 (20%) occurred in patients with underlying AOSD, 1 (6.7%) occurred in a patient with underlying sarcoidosis, and 1 (6.7%) occurred in a patient with underlying systemic sclerosis. Multiple organ failure and massive bleeding attributable to a flare of the underlying autoimmune disease or hemophagocytic syndrome were the predominant causes of death in the 15 patients (Supplementary Table 3, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.38672/abstract). The mortality rate of the patients with underlying SLE, AOSD, dermatomyositis, sarcoidosis, and systemic sclerosis was 9.8% (6 of 61), 9.7% (3 of 31), 50% (4 of 8), 50% (1 of 2), and 100% (1 of 1), respectively.

As shown in Table 3, while there was a significant difference between the sexes, there were no significant differences between alive and deceased patients with regard to age and physical and laboratory findings. The percentage of men was significantly greater in the deceased population as compared with that of the living population (60.0% versus 18.8%; $P < 0.01$). Multivariate analysis showed that factors associated with mortality included male sex (OR 6.47 [95% CI 2.06–30.39], $P < 0.01$), dermatomyositis (OR 5.57 [95% CI 1.08–28.65], $P < 0.05$), and anemia (Hgb <8 gm/dl; OR 3.74 [95% CI 1.02–13.8], $P < 0.05$) (Table 4).

DISCUSSION

In this literature survey, we reviewed a total of 116 adult cases of AAHS (proven based on pathologic evidence of hemophagocytosis). SLE and AOSD were identified as major underlying diseases. The sex ratio in adult patients with AAHS revealed a female predominance (overall male:female ratio 1:3). Similar to our observation, a female-predominant sex ratio has been described in children with MAS. In a report by Stephan et al on 24 children with MAS, 9 were boys and 15 were girls (32). In another report on MAS in patients with juvenile SLE, 89.5% of the patients were female (33). Moreover, our survey showed a female-predominant sex ratio among both SLE and AOSD patients with AAHS. The ratio of men to women was 1:4.1 among patients with underlying SLE and 1:4.2 among patients with underlying AOSD (Table 1). SLE is more predominant in the female population. In large cohorts in Europe, the US, and Latin America, female patients make up 90.8%, 88%, and 90% of the population, respectively (34–36), and the ratio of women to men varies between 4.3:1 and 11.7:1 (37). Among adults, especially among women of childbearing age, the male-to-female ratio ranges from 1:7 to 1:15 (38,39). In accordance with these facts, AAHS predominately affects women in the case of SLE. AOSD is more common among women in Eastern countries than in Western countries (40). In our survey,

more than half of the patients with underlying AOSD were from Eastern countries (17 of 31 patients), which may explain a female predominance among patients with underlying AOSD.

Fever, lymphadenopathy, hepatomegaly, and splenomegaly are cardinal symptoms of pediatric MAS. In one study of children with MAS, it was found that 100%, 58%, and 100% of patients had fever, hepatomegaly, and splenomegaly, respectively (32), whereas 86.8%, 41.8%, and 45.5% of adult patients in our survey, respectively, had those symptoms. These findings suggest that there are differences between adult and pediatric patients, especially with regard to the frequency of splenomegaly. In another study of MAS in juvenile SLE patients, fever, lymphadenopathy, hepatomegaly, and splenomegaly were found in 89.5%, 52.6%, 51.4%, and 37.8% of patients, respectively (33), which is similar to our findings in adult patients with underlying SLE (fever, lymphadenopathy, hepatomegaly, splenomegaly in 93.3%, 40.0%, 41.3%, and 34.9%, respectively). These results indicate that splenomegaly developed in only one-third of both pediatric and adult patients with underlying SLE, and thus, in the case of SLE, splenomegaly is not necessarily involved in AAHS.

