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REVIEW

Infections Associated With the Hemophagocytic Syndrome

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ABBREVIATIONS:
CAEBV = chronic active Epstein-Barr virus infection
CMV = cytomegalovirus
EBV = Epstein-Barr virus
FHL = familial hemophagocytic lymphohistiocytosis
HAART = highly active antiretroviral therapy
HHV = human herpes virus
HIV = human immunodeficiency virus
HPS = hemophagocytic syndrome
HSV = herpes simplex virus
HLH = hemophagocytic lymphohistiocytosis
IL = interleukin
IM = infectious mononucleosis
INF = interferon
IRIS = immune reconstitution inflammatory syndrome
NK = natural killer (cells)
PCR = polymerase chain reaction
TNF = tumor necrosis factor
VAHS = viral-associated hemophagocytic syndrome
VZV = varicella zoster virus

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ABSTRACT

The hemophagocytic syndrome (HPS) is an unusual but potentially fatal disease resulting from dysregulated activation and proliferation of natural killer (NK) cells and cytotoxic T cells. The term hemophagocytosis describes the pathological finding of activated macrophages, engulfing erythrocytes, leukocytes, platelets, and their precursor cells. The clinical appearance of the syndrome is heterogeneous, characterized by hemophagocytosis in bone marrow, liver, or lymph nodes, variable cytopenias, hyperferritinenia, hypercytokinemia, high fever, coagulation disorders, hepatosplenomegaly and lymphadenopathy. The syndrome can be either primary or secondary. Until recently, we believed that symptoms of HPS due to genetic causes generally arose during infancy and early childhood. The truth is that the first episode of HPS can occur throughout life, from prenatal to the seventh decade. With the availability of genetic testing, distinctions between primary (genetically determined) and secondary (acquired) forms of HPS have become increasingly blurred. Secondary or reactive HPS is associated with infections, autoimmune diseases, or malignancies. This review summarizes the pathogenesis, clinical and diagnostic features and management of HPS in the context of specific infections. It is important to realize that both primary and secondary syndromes can be precipitated by an infection, particularly Epstein-Barr virus (EBV) and other herpes viruses, human immunodeficiency virus (HIV), influenza, parvovirus, hepatitis viruses, as well as bacterial, fungal, and parasitic infections.

INTRODUCTION

The hemophagocytic syndrome (HPS) or hemophagocytic lymphohistiocytosis (HLH), also known as autosomal recessive familial hemophagocytic lymphohistiocytosis (FHL), familial erythrophagocytic lymphohistiocytosis, and viral-associated hemophagocytic syndrome (VAHS), is a life-threatening clinicopathological condition associated with excessive activation and expansion of macrophages and T cells (mainly CD8) leading to an overwhelming inflammatory reaction. The pathognomonic feature of HPS is the activation of well differentiated macrophages with prominent hemophagocytosis in bone marrow or lymph nodes. They may infiltrate almost any organ in the body and may account for many of the systemic features of this syndrome with hemophagocytosis throughout the reticuloendothelial system causing high fever, pancytopenia, hepatosplenomegaly, lymphadenopathy, liver dysfunction, coagulopathy and hyperferritinemia.

Conflict of interest: none declared

The syndrome was first described in 1939 by Scott and Robb-Smith.[1] Historically it is divided into primary or genetic HPS and secondary or reactive HPS. Genetic HPS is divided into two subgroups. The familial form, which was first described in 1952, is estimated to occur in one out of 30000-50000 births.[2] Sporadic cases of HPS with several genetic mutations have also been described.[3] Nowadays we know that primary HPS can occur at any age.[4] Underlying genetic mutation is found in only 40% of primary HPS cases.[3]

Underneath the large umbrella of reactive HPS disorders are those associated with infections, with malignancy and macrophage activation syndrome associated with inflammatory disorders such as systemic juvenile rheumatoid arthritis. No data exist on the incidence of infection-associated HPS. The association between HPS and infection is important since: a) sporadic and familial cases of HPS can be precipitated by infection; b) HPS can mimic infectious diseases, such as bacterial sepsis and leptospirosis;[5] c) HPS may obscure the diagnosis of a treatable infectious illness (visceral leishmaniasis).[6] Finally some secondary cases of HPS carry higher mortality than those in primary HPS (Table 1).

