

Childhood macrophage activation syndrome differs from infection-associated hemophagocytosis syndrome in etiology and outcome in Taiwan

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Background and Purpose: Hemophagocytic lymphohistiocytosis (HLH) is a syndrome composed of macrophage activation syndrome (MAS), infection-associated hemophagocytosis syndrome (IAHS), malignancy-associated HLH and genetic HLH. Differentiation of MAS from IAHS and other HLH is important for early appropriate treatment.

Methods: A retrospective analysis was used to differentiate childhood MAS from IAHS and other HLH in Chang Gung Memorial Hospital (CGMH), Kaohsiung. All relevant clinical features, laboratory data, treatments and outcomes were analysed.

Results: Seventeen patients with childhood HLH were found at CGMH, Kaohsiung in the past decade, and could be classified into 3 categories: IAHS (9 patients), MAS (5 patients), and HLH of unknown etiology (3 patients). The diagnosis of MAS first appeared in this hospital in 2001. Patients with IAHS tended to be younger than those with MAS. Boys were more frequently found in the IAHS group whereas girls (with systemic lupus erythematosus or juvenile idiopathic arthritis) were more frequently found in the MAS group. The majority of mortality cases were noted in the IAHS group (44%, 4/9). All patients with MAS survived with early cyclosporine A treatment.

Conclusions: Childhood MAS is different from IAHS in terms of age, gender, etiology and mortality. Early administration of cyclosporine A for MAS results in a lower mortality. Further prospective studies are required to confirm these findings.

Key words: Cyclosporine; Lymphohistiocytosis, hemophagocytic; Macrophage activation; Phagocytosis

Introduction

Macrophage activation syndrome (MAS) belongs to a subtype of hemophagocytic lymphohistiocytosis (HLH). The main clinical features of MAS are similar to other types of HLH, especially infection-associated hemophagocytosis syndrome (IAHS), showing persistent fever, hepatosplenomegaly, lymphadenopathy,

hemorrhage, central nervous system dysfunction, and characteristic laboratory findings of cytopenia, abnormal liver or renal function, hypoalbuminemia, decreased fibrinogen, hypertriglyceridemia, hypercholesterolemia, and hyperferritinemia [1]. MAS is usually associated with patients with systemic lupus erythematosus (SLE) or juvenile idiopathic arthritis (JIA), especially systemic-onset JIA (SOJIA) [1,2]. The pathognomonic feature is macrophage hemophagocytosis on bone marrow aspiration examination. The pathogenesis of HLH including MAS involves the dysfunction of natural killer (NK) cells and cytotoxic T cells leading to excessive activation and proliferation of macrophages [2-4].

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Without prompt recognition and immediate treatment, the uncontrolled inflammatory process of HLH culminates in potentially life-threatening complications. This is due to sustained levels of neutropenia, anemia, or thrombocytopenia with high risks of infection, bleeding and multiple organ failure [5,6]. The treatment regimens for MAS, IAHS and other HLH are controversial. A combination of immunosuppressant, immunomodulatory and cytotoxic treatment is frequently needed.

Recent evidence suggests that early administration of cyclosporine A (CsA) for HLH including MAS results in a better outcome [6,7]. This report presents a retrospective analysis of all childhood MAS, IAHS, and etiology-unknown HLH patients at Chang Gung Memorial Hospital (CGMH), Kaohsiung, Taiwan over the past 10 years.

Methods

Study design and patients

A retrospective analysis of all pediatric patients with HLH, including IAHS, MAS and HLH with unknown etiology in CGMH from June 1996 to May 2006 was conducted. All relevant clinical features, laboratory data, treatment and outcomes were recorded systematically. In total, 17 patients were identified. Laboratory data upon initial diagnosis of HLH were collected and analyzed.

Fifteen of the 17 patients were diagnosed in our hospital and the other 2 patients were transferred from other hospitals. All patients with IAHS or MAS had at least four of the five previously described diagnostic criteria: fever; splenomegaly; cytopenia ≥ 2 cell lines; hypertriglyceridemia and/or hypofibrinogenemia; and hemophagocytosis in bone marrow, colony-stimulating factor (CSF), or lymph nodes [8], except patient 12 and 16, who were diagnosed to be HLH with hyperferritinemia plus 3 of the 5 diagnostic criteria. Malignancy-associated HLH was not included in this study.

