INTRODUCTION

Macrophages represent the tissue component of the reticuloendothelial system, and play a wide variety of important roles in the body, including phagocytosis of microbes or foreign bodies, processing and presentation of microbial antigens, and phagocytosis and clearance of senescent or apoptotic cells. Macrophages are sometimes stimulated inappropriately via the dysregulation of host immunity and subsequently phagocytose self blood cells, causing hemophagocytic syndrome (HPS) (hemophagocytic lymphohistiocytosis, HLH) ***(Kumakura et al., 1997).***

HPS is a clinicopathological life-threatening but rare condition characterized by the activation of macrophages or histiocytes with prominent hemophagocytosis in bone marrow and other reticuloendothelial systems. Clinical characteristics of this syndrome include high fever, hepatosplenomegaly, pancytopenia, liver dysfunction, coagulopathy and hyperferritinemia ***(Fisman, 2000).***

Scott and Rob-Smith have reported a neoplastic disorder, showing hemophagocytosing histiocytes and systemic proliferation of the precursors of histiocytes in 1939. They termed this condition as histiocytic medullary reticulosis(HMR). This description might have been the first report of HPS, and was succeeded by the disease entity

of malignant histiocytosis (MH), proposed by Rappaport ***(Reiner et al., 1998).***

In 1952, familial hemophagocytic reticulosis (familial hemophagocytic lymphohistiocytosis; FHL) was reported by Farquhar and Claireaux. FHL occurs in infants and is regarded as primary HPS ***(Filipovich, 2002).***

In 1979, Risdall et al.reported nineteen patients with active viral infection, whose bone marrow showed histiocytic hyperplasia with prominent hemophagocytosis. These cases showed high fever, constitutional symptoms, liver dysfunction, coagulation abnormalities, peripheral blood cytopenias, hepatosplenomegaly and lymphadenopathy. They proposed this condition as virus-associated hemophagocytic syndrome (VAHS). VAHS is the first report of reactive or secondary HPS. To date, reactive HPS is known to be associated with not only virus but also with various types of disseminated infections, such as bacteria, tuberculosis, fungi and parasites; HPS associated with an underlying infection is therefore called infection-associated hemophagocytic syndrome (IAHS) ***(Ishi et al., 2005) .***

On the other hand, the origin of the proliferating cells in MH has been thought to be the precursor of histiocytes, but then it has been clarified that the proliferating cells are lymphoma cells. Thus, 'true MH', which is recognized as the neoplastic disease of immature histiocytes, is thought to be very rare now, and reactive HPS associated with lymphoma

is termed lymphoma-associated hemophagocytic syndrome (LAHS) ***(Schimazaki et al., 2000).***

In 1991, Wong et al.reported patients with active SLE who demonstrated reactive hemophagocytosis in bone marrow. The occurrence of hemophagocytosis was associated with activity of SLE itself, and they proposed the disease entity of acute lupus hemophagocytic syndrome (ALHS). In 1995 and 1997, cases of reactive HPS were reported, which were associated with autoimmune diseases other than SLE, and proposed a new disease entity, autoimmune-associated hemophagocytic syndrome (AAHS) ***(Kumakura et al., 2004).***

AIM OF THE WORK

This review aims at providing full knowledge of the hemophogocytic syndrome as regards its clinical types, pathophysiology, diagnosis, differential diagnosis, treatment and prognosis.

DEFINITION AND CLASSIFICATION OF HPS

Hemophagocytic lymphohistiocytosis (HLH) is a rare and potentially fatal disorder of normal but overactive histiocytes. In Hemophagocytic lymphohistiocytosis there is an overwhelming activation of normal T cells and macrophages which can cause clinical and hematological alterations. The clinical presentation is in many aspects similar to the so-called SIRS. And death is inevitable in the absence of treatment.

HLH is not a single disease, but a clinical syndrome that can be encountered in association with a variety of underlying conditions leading to the same characteristic hyperinflammatory phenotype that can be classified into primary (genetic) and secondary (acquired) types. The primary type is subclassified into familial & immune deficiency disorders (Chediak-Hegashi synd., Griscelli's synd., X-linked lymphoproliferative synd.). The acquired type is associated with other diseases (infection, metabolic diseases, autoimmune diseases, malignancies especially lymphoma) (Table 1) ***(Fisman, 2000).***

I. Genetic hemophagocytic lymphohistiocytosis:

Genetic (primary) HLH is inherited in an autosomal recessive or X-linked manner and can be divided into two subgroups: familial HLH (FHLH), first described by Farquhar

and Claireaux in 1952, and the distinct immune deficiencies Chédiak-Higashi syndrome 1 (CHS-1), Griscelli syndrome 2 (GS 2), and X-linked proliferative syndrome (XLP).

a) Familial HLH:

In FHLH, the clinical syndrome of HLH is the primary and only manifestation. In a retrospective study, the incidence was estimated as 0.12/100,000 children per year, i.e. one per 50.000 live born. There is a slight male preponderance. FHLH has been reported from many different countries. As an autosomal recessive disease, it is found especially in ethnic groups where consanguineous marriages are common. In the German Registry, half of the children with another afflicted sibling came from a consanguineous marriage and a third of the patients with presumed genetic disease because of age below 1 year, disease progression or relapse, had consanguineous parents ***(Henter et al., 1997)***.