Early diagnosis of the syndrome is rather difficult because there are no validated diagnostic criteria and the condition may be under-recognized. This review summarizes the pathogenesis, clinical and diagnostic features and management of HPS in the context of specific infections. The scope is to increase the diagnostic awareness of clinicians since management of the syndrome relay on early diagnosis and therapeutic intervention.

TABLE 1. Hemophagocytic Syndrome Classification

Primary or genetic hemophagocytic syndrome
Familial hemophagocytic lymphohistiocytosis
Immune deficiency syndromes
• Chediak-Higashi syndrome
• Griscelli syndrome
• X-linked lymphoproliferative syndrome
• Wiskott-Aldrich syndrome
• Severe combined immunodeficiency
• Lysinuric protein intolerance
• Hermansky-Pudlak syndrome
Secondary or reactive hemophagocytic syndrome
Infection associated hemophagocytic syndrome
• Virus-associated hemophagocytic syndrome
➢ Herpes virus infection (herpes simplex virus, varicella zoster virus, cytomegalovirus, Epstein-Barr virus, human herpesvirus 6, human herpesvirus 8)
➢ Human immunodeficiency virus (HIV)
➢ Other viruses: adenovirus, hepatitis viruses, parvovirus, influenza
• Other infections associated with hemophagocytic syndrome
➢ Bacteria including mycobacteria and spirochetes
➢ Parasites
➢ Fungi
Malignancy-associated hemophagocytic lymphohistiocytosis (especially lymphoma-associated hemophagocytic lymphohistiocytosis)
Macrophage activation syndrome (associated with autoimmune diseases)

PATHOPHYSIOLOGY

The hallmark of HPS is phagocytosis of blood cells and their precursors. The central pathophysiological abnormality is cytokine dysfunction, resulting in uncontrolled accumulation of activated T-lymphocytes and histiocytes in many organs. Prolonged and excessive activation of antigen-presenting cells (macrophages, histiocytes) and CD8+ T cells, and excessive proliferation and ectopic migration of T cells results in multisystem inflammation. Several groups have found depressed or absent natural killer (NK)-cell and cytotoxic T cell activity in HPS patients and family members, although NK cell activity sometimes returns to normal when patients are in remission.[7] Defective NK cell function is associated with decreased amounts of the pore-forming protein, perforin, which may also be important in regulating T cell function.

In inherited forms of HPS several defects in genes have been described that contribute to normal cytotoxic mechanisms of NK and CD8+ cytolytic T-cell killing. Defects of these cytotoxic pathways are fundamental to the current pathophysiological understanding of HPS. Defective genes are inherited from either both parents (autosomal recessive) or from the mother alone. Since 1999, five genes which correspond with five subtypes of autosomal recessive HPS have been reported (Table 2). The perforin gene (PRF1 gene) mutation was the first described in 1999. It is localized at 10q21-22 and is especially interesting because it plays a central role in NK cell activity. This is a membranolytic protein found in the cytotoxic granules of CD8+ T lymphocytes and NK cells, acting by the creation of pore-like structure in the membrane of target cells, facilitating the entrance of cytotoxic molecules such as granzoymes into the target cell cytoplasm. Most of these gene defects are related to cytolytic granule formation and NK/Cytolytic T-lymphocyte function.

