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Hemophagocytic Lymphohistiocytosis: A Four-Year Experience

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Abstract: Hemophgocytic lymphohisiocytosis is one of the Histiocytosis subgroup that results from over stimulation of macrophages in tissue. Upon presence of an underlying genetic factor it classified into 2 groups: Familial Erythrophagocytic Syndrome (FEL) and Infection Associated Hemophagocytic Syndrome (IAHS). In our center (Tabriz Children's Hospital) during recent four years (2002-2006) we finded 5 cases of this disease according to clinical and bone marrow aspiration findings. Four cases were male and one was female. All had hepatosplenomegaly and fever, 4 cases had pancytopenia and 1 last had thrombocytopenia. Four had elevated liver enzymes three were diagnosed as FEL and two as IAHS. Finally, with early diagnosis of disease, we can improve prognosis with pretreatment of chemotherapy, bone marrow transplantation and other supportive cares.

Key words: Hemophagocytosis, bone marrow, transplantation, FFL, IAHS

INTRODUCTION

Histiocytosis is the term that has been applied to a broad heterogeneous category of disorders, characterized by abnormal infiltration and accumulation of monocytes and macrophages in affected tissues (Philip and Poplack, 2006). The term "*Histiocytosis*" was proposed for the first time by Lichtenstein and Histiocytosis (1953). Although, the disorders is uncommon, but its diagnosis and treatment have been considered as a clinical challenge for pediatricians worldwide.

Three syndromes of histiocytosis have been defined, mostly based on their pathogenesis.

Langerhans Cell Histiocytosis (LCH): Formerly known as "*Histiocytosis X*", it is main proliferative disorder of Langerhans cells. The cell of LCH are characterized by reactivity for S100 (Wood *et al*., 1985), immonoreactivity for CD1a antigen (Murphy *et al*., 1983) and ultrastructural organelle kown as the Birbeck granule (Emile *et al*., 1995).

Hemophagocytic Lymphohistiocytosis (HLH): Represent the largest group of disorders and include the nonmalignant histiocytoses in the normal monocytes-macrophage frequently in a mixed lympho-histiocytic infiltrate (Philip and Poplack, 2006). It is the result of over stimulation of macrophages, their proliferation in bone marrow and infiltration into affected tissues. This disorder is classified into 2 groups: "Familial Erythrophagocytic Syndrome (FEL)", (characterized by the presence of a positive family history) (Chan *et al*., 1987) and "Infection Associated Hemophagocytic Syndrome (IAHS)".

Malignant Histiocytosis: Is the result of malignant transformation of monocyte-macrophage cell line (Philip and Poplack, 2006).

CASE REPORT

In recent four years (from March 2002-2006) all clinical, laboratory and bone marrow aspiration findings of six patients admitted to "Tabriz Children's Hospital (Philip and Poplack, 2006)" were consistent with the diagnosis of "Hemophagocytic Lymphohistiocytosis" (Table 1 and 2).

Case 1: A 20 months old girl with consanguineous parents, presented with prolonged fever and coryza. This patient was admitted to the hospital because of prolonged high-grade fever and hepatosplenomegaly. She later developed ascitis, pleural and pericardial

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Table 1: Clinical and laboratory characteristic of patient

	1	2	3	4	5
Sex	F	M	M	M	M
Age of onset (in month)	20	8	17	5	9
Lymphadenopathy	+	-	-	-	+
Hepatomegaly	+	+	+	+	+
Splenomegaly	+	+	+	+	+
Ascitis	+	+	-	+	+
Pleural effusion	+	-	-	+	+
Pericardial effusion	+	-	-	-	-
Fever	+	+	+	+	+
Seizure	+	+	-	-	-
Elevated liver enzymes	+	+	-	+	+
Leukopenia	-	+	+	+	+
Anemia	+	+	+	+	+
Thrombocytopenia	+	+	+	+	+
Elevated TG		+	+	+	+
Elevated cholestrol		+	+	+	+
Esr first hour	2	2	114	5	5
Elevated direct bilirobin	+	+	-	+	+
Familial history of similar disease	+	+	-	-	-
Activated histiocytes and hemophagocytic changes in bone marrow	+	+	+	+	+
Need to chemotherapy	+	+	-	+	+
Disease causes death	+	+	-	+	-
diagnosis	FEL	FEL	IAHS	FEL	IAHS

Table 2: Clinical and laboratory findings in the hemophagocytic lymphohistiocytoses (Philip and Poplack, 2006)

Required for diagnosis	Consistent with diagnosis
Physical examination	**Physical examination**
1. Fever	1. Jaundice
2. Splenomegaly	2. Edema
	3. Lymphadenopathy
Laboratory	**Laboratory**
1. Cytopenia(affecting 2 or 3 lineags in the peripheral blood and not caused by hypocellular or dysplastic bone marrow):	1. Increased circulating solubie IL-2 receptors
• Hemoglobin < 9 g dL^{-1}	2. Hyperferritinemia
• Platelet <100*10^9 L^{-1}	3. CSF pleocytosis (mononuclear cell)
• Neutrophilic < 1 *10^9 L^{-1}	4. Hepatic enzyme abnormalities
2. Hypertriglyceridemia or hypofibrinogenemia (fasting triglycerides > 2 mMol L^{-1} or >3 SD of the normal value for age, fibrinogen <1.5 g L^{-1} or <3 SD)	5. Increased VLDL*
	6. Decreased HDL**
	7. Decreased natural killer cell
3. Histopathologic criteria: Hemophagocytosis in bone marrow, spleen or lymph nodes,no evidence of Malignancy	

* Very low density lipoprotein, ** High density lipoprotein

effusions and seizure. Her laboratory findings included anemia, thrombocytopenia, low ESR, prolonged PT and PTT and elevated serum level of liver enzymes and bilirubin. Ultrasonographic examinations verified hepatosplenomegaly and multiple lymphoadenopathies around pancreas and liver. Bone marrow aspiration showed infiltration of activated histiocytes. The patient died following a seizure attack during her first admission.

