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Infections associated with haemophagocytic syndrome

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Haemophagocytic syndrome or haemophagocytic lymphohistiocytosis is a rare disease that is often fatal despite treatment. Haemophagocytic syndrome is caused by a dysregulation in natural killer T-cell function, resulting in activation and proliferation of lymphocytes or histiocytes with uncontrolled haemophagocytosis and cytokine overproduction. The syndrome is characterised by fever, hepatosplenomegaly, cytopenias, liver dysfunction, and hyperferritinaemia. Haemophagocytic syndrome can be either primary, with a genetic aetiology, or secondary, associated with malignancies, autoimmune diseases, or infections. Infections associated with haemophagocytic syndrome are most frequently caused by viruses, particularly Epstein-Barr virus (EBV). We present a case of EBV-associated haemophagocytic syndrome in a young adult with no known immunosuppression. We briefly review haemophagocytic syndrome and then discuss its associated infections, particularly EBV and other herpes viruses, HIV, influenza, parvovirus, and hepatitis viruses, as well as bacterial, fungal, and parasitic organisms.

Introduction

Haemophagocytic syndrome is a rare but potentially fatal disease resulting from dysregulated activation and proliferation of lymphocytes. We describe a case of haemophagocytic syndrome associated with Epstein-Barr virus (EBV) and discuss other common infections associated with the syndrome.

Case presentation

A 20-year-old white woman presented with a 2-week history of fever, fatigue, and 3 kg weight loss. The patient complained of occasional headaches without neck stiffness or photophobia, some shortness of breath on exertion, and occasional nausea.

Her past medical history was significant for Holt-Oram syndrome, an autosomal-dominant condition characterised by congenital cardiac and forelimb anomalies. At 2 months of age, the patient had surgical repair of her anomalous pulmonary venous return, ventricular septal defect, and patent ductus arteriosus. The patient was in her usual state of health until a year before her presentation, when she had primary EBV infection diagnosed with positive serologies and a positive EBV PCR assay. This episode resulted in severe pancytopenia. A bone marrow biopsy done at that time was non-diagnostic. Her blood counts normalised and repeated EBV PCR 2 months before admission was negative. She had no history of recurrent infections. The patient was a college student who abstained from sexual activity, tobacco, alcohol, and illicit drug use. She had no recent travel or tick bites. Both her mother and brother had Holt-Oram syndrome.

On physical examination, the patient was in no acute distress. Her temperature was 38.5°C, heart rate 96 beats per min, and blood pressure 106/65 mm Hg. The neck was supple. Cardiovascular examination revealed a grade 3/6 systolic murmur at the left upper sternal border, unchanged from previous examinations. She had truncated upper extremities and was missing digits on both hands from her congenital syndrome (figure 1). No rash was noted. She had no organomegaly or palpable lymphadenopathy. The rest of the physical examination was unremarkable.

Laboratory evaluation revealed a total leucocyte count of 500 cells per μL with 40% band forms, 16% neutrophils, 40% lymphocytes, and 4% monocytes, normocytic anaemia (hematocrit 25%) and thrombocytopenia (platelet count 102 000 per μL). Both the international normalised ratio (INR) and the activated partial thromboplastin time (aPTT) ratio were normal. Lactate dehydrogenase was 575 IU/L with normal liver transaminases, bilirubin, and haptoglobin levels. Multiple cultures of blood, urine, and sputum were negative for bacteria, mycobacteria, or fungi. Serological studies for HIV-1, HIV-2, hepatitis B and C, cytomegalovirus, parvovirus, and ehrlichia were negative. IgG antibodies to toxoplasma were positive but IgM antibodies were negative, consistent with previous infection. Serum cryptococcal antigen test and urine histoplasma antigen test were both negative. Tests for EBV capsid IgG antibodies and EBV nuclear antigen were positive. EBV capsid antigen IgM antibodies were negative. However, the EBV serum PCR result was 36 800 copies per mL (using the RealArt EBV PCR Kit from Artus [San Francisco, CA, USA] with a cut-off of 300 copies per mL). The bone marrow biopsy on admission showed dysplasia in all cell lines with some fibrosis, but cytogenetics were normal.