Normally there is a crosstalk between the immune system cells through contact and cytokine signaling for the homeostatic removal of cells that are superfluous or dangerous to the organism. The lack of NK cell regulation of macrophages

TABLE 2. Genes that Correspond to Familial Hemophagocytic Lymphohistiocytosis (FHL)

Gene	Protein	Action
PRF1	perforin	"killing" or elimination of abnormal immune cells
STX11 MUNC13-4 STXBP2 RAB27A	Syntaxin	facilitate the delivery of perforin to the cells which are to be killed

is assumed to lead to further activation and proliferation followed by increase in cytokine release, recruitment and proliferation of additional lymphocytes and inflammatory cells.[7] Immunologically, this uncontrolled immune response, also referred as "cytokine storm", leads to hypersecretion of proinflammatory cytokines such as interferon γ, tumor necrosis factor α (TNF-α), interleukins IL-6, IL-10, IL-12, and soluble IL-2 receptor (sCD25). Highly increased concentrations of the sCD25 are frequently detected in active HPS and correlate with poor prognosis. The end-point of these exaggerated inflammatory responses with increased cytokine secretion uncontrolled proliferation and phagocytic activity of histiocytes is responsible for necrosis and organ failure.

In acquired HPS the pathophysiology is not fully understood. The deficiency in cytolytic activity results in persistent activation of lymphocytes and histiocytes. In animal models, this is associated with failure to control infections with intracellular pathogens. Perforin knock-out mice have increased viral burden and over-whelming inflammatory response when infected with lymphocytic choriomeningitis virus[8] and are also susceptible to infections such as herpes simplex virus (HSV) and Toxoplasma gondii.[3] Decreased NK-cell cytotoxicity has also been demonstrated in reactive HPS such as Epstein-Barr virus (EBV)-associated HPS (EBV-AHPS).

CLINICAL FEATURES AND DIAGNOSIS

The heterogeneous group of HPS features sepsis-like characteristics, often resulting in multiple organ failure with high mortality. Clinical signs include prolonged fever, lymphadenopathy, hepatosplenomegaly, and occasionally a maculopapular skin rash, while laboratory findings include cytopenias, raised levels of serum ferritin, triglycerides, bilirubin, and low fibrinogen. Clinical criteria for the diagnosis of the syndrome have been recently revised (Table 3).[9] Bone marrow aspiration reveals normal maturity of all cell lineages, but infiltration with activated macrophages engulfing leukocytes, erythrocytes, platelets, and their precursors are seen. These infiltrates can be seen also in lymph nodes, liver and spleen. Some of the clinical criteria occur late in the disease process

TABLE 3. Clinical Criteria for the Diagnosis of Hemophagocytic Syndrome (HPS)

A. Molecular diagnosis (i.e. gene mutation), known to cause HLH
B. Signs and symptoms (five out of the following criteria):
(a) Fever
(b) Splenomegaly
(c) No evidence of malignancy
(d) Cytopenias (2 or 3 hematopoietic lineages on complete blood counts):
1. Hemoglobin <9.0 g/dL
2. Platelets <100x109/L
3. Neutrophils <1.0x109/L
(e) Hypertriglyceridemia and/or hypofibrinogenemia:
1. Fasting triglycerides at least 3.0 mmol/l (>265 mg/dL)
2. Fibrinogen at least 1.5 g/L
(f) Hemophagocytosis in bone marrow or spleen or lymph nodes
(g) Low or absent NK-cell activity (according to local laboratory reference used)
(h) Ferritin at least 500 μg/L
(i) Soluble CD25 (i.e., soluble IL-2 receptor) at least 2400 U/ml

HPS = hemophagocytic syndrome; HLH = hemophagocytic lymphohistiocytosis; NK = natural killer; IL = interleukin

but since the HPS is a fatal disease it is not necessary to fulfill all criteria in order to initiate therapy. If the initial biopsy does not reveal hemophagocytosis, the biopsy needs to be repeated.

The diagnostic approach proposed is a simple screening and diagnostic algorithm based on serum markers of macrophage activation (ferritin, soluble CD163 and soluble CD25) and morphological evidence of hemophagocytosis. In case of serum ferritin levels >10000 mg/L, confirmatory tests such as the assessment for morphological evidence of hemophagocytosis and quantification of soluble CD163 (sCD163) are indicated. Soluble CD163 which is dramatically increased in HPS, is the most specific monocytes macrophage marker so far, and can be measured by an enzyme-linked immunosorbent assay (ELISA). In the context of a typical clinical presentation but absence of a sCD163 increase, the measurement of sCD25 has to be considered. Complementary diagnostic procedure suggested is perforin flow cytometry (if available).

