Secondary Hemophagocytic Lymphohistiocytosis in Children : An Analysis of Etiology and Outcome

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Abstract

Fifty-two pediatric patients were diagnosed with secondary hemophagocytic lymphohistiocytosis (HLH) at the Department of Pediatrics, Siriraj Hospital between 1989 and 1998. Of these, 15 were infection-associated (IAHS), 25 were malignancy-associated (MAHS) and 12 were idiopathic HLH. Causative organisms for IAHS were *Salmonella* (3), *Staphylococcus* (2), enterobactor (2), dengue virus (3), malaria (2) and one each of Ebstein Barr virus (EBV), *Serratia marcesens* and *Penicillium maneffei*. Unlike those reported in adults and in the Western literature, 47 of 52 children in the present series were immunocompetent hosts. In addition, the proportion of MAHS was higher than expected (48.1 %). Twenty-two of 25 MAHS presented with hemophagocytic syndrome and were subsequently found to have malignant diseases. Sixty per cent of MAHS (15 cases) were associated with non-Hodgkin's lymphoma (NHL), mainly T-cell. Other malignancies included acute leukemias (7) MDS (1), Langerhans cell histiocytosis (1) and histiocytic sarcoma (1). Treatment approaches were specific therapy for individuals with known causes. Supportive treatment with blood components transfusions, steroid, intravenous immunoglobulins (IVIG), and chemotherapeutic agents, mainly vinblastine and etoposides, were used in indicated cases. Of the 52 cases, 15 (28.8%) had a fatal outcome during the acute phase, and other 4 died of their subsequent malignant diseases. There was a statistically significant association between poorer prognosis and patients' age < 3 years (p= 0.004) or MAHS (p=0.005).

Conclusion : Secondary HLH is not uncommon in Thai children who are immunocompetent. Malignancies, particulary NHL, are highly suspicious especially for cases not responsive to conventional therapy. Poor prognostic factors are age less than 3 years and MAHS.

Key word : Secondary Hemophagocytosis, Infection-Associated Hemophagocytic Syndrome (IAHS), Malignancy-Associated Hemophagocytic Syndrome (MAHS)

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Hemophagocytic syndrome (HPS) is a macrophage-related disorder of varied biological behavior according to Histiocyte Society and World Health Organization (WHO) new classification of histiocytic disorders (Table 1)[1]. HPS encompasses both primary or familial hemophagocytic lymphohistiocytosis (FHLH), which is a genetic disorder affecting natural killer (NK) cells[2], and secondary hemophagocytic lymphohistiocytosis, which appears to be a cytokine-mediated disorder triggered by various agents[3]. The syndrome is considered rare. Most reported cases from Western countries were adults and immunocompromized hosts[4]. In Asia, more cases of secondary HLH were reported in immunocompetent hosts and young children[5-7]. HLH associated with various types of infection including bacterias, viruses, fungus, and protozoas were reported and classified as infection associated hemophagocytic syndrome (IAHS)[8-21]. Secondary HLH also can be triggered by various types of malignancies, especially anaplastic large cell lymphoma (ALCL), leukemias or solid tumors, which are classified as malignancy associated hemophagocytic syndrome (MAHS)[22-29].

Pediatric HLH is different from adults in that they usually do not occur in immunocompromised hosts. More than half of the reported cases are from Asian countries and patients' age is usually less than 3 years. Infectious agents are the most common association with the syndrome, and were named IAHS. The clinical outcome is usually poor with a mortality rate of more than 50 per cent.

MATERIAL AND METHOD

Diagnosis, investigations and treatment

At the Department of Pediatrics, Faculty of Medicine Siriraj Hospital, Thailand, patients who had prolonged fever, peripheral blood cytopenias with or without other clinical symptoms of organomegaly would undergone a diagnostic bone marrow aspiration. Diagnosis of all patients with hemophagocytic syndrome was compatible with criterias adopted by the Histiocyte Society published elsewhere[30]. Blood chemistry, triglycerides, fibrinogen and coagulogram were done in most cases.

Further investigations to search for the infectious etiology of HPS includes; hemoculture, bone marrow culture, serology test for viruses, i.e. dengue, Ebstein Barr virus (EBV), adenovirus, herpes virus, cytomegalovirus (CMV) and hepatitis viruses, widal test, Weil-felix test, thick film and thin film for malaria. A search for mycobacterium infection by

Table 1. Classification of histiocytic disorders.