The patient was started on ceftazidime (2 g intravenously three times a day) for neutropenic fever. For her EBV



Figure 1: Truncated extremities in a patient with Holt-Oram syndrome and EBV-associated haemophagocytic syndrome

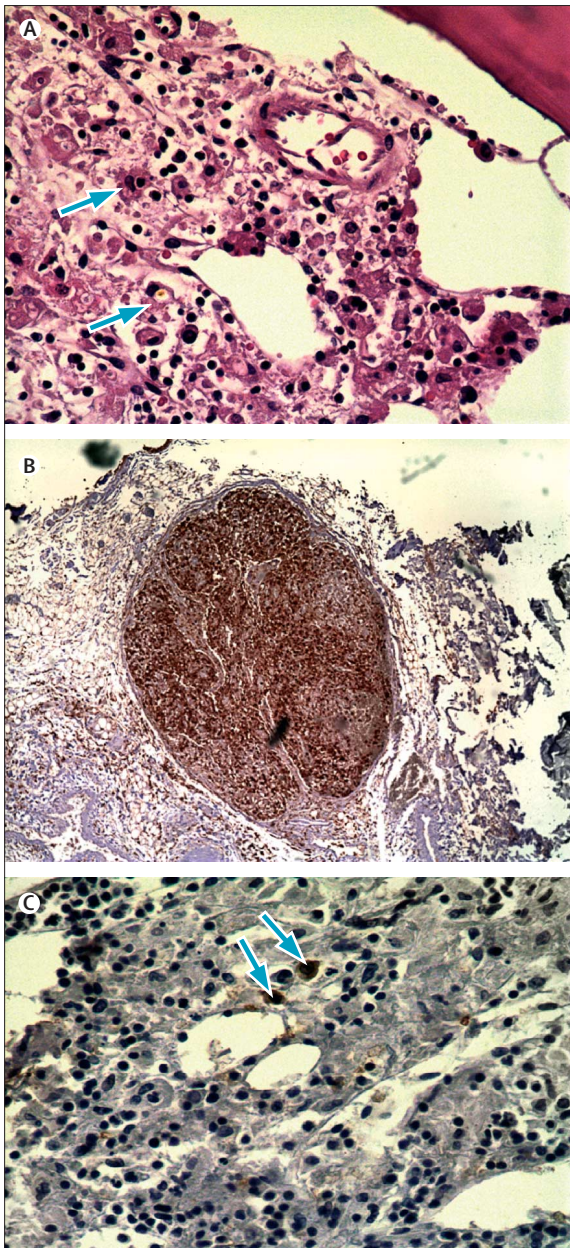


Figure 2: Autopsy results with evidence of EBV-associated haemophagocytosis

(A) Haematoxylin-eosin stain of bone marrow sample obtained on autopsy showing rare phagocytic cells with engulfed haematopoietic elements (arrows). (B) CD68 (macrophage marker) staining by immunohistochemistry showing presence of abundant macrophages within lymph nodes. (C) EBV staining by immunohistochemistry showing numerous infected cells (arrows) within lymph node.

infection, she received valaciclovir 1 g three times a day, followed by aciclovir intravenously and one dose of cidofovir (5 mg/kg intravenously). Non-steroidal anti-inflammatory drugs and steroids were given for symptomatic relief of her fever. She received several blood transfusions and various doses of granulocyte-macrophage colony-stimulating factor (GM-CSF)

injections for pancytopenia. The fever persisted, reaching as high as 40.6°C. She subsequently developed progressive hepatosplenomegaly and generalised tender lymphadenopathy.

A CT scan on hospital day 10 revealed three new lung nodules, with diffuse neck adenopathy and hepatosplenomegaly. Bronchoscopy and lavage showed active haemorrhage; stains for *Pneumocystis jirovecii*, fungal infection, acid fast bacilli, cytomegalovirus, and herpes simplex virus (HSV) were negative. A lung biopsy of the nodules revealed acute and organising pneumonia with nuclear debris suggesting the possibility of viral origin. However, immunoperoxidase stains for cytomegalovirus, HSV, adenovirus, and EBV as well as fungal stains were all negative. Transjugular liver biopsy showed centrilobular hepatocyte dropout and damage with sinusoidal histiocytic infiltrate and all stains were again negative.