HEMOPHAGOCYTIC SYNDROME AND INFECTIONS

The hemophagocytic syndrome has been associated with a variety of viral, bacterial, fungal, parasitic infections and vac-

cination. Disseminated infection with an unusual organism in a patient with HPS may represent secondary infection in an immunocompromised patient; however, the resolution of the syndrome following treatment of infection suggests that HPS is secondary to underlying infection. Nevertheless, all patients meeting the criteria for HPS should undergo a series of diagnostic tests outlined in Table 4, depending on epidemiologic data and the patient's medical history. Even if an infection known to be associated with HPS has been confirmed, T-cell lymphoma has to be ruled out.

VIRUS-ASSOCIATED HEMOPHAGOCYTIC SYNDROME

Epstein-Barr Virus (EBV)

Among virus-associated infections, the Epstein-Barr virus (EBV) is the most commonly reported trigger agent. There are two types of EBV-associated HPS. The first is during primary EBV infection and the second during a reactivation process. It seems that the incidence is high in Asian countries with predominance in female children and adolescents.[10] In adult patients the epidemiology is not well known.

In primary infection, EBV typically infects and replicates in B lymphocytes. EBV-specific cytotoxic T cells are required to regulate infected B cells, so that memory cells can be produced. Thus, EBV infection is usually maintained in an asymptomatic and latent form by the host immune system, otherwise it is occasionally symptomatic as infectious mononucleosis (IM). In the latter case serious complications can occasionally occur such as pneumonitis, hepatic failure, rupture of spleen, and central nervous system involvement.[11] However, EBV has been linked to refractory disease in EBV-associated HPS and chronic active EBV infection (CAEBV). In EBV-associated HPS it has been shown that the virus predominantly infects CD8+ T lymphocytes (occasionally CD4+, or both).[12] Failure to produce specific cytotoxic T cells, suggest NK-T cell dysfunction,[13] causing severe immunodeficiency with a very high viral load in peripheral blood.[14] It is the cytokine storm of TNF-α and INF-γ, IL-12 and IL-18 that follows. TNF-α and INF-γ play central role in the host resistance to EBV infection and especially in macrophage activation. This inflammatory cytokine overproduction causes coagulopathy and multiple organ dysfunction. Especially TNF-α causes liver dysfunction. Without immunosuppressive therapy (cyclosporine A and etoposide phosphate [VP-16]), the disease progress is rapid and life-threatening.

In patients with CAEBV, the virus primarily infects CD4+ T cells or NK cells.[15] Failure to acquire EBV-specific cytotoxic T cells, suggests NK cell dysfunction in the host immunity.[16] This condition leads to high EBV load and EBV-associated NK-cell lymphoproliferative disease (Table 5). The cytokine profile in CAEBV seems to be different from that in EBV-associated HPS. There are 3 main clinical criteria for CAEBV disease listed in Table 6.

In clinical practice it is rather difficult to distinguish between primary infection and reactivation. Most epidemiologic studies are in pediatric populations with primary infection. Serologic testing can help clinicians to make the distinction even though there are some limitations. What is important is to decide whether the disease is "high-risk" and this evaluation is a matter of clinical staging, serum viral load and EBV tropism. New laboratory methods like real-time polymerase chain reaction (PCR) can reflect viral replication and treatment efficacy while viral load can be used as a prognostic factor.[17] Cytogenetic analysis, genetic testing and chromosomal analysis are required to rule out familial hemophagocytic lymphohistiocytosis (FHL) particularly in young children, in relapsing HPS, in patients difficult to treat and patients with positive family history for EBV-associated HPS.