Disorders of varied biological behavior
Dendritic cell-related disorders
Langerhans cell histiocytosis
Secondary dendritic cell processes
Juvenile xanthogranuloma and related disorders
Solitary histiocytomas of various dendritic cell phenotypes
Macrophage-related disorders
Hemophagocytic syndromes
Primary hemophagocytic lymphohistiocytosis
(Familial and sporadic; commonly elicited by viral infections)
Secondary hemophagocytic syndromes
Infection-associated
Malignancy-associated
Others
Rosai-Dorfman disease (sinus histiocytosis with massive lymphadenopathy)
Solitary histiocytoma with macrophage phenotype
Others, including multicentric reticulohistiocytosis (often arthritis-associated) and generalized eruptive histiocytoma
Malignant disorders
Monocyte-related malignant disorders
Leukemia (FAB and revised FAB classifications)
Extramedullary monocytic tumor or sarcoma (monocytic counterpart of granulocytic sarcoma)
Dendritic cell-related histiocytic sarcoma (localized or disseminated)
Specify phenotype; follicular dendritic cell, interdigitating dendritic cell, etc.
Macrophage-related histiocytic sarcoma (localized or disseminated)

PPD skin test and gastric wash for AFB were done in patients whose etiology of fever was not established.

Empirical antibiotics were given in all cases. If symptoms of fever and cytopenias progressed or persisted for more than 3 weeks despite maximum empirical treatment for infections, a search for malignancy would be performed. This included repeated BM aspiration and biopsy, lymph node, liver or skin biopsy in indicated cases. Treatment with steroid and IVIG were started in cases that did not respond to blood and blood component transfusions and had clinical indications. Appropriate chemotherapeutic agents were given for specific types of proven malignancies. In cases with unproven malignancy, but had progressive and severe hemophagocytosis which did not respond to steroid and IVIG, chemotherapeutic agents including vinblastine and etoposide were given according to modified protocol HLH94 for hemophagocytic syndrome(30).

Studied population

Between 1989 and 1998, children aged less than 13 years whose bone marrow aspiration showed evidence of hemophagocytosis were included in the study. The patients were classified by their etiology into three groups; IAHS, MAHS and idiopathic.

Method and statistical analysis

Clinical characteristics, laboratory findings and clinical outcome of each group were reviewed and compared. Statistical analysis was performed by using Kaplan-Meier survival analysis, and chi square test. Statistical significance was considered if p value was below 0.05.

RESULTS

During the period of 10 years, 52 pediatric patients with the diagnosis of hemophagocytic syndrome (HPS) who had available follow-up data, were included in the study. The patients consisted of 33 males (63%) and 19 females (37%). Male: female ratio was 1.7:1. The sex distribution by subgroups is shown in Fig. 1. Their age ranged from 6 months to 12 years, with a mean age of 4.28 years (SD 3.85) (Fig. 2). Twenty-nine of 52 patients (56%) were aged less than 3 years. The most common clinical manifestations were prolonged fever (100%), anemia

Fig. 1. Illustrates sex distribution of patients in 3 groups of HLH; IAHS, MAHS and idiopathic. Overall male : female ratio is 1.7 : 1.

HLH = hemophagocytic lymphohistiocytosis
IAHS = infection-associated hemophagocytic syndrome
MAHS = malignancy-associated hemophagocytic syndrome