The diagnosis of Epstein-Barr virus (EBV)-associated IAHS was mainly based on a four-fold increase in EB-VCA (viral capsid antigen) immunoglobulin G titer, positive EB-VCA immunoglobulin M and/or EBV DNA detection. In the MAS group, one was associated with SOJIA and four were associated with SLE. We first reviewed the demographic data in a chronological sequence, then compared the differences of clinical and laboratory data between patients with IAHS and MAS. Finally, we examined the treatment regimens

and outcomes among IAHS, MAS, and HLH with unknown etiology.

Statistical analysis

Gender distribution and presentation of clinical symptoms of HLH patients were tested by chi-squared test. Laboratory data and age were tested by Mann-Whitney *U* test. A *p* value <0.05 was considered statistically significant.

Results

Demographic data

Over the past 10 years, a total of 17 patients with HLH were diagnosed in CGMH-Kaohsiung. These patients could be classified into 3 categories: IAHS (9 patients), MAS with rheumatic diseases including SLE and SOJIA (5 patients), and unknown etiology (3 patients). Seven of the 9 IAHS patients were males, and all of the 5 MAS patients were females. The mean age (\pm standard error of the mean [SEM]) at disease onset was 9.35 ± 1.53 years ($n = 17$). Seventy one percent (12/17) of HLH patients were diagnosed after the year 2000. All of the 5 MAS patients were diagnosed after 2001 (Table 1).

Clinical and laboratory data

The mean age at onset of IAHS was 5.51 ± 1.83 years (mean \pm SEM, $n = 9$), significantly younger than the all-female MAS patients (14.38 ± 1.54 years; $n = 5$) [$p=0.01$, Mann-Whitney *U* test]. The rates of fever development, hepatosplenomegaly, lymphadenopathy, and central nervous system symptoms (including seizure or psychosis) had no significant difference in these two groups. The IAHS patients had a higher rate of skin rash with petechiae than MAS patients ($p=0.03$, chi-squared test) [Table 2]. In the laboratory features, there were no significant differences between these groups white blood cell count, hemoglobin, liver enzymes, renal function, albumin, fibrinogen, triglyceride, cholesterol, and ferritin upon diagnosis. Thrombocytopenia ($p=0.01$), elevation of C-reactive protein ($p=0.02$) and intravascular coagulation dysfunction ($p=0.01$) were, however, noted more often in the IAHS group than the MAS group. Hemophagocytosis was found in all 13 patients with bone marrow examinations, except in patient 9 (Table 2).

Survival and mortality

The overall mortality of HLH in this series was 35% (6/17). There were 4 deaths in the IAHS group. The

Table 1. Demographic data of pediatric patients with macrophage activation syndrome (MAS) and infection-associated hemophagocytosis syndrome (IAHS)

Patient	Gender ^a	Age (years) ^b	Month and year of diagnosis	Diagnosis
1	M	14.7	August 1996	IAHS
2	M	6.0	October 1996	IAHS
3	M	1.8	May 1997	IAHS
4	F	3.4	January 1999	IAHS
5	M	1.5	March 1999	IAHS
6	F	14.0	September 2000	Unknown etiology
7	F	9.0	July 2001	MAS
8	M	1.5	July 2001	IAHS
9	F	15.8	April 2003	MAS
10	F	14.7	September 2003	MAS
11	M	14.5	March 2004	IAHS
12	F	5.8	May 2004	IAHS
13	F	18.4	July 2005	MAS
14	M	0.4	January 2006	IAHS
15	F	6.4	February 2006	Unknown etiology
16	F	14.0	March 2006	MAS
17	F	17.2	April 2006	Unknown etiology

Abbreviations: M = male; F = female

^aM/F ratio = 7:10.