TABLE 4. Diagnostic Tests

(1) Blood, mid-stream urine and sputum cultures for bacteria. Blood cultures may need to be prolonged for fungi and brucella
(2) Chest radiograph and appropriate cultures and microscopy for mycobacteria. Blood, sputum, bronchoalveolar lavage, pleural fluid, bone-marrow aspirate, cerebrospinal fluid
(3) Serological tests for acute EBV,CMV and HIV infections
(4) Peripheral blood nucleic-acid tests for evidence of replicating EBV, CMV, herpes simplex virus (HSV), varicella zoster virus (VZV), HHV-6, HHV-8, HIV, adenovirus and parvovirus B19.
(5) Serum cryptococcal antigen and serum galactomannans
(6) Serological tests for evidence of primary or reactivation of toxoplasmosis
(7) Leishmania antigen test and bone-marrow aspiration smear if epidemiologically appropriate
(8) Search for a lymphoproliferative disorder. Computed tomography (CT) scan of thorax, abdomen and pelvis to look for lymphadenopathy, lymph node biopsy (if present and accessible lymphadenopathy), serum lactate dehydrogenase (LDH), bone-marrow aspiration and trephine, immunophenotyping.

CMV = cytomegalovirus; EBV = Epstein Barr virus; HHV = human herpes virus; HIV = human immunodeficiency virus

HERPES VIRUSES OTHER THAN EBV

Cytomegalovirus (CMV)

Recent reports[18,19] have associated cytomegalovirus (CMV) infection with HPS in adult patients suffering from inflammatory bowel disease, rheumatological disease, cancer and those having undergone transplantation, but also in healthy people. CMV has been found to up-regulate TNF gene expression and may be responsible for the inflammatory pattern seen in CMV infection. TNF-α is a pro-inflammatory mediator in the

TABLE 5. Summary of Epstein-Barr Virus (EBV) Load and Host Immunity in Patients with Infectious Mononucleosis (IM), EBV-Associated HPS, and Chronic Active EBV.

Disease	EBV-Infected Cell	EBV Load and Host Immunity
Infectious mononucleosis (IM)	B cell	10 2-3 copy/μg/DNA (PBMNCs), and disappears within 4-5 weeks after normal increase of EBV-CTL
EBV-associated HPS (EBV-AHPS)	T cell (CD8+, occasionally CD4+, or both)	10 3-6 copy/μg/DNA (PBMNCs), but sometimes at the same level as IM. It gradually decreases, although can be detected 3 months after remission. An overproduction of IFN-γ TNF-α, IL-10 and IL-12 which is called "cytokine storm" causes a rapid progress of EBV-AHPS. The role of EBV-CTL has been unknown yet.
Chronic active EBV infection (CAEBV)	T cell (mainly CD4+), NK cell	10 4 copy/μg/DNA (PBMNCs), EBV load does not decrease because of insufficient EBV-CTLs. Host immunodeficiency is not only related to EBV but το other viruses as well, such as CMV.

CTL = cytotoxic T-lymphocytes; HPS = hemophagocytic syndrome; IFN = interferon; IL = interleukin; NK = natural killer (cell); PBMNC = peripheral blood mononuclear cells; TNF = tumor necrosis factor

TABLE 6. Clinical Criteria for Chronic Active Epstein-Barr Virus (EBV) Disease

1. Severe illness lasting more than 6 months. The disease begins as a primary EBV infection and characterized by an unusual pattern of anti-EBV antibodies.
   - anti-virion capsid antigens IgG ≥ 5120,
   - anti-early antigens IgG ≥ 640
   - anti-EBV nuclear antigens <2;
2. Histological evidence of major organ involvement such as interstitial pneumonia, hyperplasia of some bone marrow elements, ileitis, lymphadenitis, persistent hepatitis, or splenomegaly and
3. Increased quantities of EBV in affected tissues.

pathogenesis of Crohn's disease, and therefore anti-TNF-α antibody has gained popularity as a treatment for inflammatory bowel disease. CMV infection in patients receiving such kind of treatment has been well recognized in the literature. In a prospective observational study of 171 patients who received hematopoietic stem cell transplantation between July 2006 and December 2007, two patients developed CMV-related HPS after allogenic and one after autologous stem cell transplantation. Fever, cytopenias and hyperferritinemia were the symptoms with the higher index of suspicion leading to bone marrow aspirate, early diagnosis and appropriate treatment.[20] Specific anti-CMV therapy, like CMV hyperimmune globulin, ganciclovir or foscarnet, seems to be essential and sometimes curative in association with withdrawal of the immunomodulatory treatment.