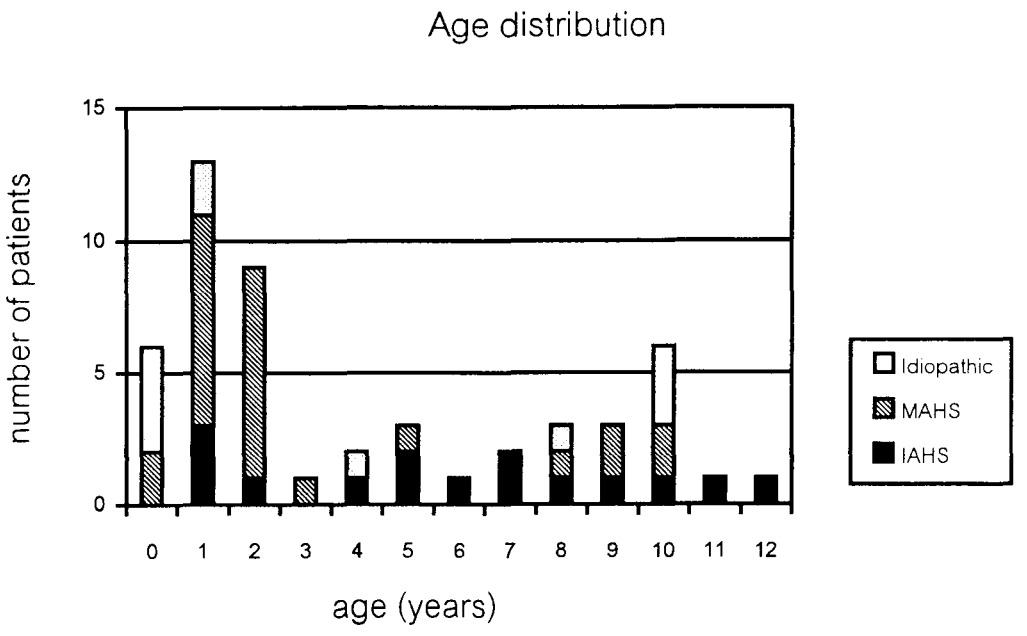

Fig. 2. Illustrates age distribution of children with HLH. Mean age is 4.28 years. Fifty-six per cent of cases are younger than 3 years. Mean age of IAHS, MAHS and idiopathic groups are 5.97, 3.44 and 3.90 years respectively.

HLH = hemophagocytic lymphohistiocytosis
IAHS = infection-associated hemophagocytic syndrome
MAHS = malignancy-associated hemophagocytic syndrome

(94.2%), hepatomegaly (94.2%) and splenomegaly (80.76%). The incidence of clinical features and abnormal laboratory findings of the 52 HLH are shown in Fig. 3.

The patients were classified by their etiology into 3 groups; IAHS, MAHS and idiopathic. The comparisons of mean age, treatment and outcome of the 3 groups of patients with HLH are shown in Table 2. A statistic analysis by using Kaplan-Meier survival analysis comparing survival of the 3 groups (n=52) shows a statistical significant difference (Fig. 4) Chi-square=10.7167, df=2, p=0.005. The comparisions of survival proportion after acute phase and at 5 years is shown in Table 3. The IAHS group (15 cases) had documented infection. Associated organisms and clinical outcome in IAHS group are shown in Table 2. All patients received empirical antibiotics therapy due to prolonged fever and neutropenia. Corticosteroid and IVIG were given to patients who had clinical indications and did not respond to blood or platelets transfusion. Only one case in the IAHS group who had Dengue hemorrhagic fever died from massive hemorrhage, hepatic and renal failure. Fourteen patients survived the acute phase. One patient with Penicillosis found to have HIV infection[12], survived the acute phase but was lost to follow-up. Five-year disease free survival (DFS) was expected to be 93 per cent by Kaplan-Meier survival analysis.

All of the cases in the MAHS group had pathological proven diagnosis of malignancies. The authors report in this series a higher proportion of MAHS. Three cases, one each of acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML) and acute erythroleukemia (AEL), developed HPS after the treatment of acute leukemias and therefore, they were immunocompromised hosts. Two other cases developed ALL 2 and 10 months after HLH. The other 20 cases (80 %) developed HPS with masked hematolymphoid malignancies in the background. Among these, 15 cases were lymphoma mainly T-cell. Most diagnosis was made from bone marrow aspirations although multiple aspirations were often required. The diagnosis of five patients