^bMean \pm standard error of the mean = 9.35 \pm 1.53.

patients with IAHS received a relatively intensive therapy including etoposide (VP-16), but relatively late administration of CsA (Table 3). No mortality was noted in the MAS group. The patients with MAS received mainly early CsA administration but not VP-16. In the IAHS group, 67% of patients (6/9) had EBV-related disease, associated with a higher mortality, although an extensive combination therapy was employed (Table 3).

Discussion

HLH is a syndrome composed of different disease entities classified into two groups, genetic and acquired HLH [4]. Genetic HLH includes familial HLH, and immunodeficiency-associated HLH. Acquired HLH diseases include infection-associated hemophagocytic syndrome (IAHS), rheumatic diseases associated with MAS, inborn errors of metabolism and malignancy-associated HLH. Both groups present similar clinical manifestations, related to the hyperinflammation induced by ineffectively activated T lymphocytes and histiocytes with hypersecretion of pro-inflammatory

cytokines, such as interferon-gamma, tumor necrosis factor-alpha (TNF- α), interleukin-6, and macrophage-CSF [3,9,10]. In addition, NK cell dysfunction is involved in immunologic abnormality leading to HLH [2,4].

IAHS can be induced by various infectious organisms, mostly viruses, but also bacteria, fungi and protozoa [5,6,11]. EBV was the major triggering virus in children with IAHS, which is consistent with the finding in our report. It is not sufficient to control HLH with anti-infective therapy alone. Moreover, patients with familial HLH are usually triggered by infectious agents and show similar features to those of IAHS. Thus, patients with recurrent IAHS at a relatively young age should be further evaluated and differentiated from familial HLH.

MAS can occur in any systemic rheumatological disorder, but is most commonly associated with SOJIA [1]. In our analysis, MAS was more frequent in females with SLE. This may be because the prevalence of pediatric SLE in Chinese is higher than that in Caucasians [12]. The possible triggers for MAS include infectious agents (such as EBV, varicella-zoster virus, Coxsackie virus B1, *Salmonella enteritidis*, *Pneumocystis carinii*, parvovirus B19), and medications (such as aspirin, non-steroidal anti-inflammatory drugs, methotrexate, sulphasalazine, and gold salt injections) [6,13]. The SLE patients with MAS in this study received prednisolone, hydroxychloroquine or azathioprine, but none of those implicated above. Thus, the trigger factors for the MAS in our SLE patients may be related to infectious agents.

In this study, we did not find any patient that could be classified as familial HLH. This may be because the genetic background of Chinese is not susceptible to HLH, or because the diagnostic tools are not well developed in our hospital. Recently, a number of genes have been implicated in the susceptibility to familial HLH, including *PRF1*, *UNC13D* and *STX11* [14-17]. These genes are involved in the process of cytotoxic activity of NK cells and cytotoxic T cells with the release of cytolytic granules such as perforin, and granzymes to kill the target cell. Patient 14 was a case with recurrent HLH at a young age. In this condition, familial HLH should be differentiated from IAHS with further evaluation. Based on the newly developed molecular technologies, we may be able to identify patients with familial HLH in the future.

Recently, it has been recommended that the diagnosis of HLH be based on the presence of 5 of the

Table 2. Comparison of clinical and laboratory data between infection-associated hemophagocytosis syndrome (IAHS) and macrophage

Variable	IAHS					
	1	2	3	4	5	8
Patient no.						
Clinical symptoms						
Fever	+	+	+	+	+	+
Hepatosplenomegaly	+/-	+/-	+/+	+/-	-/-	+/+
Lymphadenopathy	-	-	-	-	-	-
Skin rash	-	Petechiae	-	Petechiae	-	-
CNS	-	-	Lethargy	-	-	-
Laboratory data at onset						
WBC count ($\times 1000/\text{mm}^3$)	1.45	0.30	1.50	1.40	1.40	2.00
Platelet ($\times 1000/\text{mm}^3$)	98.90	4.00	2.50	1.00	2.40	1.50
Hemoglobin (g/dL)	12.10	7.90	9.50	8.30	9.60	9.20
CRP (mg/L)	166	256	76.1	231.5	69.3	184
AST/ALT (U/L)	582/-	17/19	900/-	229/78	116/173	82/38
BUN/Cr (mg/dL)	23/1.40	9/0.50	40/1.40	29/1.00	10/0.30	17/0.20
Albumin (g/dL)	-	3.50	2.50	2.10	-	-
Fibrinogen (mg/dL)	-	-	-	-	380.00	-
Triglyceride (mg/dL)	142.00	74.00	948.00	193.00	358.00	-
Cholesterol (mg/dL)	101.00	121.00	86.00	59.00	137.00	-
Ferritin (ng/mL)	-	141.00	2510.00	-	-	-
PT/aPTT	↑	↑	↑↑	↑↑	-	-
Bone marrow with hemophagocytosis	+	+	+	+	+	+