On hospital day 15, the patient had increasing respiratory distress followed by altered mental status and multiorgan failure. She had a nadir leucocyte count of 0.5 cells per μL , a haematocrit of 16.8%, and a platelet count of 8000 per μL . Her creatinine peaked at 3.2 mg/dL, requiring haemodialysis. The aspartate aminotransferase and total bilirubin levels reached 2132 IU/L and 16 mg/dL, respectively. Ferritin level was higher than 4800 ng/mL and triglycerides were 381 mg/dL. She developed disseminated intravascular coagulation (D-dimer 4456 ng/mL, INR 8.3, aPTT 152 s, fibrinogen less than 60 mg/dL). The EBV PCR continued to increase from 443 000 copies per mL to 974 000 copies per mL.

High dose steroids were given. She was then transferred to the intensive care unit and died on hospital day 19 despite maximum support. Autopsy revealed proliferation of macrophages and haemophagocytosis in the bone marrow, lymph nodes, and spleen with positive immunohistochemistry for EBV (figure 2). The patient met the criteria for EBV-associated haemophagocytic syndrome, including persistent fever, splenomegaly, severe pancytopenia, liver test abnormalities, elevated ferritin, and histological evidence of haemophagocytosis. Other haemophagocytic syndrome criteria were not fulfilled since genetic mutational analysis, evaluation of natural killer (NK)-cell cytotoxicity, and soluble CD25 levels were not obtained pre-mortem.

Haemophagocytic syndrome

Definition

Haemophagocytic syndrome, or haemophagocytic lymphohistiocytosis, is a life-threatening clinicopathological entity characterised by an impaired or absent function of NK cells and cytotoxic T cells. This dysregulation results in uncontrolled and ineffective immune activation leading to cellular damage and multiorgan dysfunction as well as proliferation and activation of benign macrophages with haemophagocytosis throughout the reticuloendothelial system

causing pancytopenia, hepatosplenomegaly, and lymphadenopathy.¹

Classification

Haemophagocytic syndrome was first described in 1939 by Scott and Robb-Smith.² The disorder is divided into primary or genetic haemophagocytic syndrome and secondary or reactive haemophagocytic syndrome (panel 1).¹ Historically, this distinction helped to differentiate between cases of haemophagocytic syndrome that presented during infancy and caused a high rate of mortality (defined as primary haemophagocytic syndrome) from cases of the syndrome that were caused by other aetiologies, presented later in life, and had a better prognosis (secondary haemophagocytic syndrome). However, this distinction may be artificial. First, primary haemophagocytic syndrome can occur at any age, not just during infancy or early childhood.³ Second, an underlying genetic mutation is found in only 40% of all primary haemophagocytic syndrome patients.¹ Third, both primary and secondary syndromes can be precipitated by an infection,⁴ and finally, some secondary cases of haemophagocytic syndrome carry a higher mortality than those seen in primary haemophagocytic syndrome.

Genetic haemophagocytic syndrome

Genetic haemophagocytic syndrome is divided into two subgroups depending on whether it is associated with immune deficiencies or not. The familial form of haemophagocytic lymphohistiocytosis was first described in 1952,⁵ and is estimated to occur in one out of 30 000–50 000 births.⁶ Familial haemophagocytic lymphohistiocytosis will manifest in the first year of life in 70–80% of cases. Several other genetic mutations occurring in sporadic cases of haemophagocytic syndrome have been described.¹

To our knowledge, this is the first reported case of haemophagocytic syndrome in a patient with Holt-Oram syndrome, a disorder caused by mutations in the transcription factor TBX5, which has a role in cardiac and limb formation. Holt-Oram syndrome is not associated with any immune deficiency state and does not result in increased susceptibility to infections.