Case 2: Our second case was the younger brother of the first case, 8 months old when presented with fever and hepatosplenomegaly after symptoms resembling common cold. Later, this patient was admitted several times due to anemia, thrombocytopenia, leukopenia, ascitis and seizures. His bone marrow aspiration showed infiltration of activated histiocytes and hemophagocytosis. The patient's fate was not different from his elder sister as he died despite of intensive treatment with glucocorticoids and vinblastin

Case 3: Third case was a 17 months old boy, presented with fever, cough and hepatosplenomegaly. This patient was admitted to our center because of signs and symptoms of pneumonia that had been begun three weeks prior to admission. He later developed pericardial effusion. Further investigations revealed pancytopenia, activated histiocytes and hemophagocytic changes in bone marrow. The patient was discharged from hospital after full remission of the disease.

Case 4: A five months old male infant presented with fever, hepatosplenomegaly and cholestasis after four weeks of an illness with common-cold-like symptoms. Later, pancytopenia and elevated liver enzymes were seen in his repetitive admissions. His bone marrow study revealed activated histiocytes and hemophagocytic changes. The patient expired from pulmonary hemorrhage, in spite of treatment with vinblastin, ethoposide and glucocorticoids.

Case 5: The fifth patient, a 9 months old boy who presented with acute development of jaundice, anemia and hepatosplenomegaly. This patient developed ascitis and pleural effusion during his hospital course. Further investigations showed pancytopenia and elevated serum levels of triglyceride, bilirubin and liver enzymes. Activated histiocytes and hemophagocytic changes were seen in his bone marrow aspirates. This patient recovered after antibiotic therapy and some supportive measures and discharged from hospital with remission of all signs and symptoms.

DISCUSSION

Hemophagocytic Lymphohistiocytosis (HLH) falling into the class II histiocytoses category consist of those in which reactive cells of the mononuclear phagocytic cell series, excluding Langerhans' cells, are found in the lesions.Malignant transformation is not seen in HLH (and is reserved for malignant histiocytosis). HLH disorders are divided into 2 subgroups: FEL and IAHS, mostly

regarding to genetic background and familial history of similar deasise. An autosomal recessive inheritance has been recognized for FEL,since the initial studies of Farquhar and Claireaux (1952).

FEL is an almost always rapidly fatal course (unless being treated by bone marrow transplantation). Recently, several specific chromosomal abnormalities have been documented in FEL these include linkage to 9q21.3-22 and 10q21-22 and possibly to other loci (Ohadi *et al*., 1999; Dufourcq-Lagelouse *et al*., 1999). The serum level of interleukin-2 (IL-2) is decreased in these patients, secondary to an increase in serum level of Soluble IL-2 Receptor (SIL2-R) (Komp *et al*., 1989). This results in abnormal regulation of immune response and over production of cytokines by T-cells, leading to proliferation of macrophage-monocyte cell line.the pathophysiology of disease include an element of immuonodeficency that may be responsible for opportunistic infections (Ladisch *et al*., 1978). In IAHS similar changes occur but no genetic predisposition is seen. Excessive proliferation of histiocytes can result in dysfunction of reticuloendothelial system (including: bone marrow, spleen, red pulp, hepatic sinusoids and lymph nodes). Disease usually presents with fever, weight loss, hepatosplenomegaly, pancytopenia, hepatic dysfunction, coagulopathies and neurological disorders (seizure). Symptoms often present after an infectious disease. A combination of clinical evidences, laboratory findings and bone marrow aspirate, frequent benign-appearing histiocytes, are necessary to confirm the diagnosis (Philip and Poplack, 2006). These criteria are shown in Table 2.

The management of this disease is mainly based on supportive measures and treatment of hematological disorders, coagulopathies and predisposing infections (acyclovir for EBV). Immunosuppressive drugs such as vinblastin and ethoposide are recommended for treatment of FEL (Fischer *et al*., 1985) and etoposide and cyclosporine for IAHS (Henter *et al*., 1997). However; FEL often has a fulminant course and most patients die from disease shortly after presentation or even diagnosis. Allogenic bone marrow transplantation is considered the treatment of choice when an appropriate donor is available. According to results of a recent study, allogenic bone marrow transplantation resulted in a 62% estimated 3-year survival (Henter *et al*., 2002), whereas FEL is almost uniformly fatal when treated only with chemotherapy (Arico *et al*., 1996). Plasma exchange therapy is another experimental treatment whose effectiveness is under study (Ladisch *et al*., 1982).

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