Abbreviations: CNS = central nervous system; WBC = white blood cell; CRP = C-reactive protein; AST = aspartate aminotransferase; ALT = aspartate aminotransferase; = present; - = absent; ↑ = 1.5-fold greater than control; ↑↑ = 3.0-fold greater than control; N = normal

^aPatient with recurrence of hemophagocytic lymphohistiocytosis. Continuous variables were tested by Mann Whitney *U* test, while clinical ^b*p* < 0.05.

following 8 criteria: fever; splenomegaly; cytopenia ≥ 2 cell lines; hypertriglyceridemia and/or hypofibrinogenemia; hyperferritinemia; elevated soluble interleukin-2 receptor (sCD25); decreased or absent NK cell activity; and hemophagocytosis in bone marrow, CSF, or lymph nodes [5,18]. If laboratory techniques such as measurement of sCD25 and NK cell activity are not readily available, the criteria should be revised accordingly,

so that early diagnosis and immediate treatment for HLH to prevent fatal outcome may be achieved. In addition, repeated examinations of bone marrow aspiration are sometimes needed to rule in HLH, and to rule out malignant disorders.

Different treatment options for HLH should be considered for various disease entities. The primary aim of therapy is to suppress the hyperinflammation. It

Table 3. Comparison of survival and mortality among hemophagocytic lymphohistiocytosis patients according to treatment regimens and

Category	Mortality							
	2	3	11	12	6	15	1	4
Etiology	EBV	EBV	EBV	IAHS	Unknown	Unknown	EBV	EBV
Gender	M	M	M	F	F	F	M	F
Age (years)	6.0	1.8	14.5	5.8	14.0	6.4	14.7	3.4
Treatment								
Steroids	+	+	MP	+	MP	-	+	+
IVIg	+	+	+	+	-	-	+	+
CsA	-	-	-	+	+	-	-	-
VP-16	+	+	-	+	-	-	-	+
Cause of death	Pneumonia MOF	Pneumonia MOF	GI bleeding, MOF	Sepsis MOF	Pulmonary edema, MOF	Pulmonary edema, MOF	-	-

Abbreviations: EBV = Epstein-Barr virus; IAHS = infection-associated hemophagocytosis syndrome; CMV = cytomegalovirus; JIA = juvenile idiopathic arthritis; + = present; - = absent; MOF = multiple organ failure; GI = gastrointestinal; MP = methylprednisolone pulse therapy; F = female

activation syndrome (MAS) patients

			MAS					<i>p</i>
11	12	14 ^a	7	9	10	13	16	
+	+	+	+	+	+	+	+	0.19/0.14
+/+	-	-/+	-/-	-/-	-/-	+/-	-/-	
+	-	+	-	+	+	-	-	0.48
Petechiae	Petechiae	Petechiae	-	-	-	-	-	0.03 ^b
-	Lethargy	-	Seizure	-	Seizure	-	Psychosis	0.15
10.60	0.20	2.70	10.70	1.20	7.87	2.80	17.10	0.08
82.00	10.00	10.00	55.00	112.00	89.00	21.00	366.00	0.01 ^b
8.80	8.50	8.40	7.90	9.90	14.00	6.70	13.30	0.6
53.1	324.6	70	47.5	6.4	56.3	3.9	14.8	0.002 ^b
123/50	27/79	96/64	4379/1039	230/117	2534/375	162/87	40/22	0.19/0.14
84/1.80	7/0.50	3/0.20	21/0.70	1/0.60	10/0.80	11/0.70	122/4.10	0.89/0.43
2.80	2.30	2.10	1.70	2.30	-	2.40	3.00	0.76
-	543.00	-	96.60	239.00	141.00	-	250.00	0.13
212.00	102.00	138.00	-	182.00	164.00	346.00	1136.00	0.36
79.00	-	61.00	-	-	119.00	82.00	562.00	0.38
11,874.50	556.60	1381.90	-	3439.70	73,968.00	4195.70	2365.80	0.19
↑	↑	↑↑	↑↑	N	↑	N	N	0.01 ^b
+	+	+	+	-	+	+	+	0.16