In terms of laboratory findings, there were considerable differences between patients with underlying SLE and those with AOSD. The mean WBC counts and ALT levels were significantly lower among patients with underlying SLE than among those with underlying AOSD. Interestingly, low CRP levels were characteristic of patients with underlying SLE. Twenty-eight percent of patients with underlying SLE had CRP levels of $\leq$0.3 mg/dl, and 50% had CRP levels of $\leq$1.0 mg/dl. Because patients with active SLE (except those with active lupus serositis and chronic synovitis) do not usually have elevated CRP concentrations (41), normal or low CRP levels may be also characteristic of AAHS with underlying SLE.

Hyperferritinemia is a common feature of virus-associated hemophagocytic syndrome (42). However, in our survey a considerable number of patients did not have hyperferritinemia. Serum ferritin levels did not exceed 500 μg/liter in 22% of patients with histologically proven disease. In particular, 23.9% of patients with underlying SLE did not have hyperferritinemia ($>$500 μg/liter). Further, in a report on children with juvenile SLE–associated MAS, 6.3% did not have concomitant hyperferritinemia (33). On the other hand, ferritin levels were markedly elevated in patients with underlying AOSD as compared with those with underlying SLE. We have no satisfactory explanation for this phenomenon, but intensive hemophagocytic activity and/or a mechanism underlying hemophagocytic syndrome may be involved. The reason ferritin levels are not elevated in some patients remains unclear and warrants further clarification.

Moreover, we compared clinical findings between SLE patients with low ferritin levels and SLE patients with high ferritin levels (Supplementary Table 2, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.38672/abstract), and found differences in serum liver enzyme and CRP levels between the 2 groups. Serum AST, LDH, and CRP levels were significantly higher in patients with high ferritin levels than in patients with low ferritin levels. Thus, lupus patients with high ferritin levels seem to have laboratory features similar to those of patients with underlying AOSD or infection-associated hemophagocytic syndrome. However, a slight elevation of AST, LDH and CRP levels was characteristic of the patients with low ferritin levels. It may be difficult, therefore, to distinguish lupus flares from hemophagocytic syndrome, especially among lupus patients with low ferritin levels. In addition, whether hemophagocytic syndrome is or is not present remains unclear in these cases, unless a pathologic examination is performed. Pathologic examinations, such as bone marrow aspiration, may be the most sensitive means of diagnosing this syndrome.

In this study, we included only patients with histologically proven hemophagocytosis. Pathologic features of hemophagocytic syndrome indicate an infiltration of benign-appearing histiocytes with hemophagocytosis. Histiocytes are often vacuolated, with phagocytosis of erythrocytes, erythroblasts, neutrophils, and/or platelets. An increase in the number of histiocytes is usual in bone marrow. Histiocytes are present in various quantities, ranging from a slightly greater prominence to a replacement of hematopoietic tissue. Histiocytic hemophagocytosis itself is not necessarily abnormal, since histiocytes or macrophages can engulf aged or dying hematopoietic cells to keep the tissue in homeostasis. As a result, it is important to define what constitutes a distinctive presence or sufficient numbers of hemophagocytic histiocytes in bone marrow in order to diagnose hemophagocytic syndrome. Favara has noted that "No quantitative data are available, but if careful study of three or more smears fails to demonstrate an average of at least two hemophagocytic cells per slide, one cannot be confident of the significance of finding that rare cell" (43), whereas Tsuda has defined quantitative

numbers of hemophagocytic histiocytes in bone marrow as ≥3% or 2,500 cells/μl of mature histiocytes with prominent hemophagocytosis as being sufficient to diagnose hemophagocytic syndrome (44).

A therapeutic regimen for primary HLH includes immunosuppressive drugs and/or proapoptotic chemotherapy, and the FHLH Study Group has developed immunochemotherapy regimens (HLH-94 and HLH-2004). The HLH-2004 protocol consists of a 2-week induction phase that includes etoposide, cyclosporine, and dexamethasone, and intrathecal therapy with methotrexate and corticosteroids in selected patients (45). Subsequent hematopoietic stem cell transplantation is recommended for the cure of primary HLH, but there are not sufficient data to demonstrate whether all patients with secondary hemophagocytic syndrome require the full HLH protocol.