Human Herpes Virus 8 (HHV8)

Human herpes virus 8 (HHV8) in immunocompromised (HIV positive, lymphoproliferative disorder or transplant recipient) and in immunocompetent patient has been associated with HPS. Treatment options with etoposide, splenectomy, rituximab or antiviral agents have also been described.[21,22]

Human Immunodeficiency Virus (HIV)

In the context of HIV infection, HPS is associated with a wide variety of underlying disorders. Bacterial, mycobacterial, fungal, protozoal, viral or neoplastic diseases can be implicated in its process. Cases where HIV infection was the only identifiable etiologic factor have been described in the literature, and this seems to be independent of the CD4 cell count. According to a clinicopathologic study of 56 autopsy cases of HIV positive patients the incidence of hemophagocytosis was 20% but clinical HPS was rather rare.[23] HPS has been described in three different occasions; in the acute HIV seroconversion phase, in the setting of immune reconstitution inflammatory syndrome (IRIS) within 1 to 3 weeks following initiation of highly active antiretroviral therapy (HAART), or 6 weeks after the initiation of HAART.[24]

Common viral triggers of HPS in the HIV patient are HHV8 (Kaposi's sarcoma associated herpes virus), EBV, and CMV, with a number of cases reported in the literature. EBV-associated HPS seems to be more common in HIV infected children than in adults.[25,26] The relationship between EBV, lymphoma and HPS seems to be complex. We know that T-cell lymphomas can occur after HPS treatment in HIV infected children.[27] In similar HIV negative patients suffering from HPS, it has been demonstrated that T cell proliferation can induce clonality, suggesting a possible pathogenic pathway in EBV-related lymphomas. Opportunistic infections that frequently coexist are mycobacterial (Mycobacterium tuberculosis, kansasii, avium intracelullare) in the context of disseminated disease and advanced immunosuppresion. Other diseases like toxoplasmosis and histoplasmosis have to be rule

out in the HIV infected patient presenting with HPS.

There is a great difficulty to differentiate HPS in HIV positive patients because most of the features are nonspecific and could be attributed directly to the HIV infection. The Histiocyte Society guidelines[7] can be challenging since some of the criteria may be fulfilled at a later stage in the disease. The delay in the diagnosis of the syndrome can be potentially fatal since life-saving interventions may be delayed.

Treatment options with etoposide, cyclosporine and dexamethasone (revised as the HLH-2004 International study), are proposed since HIV infection is not in the exclusion criteria, and HIV-associated HPS is often fulminant and aggressive. Pathogen-appropriate therapy is crucial when any associated organism is suspected. Exception is the EBV-specific antiviral therapy since it has not been demonstrated to be effective in treating the syndrome.

Influenza and other Viruses

Reactive HPS has been reported in the literature with all influenza viruses (human/avian or H5N1/swine). Symptoms and laboratory findings are similar in both clinical entities with pancytopenia, hemophagocytosis and cytokine storm been the most common findings.

As for the avian influenza, recent studies have shown that the high fatality rate is a consequence of an overactive inflammatory response. The most important feature of A/H5N1 immunopathogenesis is the exaggerated production-secretion of pro-inflammatory cytokines. This phenomenon is blamed on the emergence of lethal clinical symptoms such as extensive pulmonary edema, acute bronchopneumonia, alveolar hemorrhage, acute respiratory distress syndrome, and of course reactive hemophagocytosis. Clinical studies have pointed out that mutations of some viral genes (NS1, PB2, HA and NA) are responsible for the cytokine storm. It has been demonstrated that recombinant hemagglutinin (H5) from a H5N1 virus may suppress the perforin expression and reduce cytotoxicity of human CD8+ T cells to kill H5-bearing cells. The persistence of H5 presenting cells provides sustained stimulation and leads to a marked lymphoproliferation and IFN-γ hyperproduction. It is proposed that IFN-γ hyperproduction may explain macrophage overactivation and subsequent hypercytokinemia and hemophagocytosis in severe human cases of avian influenza.[28]