The onset of disease is below 1 year of age in 70-80% of the cases. A symptom-free interval after birth is typical; only about 10% of the patients become symptomatic within the 1st 4 weeks, and a few may have symptoms already at birth. Several late-onset cases in adolescence and even adulthood have been reported. In the same family, the age of onset is usually similar in the first and second affected child, but a time lag of 1-3 years is possible ***(Clementi et al., 2002)***.

Table (1): Classification of hemophagocytic lymphohistiocytois

Genetic HLH

- Familial HLH (Farquhar disease)

  Known gene defects

  Unknown gene defects
- Immune deficiency syndromes

  Chédiak-Higashi syndrome 1

  Griscelli syndrome 2

  X-linked lymphoproliferative syndrome

Acquired HLH

- Exogenous agents (infectious organisms, toxins)
- Infection-associated hemophagocytic syndrome (IAHS)
- Endogenous products (tissue damage, metabolic products)

Rheumatic diseases

- Macrophage activation syndrome (MAS)

Malignant diseases

- Lymphoma-associated hemophagocytic syndrome.
- Others; e.g. multiple myeloma, acute leukemia, hepatocellular carcinoma.

(Fisman, 2000)

b) Immune deficiency syndromes:

CHS 1, GS 2 and XLP are immune deficiencies in which the development of HLH is sporadic, though frequent. HLH is often the presenting symptom, but may also occur later during the course of the disease.

Patients with CHS 1, an autosomal recessive disease, express variable degrees of oculocutaneous albinism, easy bruising and frequent pyogenic infections, due to decreased chemotaxis and bactericidal activity. Their white blood cells exhibit characteristic giant inclusion bodies (lysosomes), which resemble Doehle bodies in granulocytes and are of purple color in lymphocytes and monocytcs. These can be easily identified in a blood or bone marrow smear. The clinical picture of HLH in CHS 1, also called the "accelerated phase," cannot be distinguished from other genetic or acquired HLH forms ***(Shiflett et al., 2002)***.

Patients with GS 2 another autosomal recessive disease with hypopigmentation, have various degrees of neutrophil dysfunction, but lack the giant granules. Episodes of HLH are frequent and life-threatening ***(Klein et al., 1998).***

XLP, also called Purtilo syndrome, is transmitted in an X-linked way. HLH triggered by Epstein-Barr virus (EBV) is the cause of death in half of the patients. Other

manifestations are hypogammaglobulinemia, malignant lymphoma or aplastic anemia ***(Purtilo et al., 1997)***.

II. Acquired hemophagocytic lymphohistiocytosis:

Acquired (secondary) forms of HLH can occur in all age groups. There are no data about the incidence of acquired forms. From numerous case reports, however, it appears that acquired cases are more common than genetic cases.

The clinical picture of HLH can be induced by a variety of infectious organisms. The first report was by **Risdall et al**., who described several patients, mostly adults after organ transplantation, the majority of whom had evidence of a viral infection and presented with clinical signs and symptoms of HLH. It was designated as virus-associated hemophagocytic syndrome (VAHS). Subsequently, it became clear that occasionally also other organisms could trigger HLH, such as bacteria, protozoa or fungi ***(Janka et al., 1998)***. Among these, infection by Leishmania seems to be a frequent trigger. It also accounted for 12% of the acquired cases in the German Registry, and as in the report by Gaignaire, the majority of the patients had not visited a foreign country. The term infection-associated hemophagocytic syndrome (IAHS) is now commonly used instead of VAHS ***(Gagnaire et al., 2000).***

Whereas in the first report by ***Risdall et al***. the majority of the patients had an acquired iatrogenic immune deficiency, most patients in subsequent reports had no known genetic or acquired immune defect. Not unlike familial HLH, IAHS proved to be a dangerous disease: a review of the published cases in children diagnosed with IAHS before 1996 reported a mortality of 50%. In this series most patients had only received supportive care. More than half of the patients were from the Far East, and EBV was the triggering organism in 74% of the children in whom an infectious agent could be identified ***(Janka et al., 1998)***.