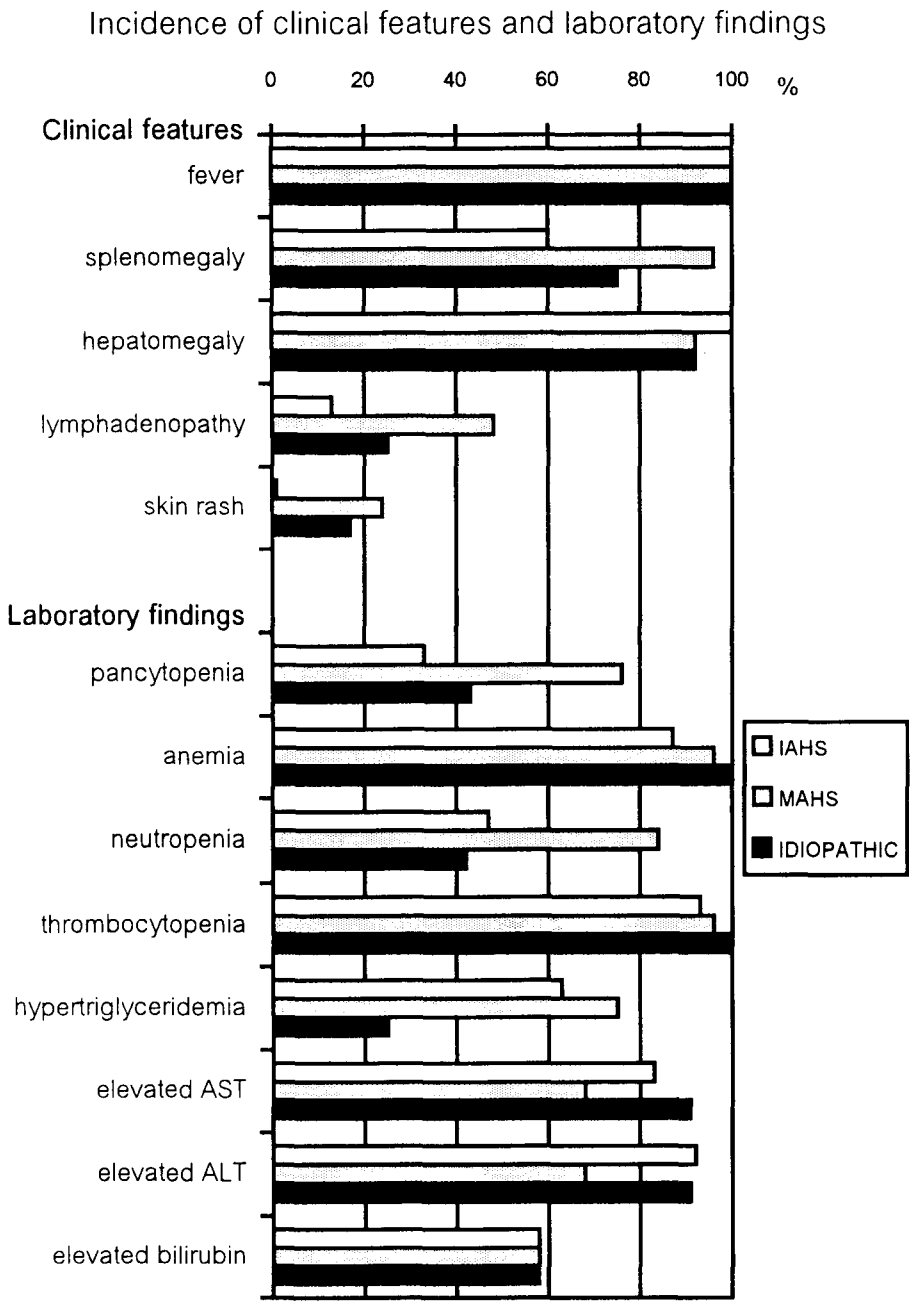

Fig. 3. Incidence of clinical features and abnormal laboratory findings in HLH.

HLH = hemophagocytic lymphohistiocytosis

Table 2. Comparisons of mean age, treatment and outcome of 3 groups of patients with HLH.

	IAHS	%	MAHS	%	Idiopathic	%	Total	%
No of cases (n)	15		25		12		52	
Mean age (yr)	5.97		3.44		3.90		4.28	
Treatment								
Specific treatment	15	100	21	92	NA		36	69
Antibiotics	15	100	25	100	12	100	52	100
IVIG	6	40	15	60	5	42	26	50
Corticosteroid	1	7			1	8		
Chemotherapy	1	7	21	84	1	8	23	44
Supportive	15	100	25	100	12	100	52	100
Recovered from HPS	14	93	13	52	10	83	36	69
Dead from HPS	1	7	12	48	2	17	16	31
Dead from subsequent disease	0		4	16	0		1	2
Lost to follow-up	1	7	2	8	1	2	4	8

IAHS = infection-associated hemophagocytic syndrome, MAHS = malignancy-associated hemophagocytic syndrome, IVIG = intravenous immunoglobulins, HPS = hemophagocytic syndrome

Table 3. A statistic analysis of the outcome for each etiology group.