In addition, a particular therapeutic strategy for AAHS or MAS has not been established to date. Herein, we showed that 98.3% of adult patients with AAHS received corticosteroids. Corticosteroids were initially attempted either alone or in combination with other immunosuppressants, and were effective in 57.7% of patients. Corticosteroids alone induced a favorable response in more than half of the patients (52.9%). The results suggest that corticosteroids are the mainstay of initial treatment of adult patients with AAHS. The efficacy of cyclosporine, in combination with corticosteroids, has been reported in the treatment of MAS occurring in children with juvenile arthritis (46), and there have since been several additional reports regarding the efficacy of cyclosporine in combination with corticosteroids in the treatment of pediatric patients with MAS (32,47,48). Results of our survey indicate that corticosteroids in combination with other immunosuppressive medications, such as cyclosporine, IV CYC, or IVIG, exerted favorable effects, as compared with corticosteroids alone (75.0% versus 52.9%; $P < 0.05$). The combination of corticosteroids with other immunosuppressive medications seems to be beneficial in aggressive or severe cases.

Second-line treatments for patients with corticosteroid-refractory disease included cyclosporine, IV CYC, and IVIG. Overall efficacy of IV CYC was significantly superior to that of cyclosporine or IVIG (Table 2). Since CYC is one of the most potent immunosuppressive therapies, and has been used to treat severe manifestations of a variety of autoimmune and inflammatory diseases, it might be possible to use IV CYC to treat patients with underlying AOSD who have treatment-refractory or life-threatening disease. However, IV CYC is associated with bone marrow suppression, severe infections, secondary malignancy, hemorrhagic cystitis, and ovarian failure, and thus safer and more effective therapies are required. Biologic agents are in fact beneficial for some patients with refractory AAHS (Supplementary Table 1, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.38672/abstract and refs. 28, 31, 46, 50, 51, 56). These agents have proved to be highly effective in both corticosteroid- and disease-modifying antirheumatic drug–resistant AOSD (49). To date, neither large nor randomized trials have been completed to ensure the efficacy of biologic agents versus conventional immunosuppressants in AAHS, and the efficacy of biologic agents in the treatment of this syndrome is currently under investigation.

The mortality rate among patients with AAHS was estimated to be 12.9%. Male sex, dermatomyositis, and anemia (Hgb <8 gm/dl) were identified as factors associated with mortality. Other factors, such as advanced age, presence of coagulopathy, and high levels of serum ferritin, were not significant predictive factors for the risk of death. Recognition of these risk factors may be helpful for the management of the disease, and more prompt and intensive therapy may be required to reduce mortality rates in patients who have these particular risks.

Lastly, there are currently no validated diagnostic criteria for AAHS or MAS secondary to autoimmune diseases. Diagnostic criteria for HLH established in 1991 and revised in 2004 were designed for the diagnosis of primary HLH (45), but many physicians in practice use the same criteria to diagnose secondary HLH/MAS. These criteria pose particular problems for the diagnosis of AAHS, since some clinical and laboratory criteria for HLH, such as fever, splenomegaly, and cytopenias, may also be present as part of the underlying autoimmune disease itself. Moreover, patients with autoinflammatory diseases, including systemic juvenile idiopathic arthritis and AOSD, usually have high levels of WBCs, neutrophils, platelets, and fibrinogen as a feature of disease activity, and making diagnosis of hemophagocytic syndrome/MAS is difficult in these patients (50). As a result, validated diagnostic criteria for AAHS that are unrelated to typical findings of underlying autoimmune disease are urgently needed. Our ultimate goal is to elucidate the pathogenic mechanisms of this syndrome and develop treatments aimed at the underlying pathologic process.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Kumakura had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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