The presence of an infection was originally thought to discriminate between familial and acquired forms. However, it is now clear that most episodes in the genetic forms of HLH are also triggered by infections. This cannot be emphasized enough since appropriate therapy should not be withheld when an infectious agent has been found ***(Arico et al., 1996)***.

Acquired HLH in association with malignant diseases, especially lymphomas (lymphoma-associated hemophagocytic syndrome, LAHS), is for unknown reasons more common in adults than in children. HLH can develop before or during treatment, associated with an infection or without a known triggering factor. In children HLH occurs especially in large cell aplastic lymphomas.

Cases formerly diagnosed as histiocytic medullary reticulosis or malignant histiocytosis included patients with LAHS, but also IAHS ***(Miyahara et al., 2000).***

A series of adult patients with HLH and a variety of autoimmune diseases including lupus, rheumatoid arthritis, Still's disease, polyarteritis nodosa, mixed connective tissue disease, pulmonary sarcoidosis, systemic sclerosis, and Sjogren's syndrome has been reported. Some of these patients developed HLH following infection with a microorganism while others developed HLH with the onset of their primary disease ***(Dhote et al., 2003).***

Cytophagic histiocytic panniculitis, a rare systemic disorder consisting of lobular panniculitis, fever, hepato-splenomegaly, liver failure, infiltration with cytophagic histiocytes, and an association with subcutaneous panniculitis-like T-cell lymphoma, may also have features of secondary HLH ***(Marzano et al., 2000).***

PATHOPHYSIOLOGY OF HPS

The pathophysiology of HPS and related disorders appears to involve the excessive activation of lymphocytes and macrophages resulting in cytokine production by these cells, inhibition of apoptosis and genetic mutatios that also contribute in the pathophysiology of HLH ***(Takada et al., 2004)***.

This profound cytokine activation results in the organ dysfunction characteristic of the disorder, including hyperferritinemia and hyperlipidemia, as well as macrophage activation. The resulting organ infiltration and excessive phagocytosis in the bone marrow, liver, and other organs result in the clinical features of the syndrome. Similar observations are noted in the closely related disorder macrophage activation syndrome (MAS), which occurs in patients with systemic onset juvenile rheumatoid arthritis (SOJRA) and other autoimmune diseases ***(Takada et al., 2003)***.

At an early stage, decreased proliferative responses to mitogenic stimulation were reported in FHL patients. Another early, striking and important, but for long unexplained, finding in FHL patients was their low or absent T and NK-cell-mediated cytotoxic activity, activity that was restored subsequent to BMT ***(Egeler et al., 1998).***

A third remarkable feature, a pronounced hypertriglyceridemia associated by a profound reduction of the lipoprotein lipase activity, has now been suggested to be caused by pro-inflammatory cytokines. Interestingly, hypertriglyceridemia and lipoprotein lipase suppression was actually a key to the initial purification of TNF-α. Overall, there is a striking similarity between the biologic changes induced by pro-inflammatory cytokines and the clinical and laboratory findings in FHL ***(Henter et al., 1998)***.

Cytokines reported to be commonly elevated in FHL include soluble interleukin (IL)-2 receptor, IL-6, interferon-γ, and TNF-α , i.e., pro-inflammatory cytokines produced by Th1 cells . Later studies revealed elevated plasma levels of IL-12 and IL-10. The first stimulates the production of Th1 cytokines, and the second suppresses Th1 responses. By contrast, the Th2-stimulating IL-4 was not increased ***(Osugi et al., 1997).***

I. Role of apoptosis inhibition in HLH:

The underlying mechanism resulting in this symptom-inducing hypercytokinemia remained to be elucidated. Subsequent cytokine studies revealed, surprisingly, low levels of IL-1β but elevated levels of the IL-1 receptor antagonist. This suggested a possible defect of IL-1b converting enzyme (ICE)—a member of the caspase family (caspase 1)—and in 1996 led to the hypothesis that a genetic defect affecting apoptosis

(programmed cell death) was of pathophysiologic importance in the disease (Fig. 1). This hypothesis was supported by other observations, such as the deficient cytotoxicity and the accumulation of non-malignant cells ***(Henter et al., 1998).***