	IAHS	MAHS	Idiopathic
Survival proportion after acute phase (%)	93	56	83
Survival proportion at 5 year (%)	93	36	83
95%CI* for proportion (Wilson method) (%)	70.2 to 98.8	20.2 to 55.5	55.2 to 95.3
Standard error	0.064	0.096	0.108

* 95% confidence interval
IAHS = infection-associated hemophagocytic syndrome,
MAHS = malignancy-associated hemophagocytic syndrome

were made only from bone marrow biopsy, 2 from lymph node biopsy, and one each from splenectomy and liver biopsy. Post mortem diagnosis were achieved in 2 cases. Malignant diseases associated with HPS in this series are shown in Table 5. All, except 4 MAHS who died shortly after admission, received chemotherapy to treat their underlying malignancies. One patient with peripheral T-cell lymphoma (PTCL) received high dose chemotherapy followed by autologous peripheral blood stem cell transplantation (PBSCT) and is now disease free 6 years post transplantation. Twelve MAHS patients (48%), 9 of which were lymphomas, died during the acute phase. Another 4 patients died from their subsequent malignancies. The Kaplan-Meier survival analyses are shown in Fig. 4. Survival in the acute phase was 52 per cent but five-year DFS was expected to be 36 per cent for the MAHS group.

Twelve patients were classified in the idiopathic group. Extensive work-up included; hemoculture, serology for several viruses, autoimmune work up and bone marrow aspiration were performed and excluded any known etiology. Two patients died in the acute phase and 10 of 12 (83%) survived. The survival analysis is also shown in Fig. 4.

The survival of patients aged less than and more than 3 years were comparatively analysed and revealed a poorer prognosis for the former with statistical significance (p=0.004). The Kaplan-Meier survival curves comparing the outcome between the group of patients aged less than (n=29) and more than (n=23) 3 years are shown in Fig. 5. A comparative study of patients who received (n=30) and did not receive (n=22) IVIG were also analysed but the outcome had no statistically significant difference. (p>0.05)

DISCUSSION

In this report, the authors retrospectively analysed 52 patients with secondary HLH. Unlike

Table 4. Associated organisms and clinical outcome in IAHS diagnosed at Siriraj Hospital between 1989-1998 in 15 patients.

Organisms	N	Treatment	Alive		Dead	
			n	%	n	%
Bacteria						
Salmonella spp	3	Antibiotics, IVIG (1/3)	3	100	0	
Enterobactor	2	Antibiotics, IVIG (1/2)	2	100	0	
Staphylococcus	2	Antibiotics, IVIG, steroid (1/2)	2	100	0	
Serratia marcescens	1	Antibiotics	1	100	0	
Virus						
Dengue	3	Antibiotics, IVIG (1/3)	2	67	1	33
Ebstein-Barr virus	1	Antibiotics, steroid, IVIG, etoposide, vinblastine	1	100	0	
Parasites						
Malaria *(P vivax 1, P falciparum 1)*	2	Anti-malarial drug	2	100	0	
Penicillium marneffei	1	Antibiotics, antifungal, IVIG	1	100	0	

Table 5. Malignant diseases in 25 patients with MAHS diagnosed at Siriraj Hospital between 1989-1998.

Diagnosis	N
Large cell lymphoma	
T cell (TCL)	7
Anaplastic large cell (ALCL)	1
Non-hodgkin's lymphoma, unclassified	7
Acute leukemias	
Acute lymphoblastic leukemia	3
Acute myeloblastic leukemia	1
Acute erythroleukemia	3
Myelodysplastic syndrome	1
Langerhans'cell histiocytosis	1
Histiocytic sarcoma	1

in other literature, identifying causes were found in the majority of cases (76.9%) and cases with MAHS presented in a higher proportion (48%).

Infection-associated HLH

The mean age of IAHS group in this study was higher than other groups. The causative organisms in this report were mainly bacterias, especially salmonella species. Many other patients with salmonella infection and other bacterial sepsis who were treated at our department had cytopenias but to a lesser extent and bone marrow examination was not persued. Thus, the incidence of HLH associated with salmonella infection or other gram-negative bacterias may be even higher. Two patients with malaria and one with Penicillosis were diagnosed from bone marrow aspiration specimen. The one with P. maneffei was consequently found to have transplacental transmitted HIV infection and was the only case with underlying immunocompromised in the IAHS group.