HPS has been reported in patients infected by parvovirus B19 with very good prognosis, without specific treatment. HAV, HBV, enterovirus, adenovirus, measles, mumps, rubella, dengue, hantavirus infection, BK virus have all been found to be associated with the syndrome too. Corticosteroids, etoposide, and intravenous immunoglobulin have been used sporadically with variable success rate.

Bacteria-associated HPS

The pathophysiology of infection-associated HPS with nonviral pathogens may be related to the production of high levels of activating cytokines by the host lymphocytes and monocytes. Infecting organisms trigger the T helper cell 1 (Th1) immune response and the reactivation of HPS may suggest that a poorly regulated or inappropriate Th1 response exists.

Tuberculosis-associated HPS

Secondary HPS has been frequently associated with intracellular pathogens. Even though the pathophysiological response of the host immune system to the invading organism is not fully understood, it is hypothesized that functional deficiencies of cytoxic T cells and NK cells may develop during the illness. It is the infecting organism (e.g., Mycobacterium tuberculosis, Salmonella Typhi, and Leishmania sp.) that triggers Th1 immune response[29] and experimental animal studies have told us that immunological control of M. tuberculosis infection requires potent Th1 cell immunity.[30] Reactive hemophagocytic syndrome results from a poorly regulated or inappropriate response to intracellular pathogens due to defective Th1 immune stimulation. Survival and proliferation of the organisms result in increased cytokine production by host lymphocytes and monocytes and uncontrolled macrophage activation.

According to a recent review with 36 cases,[31] fever was the most common clinical finding, and hepatosplenomegaly the second most common. Many cases were diagnosed as extrapulmonary tuberculosis. All patients experienced evidence of hemophagocytosis in biopsy specimens. Mortality rate was surprisingly high (50%), and failure of therapy was attributed to initiation of therapy late in the course of the illness. Early consideration of the disease in the differential diagnosis is very important as the disease progresses rapidly, and antituberculous therapy and immunomodulatory therapy (corticosteroids, intravenous immunoglobulin, antithymocyte globulin, cyclosporine A, and etoposide) seem to be associated with better outcomes. Hemophagocytic syndrome has also been reported after BCG vaccination.[32]

Brucellosis

Brucellosis is a zoonosis and Brucella melitensis is the most common organism isolated. The manifestations of the disease can be protean, involving almost any system but the commonest presenting feature is fever. Hemophagocytosis in Brucella infection has been described by several authors and it is a known cause of secondary hemophagocytic lymphohistiocytosis.[33] Prolonged treatment protocols of the disease seem to cure the HPS too.

Leptospira infection

Most healthy individuals develop immunity against Leptospira without subsequent damage and frequently even without experiencing any clinical symptoms. Only a minority of those with a positive serum IgG titer against Leptospira has suffered acute leptospirosis (Weil's disease). In rare and extreme cases, Leptospira infection causes severe and life-threatening HPS,

so it has to be part of its differential diagnosis. In the case of Leptospira-triggered HPS, this may be related to the genetic composition of Leptospira spp., which codes for the enzymes of a complete heme biosynthetic pathway and can perfectly utilize exogenous heme sources.[34] For Leptospira-triggered HPS, solely antibiotic treatment is not sufficient and specific therapy like immunosuppressive treatment containing corticosteroids, high-dose intravenous immunoglobulin or etoposide may be used.

Leishmania

Because Leishmania donovani can cause HPS but also can mimic the syndrome (organomegaly, cytopenias), a bone marrow aspirate is needed to determine the correct diagnosis. Treatment of Leishmania -triggered HPS with amphotericin B is usually sufficient.