alanine aminotransferase; BUN = blood urea nitrogen; Cr = creatinine; PT = prothrombin time; aPTT = activated partial thromboplastin time; +

symptoms were tested by chi-squared test.

is usually not sufficient to control HLH with anti-infective therapy and/or intravenous immunoglobulin. The initial treatment protocol recommended by the HLH 2004 consensus included a combination therapy with dexamethasone, CsA, and etoposide. Itrathecral therapy with methotrexate and prednisolone is suggested by progressive neurological symptoms, or if an abnormal CSF finding has not improved. Dexamethasone is

preferred to prednisolone, due to better penetration of the blood-brain barrier. CsA therapy (dose range 3-7 mg/kg/day intravenously and trough levels between 200 and 400 ng/mL) during the early stage of the disease course has been found to yield a better outcome [6,7]. The possible mechanism of CsA therapy for HLH is related to inhibition of calcineurin and dephosphorylation of nuclear factor of activated T cells,

complications

Survival								
5	8	14	17	7	9	10	13	16
EBV	IAHS	CMV	Unknown	JIA	SLE	SLE	SLE	SLE
M	M	M	F	F	F	F	F	F
1.5	1.5	0.4	17.2	9.0	15.8	14.7	18.4	14.0
-	+	+	+	+	MP	MP	+	MP
+	+	+	+	+	-	+	+	+
-	-	+	+	-	-	+	+	+
-	+	+	+	+	-	-	-	-
-	-	-	-	-	-	-	-	-

arthritis; SLE = systemic lupus erythematosus; IVIG = intravenous immunoglobulin; CsA = cyclosporine A; VP-16 = etoposide; M = male;

resulting in the down-regulation of cytokine production and inhibition of the early phase of T-cell activation [19]. In our experience, the levels of CsA are frequently affected by drug interaction so that frequent monitoring of CsA plasma levels is indicated.

Another study supports the early use of etoposide for the treatment of patients with IAHS because IAHS patients who did not receive etoposide within the first 4 weeks had a 14-fold higher mortality rate than those who did [20]. For a patient with poor response to the initial treatment, a series of bone marrow aspiration examinations may be helpful in evaluating either persistent hyperinflammation or myelosuppression by the treatment. Repeated measurements of ferritin levels are also important in determining the treatment dose and course.

For those patients who have less severe symptoms in the early stages of the disease, or do not fulfill the aforementioned criteria, intravenous immunoglobulin therapy may be helpful. A case report showed a good response with anti-TNF- α (etanercept) therapy for MAS with SOJIA [21]. The outcome in this patient suggests that etanercept might be an effective alternative regimen for MAS treatment.

Methylprednisolone pulse therapy may be considered in the early phase for MAS before the use of CsA. For those resistant to methylprednisolone pulse therapy, CsA or etoposide should be considered for further therapy. Some patients may develop re-activation or recurrence of HLH. The immunosuppressive treatment should be restarted and a prolonged therapy may be required. For certain patients with familial HLH, stem cell transplantation is curative. In conclusion, with progress in the development of laboratory techniques, more acquired childhood HLH such as MAS will be diagnosed in Chinese societies where SLE has a higher prevalence. Clinicians should be alert to this potentially fatal disease, and to the life-saving role of early CsA treatment.

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