Viral associated HLH (VAHS) as originally described by Risdall et al in 1979[31] was found in 4 cases in the present series. Interestingly, three of them had dengue hemorrhagic fever. One patient in this group, who had dengue hemorrhagic shock syndrome and developed hepatic and renal failure, died shortly after admission. The pathophysiology of this HPS may be due to viral induced, or associated with multiple organs failure as described by Gauvin F et al[32]. The cytokines released which were responsible for plasma leakage syndrome and shock stage in dengue shock syndrome must be another possibility, which play a major role in causing HPS in dengue infection.

EBV- associated HLH was known to have the worst prognosis in IAHS[33-37]. The authors reported here a 4 year-old boy who presented with typical clinical manifestations of infectious mononucleosis syndrome; prolonged fever, tonsillar patches, hepatosplenomegaly, cervical lymphadenopathy and jaundice. His serology study proved to be acute EBV infection. He developed progressive and severe pancytopenia with severe hepatic dysfunction. Corticosteroid and IVIG therapy failed to improve his clinical course. Liver and lymph node biopsy were performed and underlying malignancy was ruled out. He was then treated with the combination of

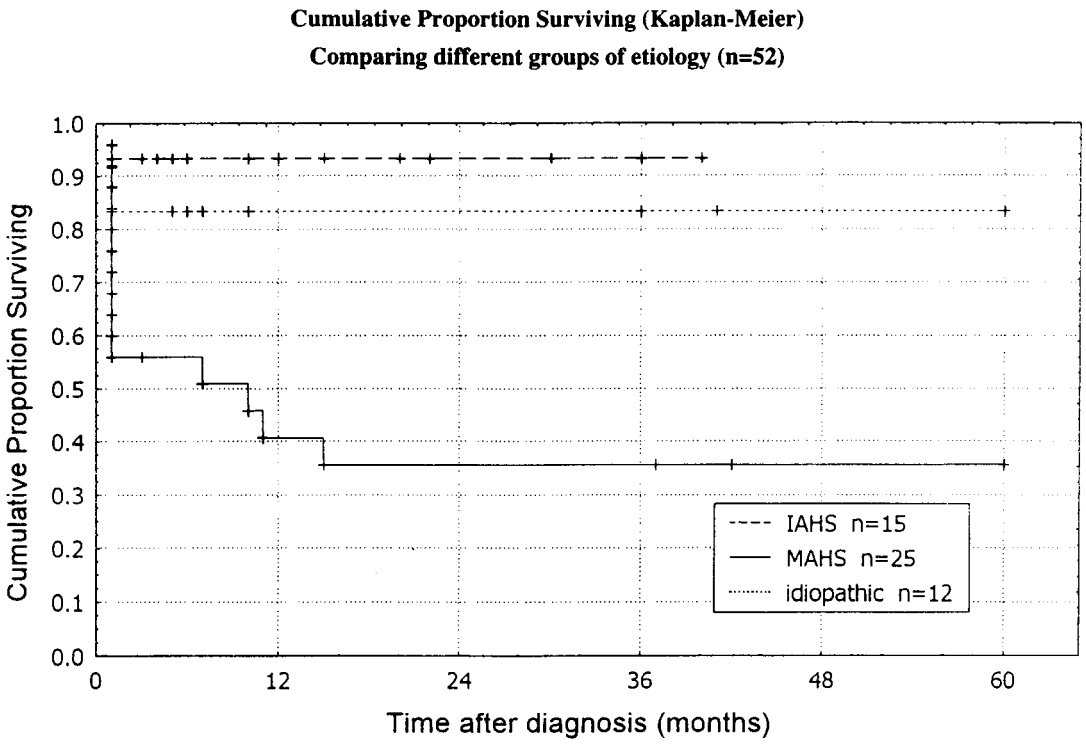

Fig. 4. Kaplan-Meier survival analysis of 52 HLH patients by etiology groups. The difference is statistically significant (p = 0.005). The 95 per cent confidence interval (95%CI) for the difference is 0.342 to 0.798.