Fungi

Hemophagocytic syndrome has also been described with Candida spp, Cryptococcus spp, Pneumonocystis spp, Histoplasma spp, Aspergillus spp, and Fusarium spp. It seems that fungal associated HPS occurs most commonly during HIV, lymphoma, malignancy, steroid use, and transplantation.

Other Infections

Campylobacter, fusobacterium, mycoplasma, chlamydia, and Lyme disease, legionnella, typhoid, rickettsia, ehrlicia, malaria (Plasmodium falciparum and Plasmodium vivax), toxoplasma, babesiosis, and strongyloidiasis have all been described with HPS.

PROGNOSIS AND THERAPY

The initiation of immune-chemotherapy according to the HLH-94 protocol has changed dramatically the physical history of the disease in children with FHL or HPS associated with hereditary immunodeficiencies and EBV-associated HPS. In most cases, disease activity is stabilized with dexamethasone, etoposide/VP16 and cyclosporine A, being the backbone of the HLH-2004 protocol. The next step is allogenic stem cell transplantation, which is the curative option.

There are several differences between childhood and adult HPS. The maturity of the immune system may partially explain these differences but also the underlying disorders are different for several reasons. EBV infection is a very good example, where primary infection is rare in adults since it is usually acquired during childhood or adolescence.

Treatment strategies vary significantly in accordance with the clinical features of EBV infection. Mild EBV-associated HPS can regress spontaneously, while antiviral agents like acyclovir, gancyclovir and cidofovir have proved ineffective in acute EBV infection (IM). In severe HPS treatment options vary between conservative treatment without etoposide, immunochemotherapy with etoposide (HLH-94/2004), and hematopoietic stem cell transplantation. It is really interesting that the survival benefit of etoposide-containing treatment begins within 4 weeks of diagnosis which give clinicians a therapeutic window of conservative treatment or even observation. Treatment strategies like corticosteroids, cyclosporine A, intravenous immunoglobulin, plasma exchange, even splenectomy have been used. Infection control is a necessary step in optimal treatment due to neutropenia-associated opportunistic infections. Eradication of clonally proliferating EBV-containing T cells and NK cells by immunochemotherapy or even hemopoietic stem cell/bone marrow transplantation is the last treatment option and resort for refractory EBV-associated HPS.

Regarding EBV-associated HPS, early immunochemotherapy results in high response rates, but for the other infection-associated HPS, specific treatment guidelines do not exist. Patients with reactive HPS associated with an infectious organism except leishmaniasis, should start specific therapy since pathogen specific therapy cannot stabilize the disease activity by itself. Only 60-70% of patients gain full recovery with treatment of the underlying infection alone.[35]

Prognostic factors have been described recently for childhood HPS and adults >30 years. In the first setting are the presence of a hereditary disorder, underlying EBV infection or malignancy, diffuse intravascular coagulation, neutropenia, central nervous system involvement, various laboratory markers and initial treatment response.[36] Prognostic factors for adults are coagulopathy, hyperferritinemia, increased β2-microglobulin, anemia, thrombocytopenia and jaundice.[37] It seems that for low-risk situations, corticosteroids and/or intravenous immunoglobulins or cyclosporine A may be enough, but for high-risk cases etoposide therapy is recommended. Appropriate screening of the underlying causative organism is crucial. Plasmapheresis and blood exchange have been described in various case reports with good results,[38] as well as anti- TNF-α treatment (infliximab, etanercept).[39]

CONCLUSION

Herein we reviewed hemophagocytic syndromes associated with a variety of infectious agents. Clinicians should be aware of the occurrence of this fatal syndrome, since early diagnosis could change the natural history of the illness. Specific therapeutic decisions according to the triggering pathogen and the genetic predisposition of the patient are available in many cases, but HPS diagnosis in adult patients is still too often missed or delayed and treatment options are based on small case studies. Finally, better understanding of the pathophysiology of the HPS may clarify the interactions between immune system pathways and infections.

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