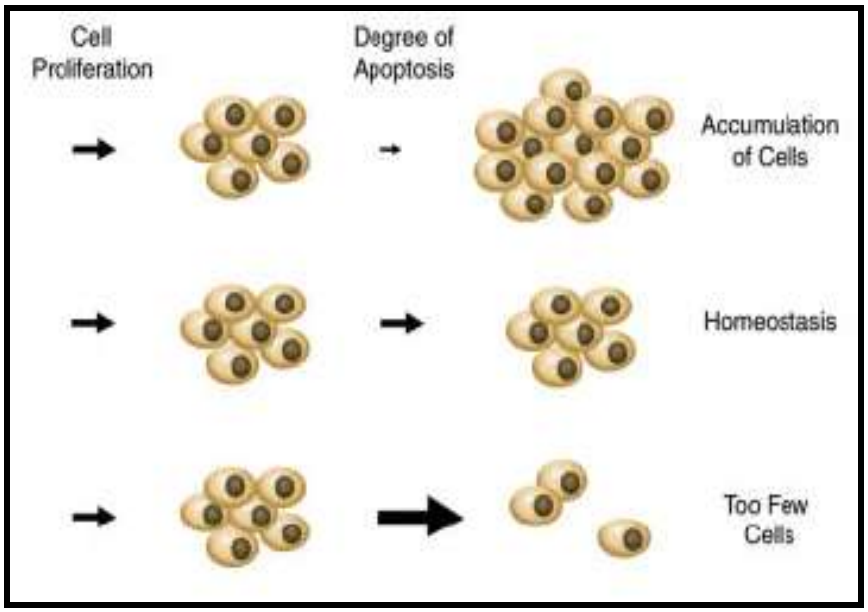

Figure (1): Simplified illustration of the contribution of apoptosis to tissue homeostasis. According to this construct, FHL is caused by reduced triggering of apoptosis, and results in an inappropriate proliferation of cells, as illustrated in the upper part of the figure ***(Fadeel et al., 1999).***

Analyses of apoptosis induction in IL-2-activated lymphocytes from FHL patients later confirmed a markedly reduced degree of spontaneous activation of caspase-3-like enzymes in patients sampled prior to etoposide therapy. It was also shown that cells obtained from these patients are susceptible to apoptosis triggering in vitro, indicating that it is the physiological trigger of apoptosis in vivo that may be deficient ***(Fadeel et al., 1999).***

The hypothesis that the accumulation of cells in FHL might be due to defective triggering of apoptosis was further supported by observations made in autoimmune lymphoproliferative syndrome (ALPS) which has clinical features similar to FHL. There, inherited mutations were documented in the gene encoding Fas, a key regulator of apoptosis. The FHL studies provided suggestions for future investigations, attempting to characterize the underlying aberrations at the molecular level. The major pathways in apoptosis triggering, such as the Fas ligand and the perforin-granzyme system, were suggested to be brought into sharper focus ***(Fadeel et al., 1999)*** (Fig. 2).

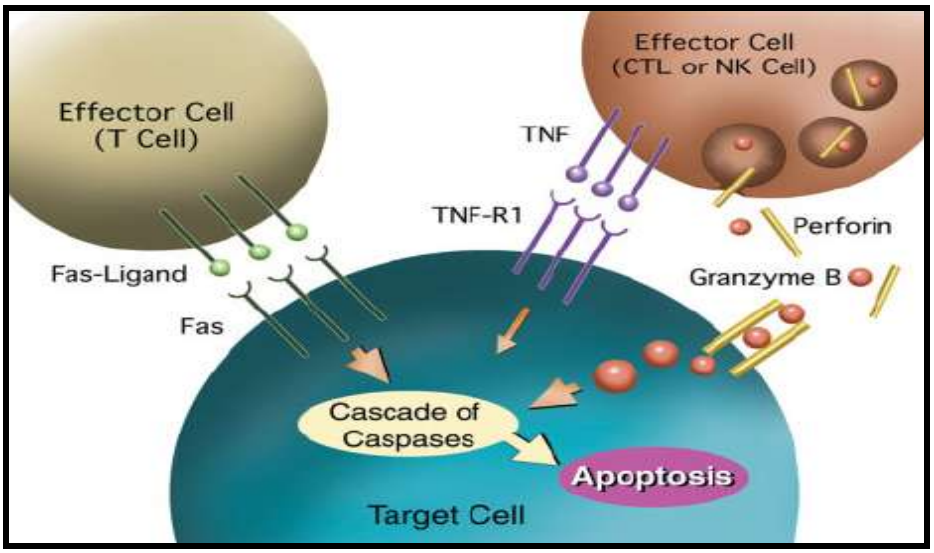

Figure (2): Schematic illustration of major pathways involved in apoptosis triggering. Effector cells such as the cytotoxic T lymphocyte (CTL) and NK cells may initiate apoptosis of target cells through the release of granzyme B and perforin. Perforin perforates the cell membrane allowing entrance of the toxic granzyme into the target cell. Other mechanisms to induce apoptosis include the tumor necrosis factor (TNF) pathway and Fas/Fas ligand interaction. Fas is deficient in ALPS type I, whereas ALPS type II affects caspase 10 in the cascade of caspases. In FHL, mutations in the gene encoding perforin have been revealed recently ***(Ericson et al., 2001).***