HLH = hemophagocytic lymphohistiocytosis

vinblastine and etoposide, which resulted in dramatic response. The chemotherapy had to be continued for 4 months until his clinical remission and the patient has remained free of symptoms for 4 years without therapy.

Malignant-associated hemophagocytic syndrome (MAHS)

The most often reported lymphoma associated HLH (LHLH) in the literature is anaplastic large cell lymphoma, T/NK cell lymphoma, and adult B-cell lymphoma[24,27,29,38-41]. Eight cases in this series were T-cell lymphoma and 7 others were unspecified type diffuse non-Hodgkin's lymphoma. In most cases, initial bone marrow aspirations were nondiagnostic. The patients often underwent multiple bone marrow aspirations and biopsies, or biopsies from lymph nodes, liver or skin before the diagnosis was made. It is important to be able to recognize the small population of neoplastic cells in the bone marrow smear, which should lead to prompt treatment of the underlying malignancies. Flow cytometry and immunopathology may help in the diagnosis of T or B cell lymphoma. Clonal proliferation and cytogenetic studies may also be helpful to confirm a diagnosis of malignancy. The death rate during the acute phase was high in LHLH (60%) compared to other associations (30%) in the MAHS group. The survival analysis comparing outcome of the three etiology groups confirmed the poorest prognosis of MAHS with statistical significance.

B-cell lymphoma-associated hemophagocytic syndrome (B-LAHS) is extremely rare in Western countries but has recently been increasingly reported in Asian literature, especially Japan[27,28]. Most cases were reported in adult patients. The authors

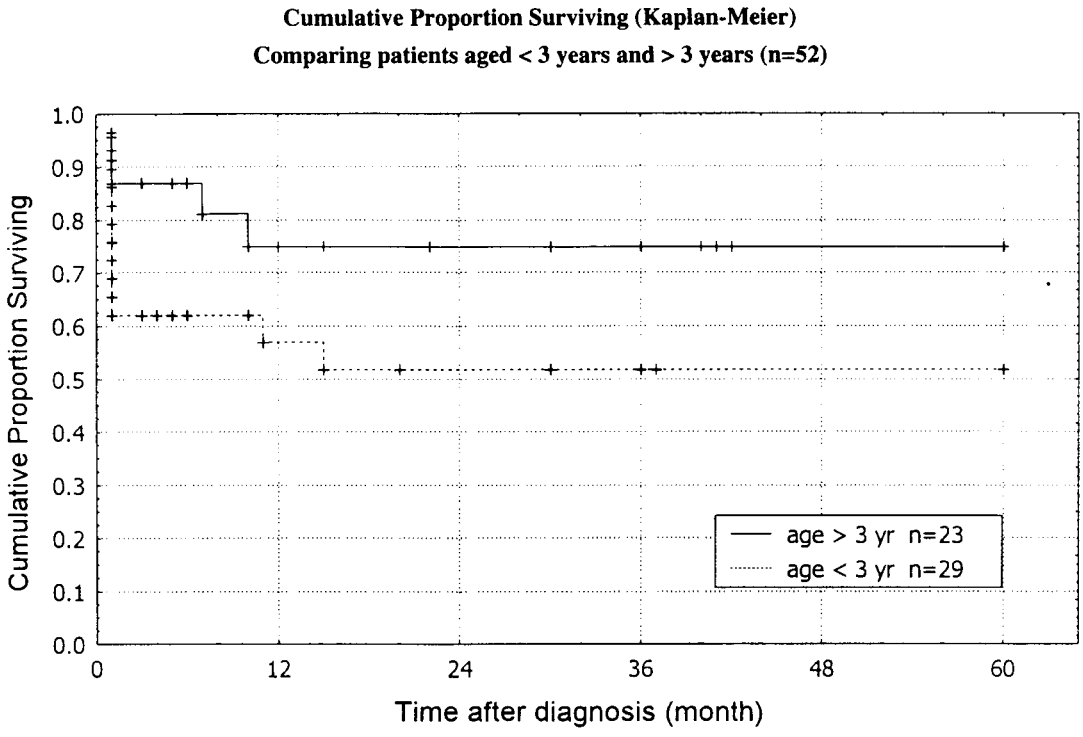

Fig. 5. Kaplan-Meier survival analysis of 52 HLH patients, comparing 2 age groups; >3 years and <3 years. The difference is statistically significant (p = 0.004). The 95 per cent confidence interval (95%CI) for the difference is 0.342 to 0.798.

HLH = hemophagocytic lymphohistiocytosis

did not confirm the diagnosis of B-LHLH in this pediatric series. The prognosis was usually poor and may need high-dose chemotherapy followed by PBSCT to improve the survival rate.

Idiopathic Hemophagocytic lymphohistiocytosis (Idiopathic HLH)

An extensive evaluation for an infectious agent, autoimmune disease or malignancy failed to identify the cause in this group of patients. Limited availability for several virus serology tests in the institute limited the diagnosis of VAHS. Most cases in this group should have been classified in the IAHS group. They were treated with supportive approaches and the outcome was not significantly different from those of the IAHS group. In infant HLH, a primary or familial hemophagocytic lymphohistiocytosis should always be a differential diagnosis. Prompt treatment with chemotherapy and stem cell transplant may help children with this diagnosis.

SUMMARY

In children with hemophagocytic lymphohistiocytosis, an extensive investigation for infectious pathogen is strongly recommended. For patients who had a progressive clinical course after appropriate antimicrobial and full supportive therapy, especially those aged less than 3 years and massive hepatosplenomegaly, an evaluation for malignancy, especially lymphoma should be aggressively pursued. Prompt treatment appropriate for the underlying etiology of HLH is the key for success in improving the outcome of this fatal syndrome.

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กลุ่มอาการฮีโมฟาโกซัยโตซิสทุติยภูมิในเด็ก : การศึกษาสาเหตุและผลการรักษา

กวิวัณณ์ วีรกุล, พ.บ., กลีบสไบ สรรพกิจ, พ.บ.*,*
วรวรรณ ตันไพจิตร, พ.บ., จุฬารัตน์ มหาสันทนะ, พ.บ.*, นงนภา จิรรัตนโสภา, พ.บ.**

การศึกษาผู้ป่วยเด็ก 52 รายที่ได้รับการวินิจฉัยว่าเป็นกลุ่มอาการฮีโมฟาโกซัยติค ที่ภาควิชากุมารเวชศาสตร์ โรงพยาบาลศิริราช ระหว่างปี พ.ศ. 2533–2542 พบว่าสัมพันธ์กับการติดเชื้อ 15 ราย สัมพันธ์กับโรคมะเร็ง 25 ราย และไม่พบสาเหตุ 12 ราย เชื้อสาเหตุที่พบบ่อยที่สุดได้แก่ เชื้อซัลโมเนลลา และ ไวรัสเดงกี ส่วนมะเร็งที่พบบ่อยที่สุดได้แก่มะเร็งต่อมน้ำเหลือง (ร้อยละ 60) โดยเฉพาะอย่างยิ่งชนิด T cell ในรายงานนี้พบอัตราส่วนของผู้ป่วยที่มีความสัมพันธ์กับมะเร็งมากกว่าในรายงานอื่น ๆ ผู้ป่วย 22 รายจาก 25 รายมีภาวะฮีโมฟาโกซัยติคเป็นอาการนำมาก่อนการวินิจฉัยโรคมะเร็ง การรักษาประกอบด้วยการรักษาเฉพาะ ในรายที่ทราบสาเหตุ และการรักษาประคับประคองด้วยเลือดและส่วนประกอบของเลือด การให้สเตียรอยด์ การให้อิมมูโนโกลบูลินทางเส้นเลือดดำ และการให้ยาเคมีบำบัด อัตราตายจากกลุ่มอาการฮีโมฟาโกซัยติคเท่ากับร้อยละ 28.8 ปัจจัยเสี่ยงที่ทำให้การพยากรณ์โรคเลวได้แก่การมีอายุน้อยกว่า 3 ปี (p=0.004) และการสัมพันธ์กับโรคมะเร็ง (p=0.005)

คำสำคัญ : กลุ่มอาการฮีโมฟาโกซัยติค, ทุติยภูมิ, กลุ่มอาการฮีโมฟาโกซัยติคจากการติดเชื้อ, กลุ่มอาการฮีโมฟาโกซัยติคจากโรคมะเร็ง

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จดหมายเหตุทางแพทย์ ฯ 2545; 85 (ฉบับพิเศษ 2): S530–S541

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