Reactive haemophagocytic syndrome

Infection has an important role in the aetiology of haemophagocytic syndrome;⁷ however, no data exist on the incidence of infection-associated disease. Haemophagocytic syndrome can clinically mimic an infection and obscure its coexistence. An infection can precipitate both primary and secondary haemophagocytic syndrome. A better understanding of the pathophysiology of haemophagocytic syndrome may clarify the interactions between infection and the immune system.

The first description of virus-associated haemophagocytic syndrome, made in 1979 by Risdall and colleagues,⁸ comprised 19 patients, most of whom were immuno-

compromised. Most patients in subsequent reports had no known genetic or acquired immunodeficiency. A review of the published cases by Janka and colleagues⁹ showed that of 219 children diagnosed with infection-associated haemophagocytic syndrome before 1996, more than half were from east Asia. Overall mortality was 52% (103 of 198 children died) but was higher in patients with EBV-associated disease (72 [73%] of 99 children with EBV died). EBV was the triggering virus in 121 (74%) of 163 children.

Pathophysiology

A defect in granule (perforin/granzyme)-mediated cytotoxicity, which is important in both the killing of infected cells and the termination of the immune response,¹⁰ seems to be the underlying factor that predisposes an individual to haemophagocytic syndrome. Since 1999, several genetic loci related to the activity of perforin and granzyme granules have been associated with genetic haemophagocytic syndrome, thus explaining the impaired or absent function of NK cells and cytotoxic T cells characteristic of the disease.¹¹ A defective triggering

Panel 1: Haemophagocytic syndrome classification

Primary or genetic haemophagocytic syndrome

Familial haemophagocytic 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 haemophagocytic syndrome

Infection associated haemophagocytic syndrome

- Virus-associated haemophagocytic syndrome
 - Herpes virus infection (herpes simplex virus, varicella zoster virus, cytomegalovirus, Epstein-Barr virus, human herpesvirus 6, human herpesvirus 8)
 - HIV
 - Other viruses: adenovirus, hepatitis viruses, parvovirus, influenza
- Other infections associated with haemophagocytic syndrome
 - Bacteria including mycobacteria and spirochaetes
 - Parasites
 - Fungi

Malignancy-associated haemophagocytic lymphohistiocytosis (especially lymphoma-associated haemophagocytic lymphohistiocytosis)
Macrophage activation syndrome (associated with autoimmune diseases)

Adapted from reference 1.

Panel 2: Diagnostic guidelines for haemophagocytic syndrome

The diagnosis of haemophagocytic syndrome is established by fulfilling one of the following criteria:

- 1 A molecular diagnosis consistent with haemophagocytic syndrome (eg, PRF mutations, SAP mutations, MUNC13-4 mutations)
- 2 Having five out of eight of the following
 - Fever
 - Splenomegaly
 - Cytopenia (affecting more than two cell lineages, haemoglobin $\leq 9\text{g/dL}$, $<100\,000$ platelets per μL , neutrophils <1000 cells per μL)
 - Hypertriglyceridaemia (triglycerides $\geq 265\text{ mg/dL}$) and/or hypofibrinogenaemia (fibrinogen $\leq 150\text{mg/dL}$)
 - Haemophagocytosis in the bone marrow, spleen, or lymph nodes without evidence of malignancy
 - Low or absent natural killer cell cytotoxicity
 - Hyperferritinaemia (ferritin $\geq 500\text{ ng/mL}$)
 - Elevated soluble CD25 (interleukin-2R α chain $\geq 2400\text{ IU/mL}$)

Adapted from reference 15.

of apoptosis in familial haemophagocytic lymphohistiocytosis has also been described.

The pathophysiology of acquired haemophagocytic syndrome is not fully understood. The deficiency in cytolytic activity results in persistent activation of lymphocytes and histiocytes. This uncontrolled immune response leads to hypersecretion of pro-inflammatory cytokines (such as interferon γ , tumour necrosis factor α [TNF α], interleukin 6, interleukin 8, interleukin 10, interleukin 16, interleukin 18, and macrophage colony-stimulating factor [M-CSF]), an upregulation of adhesion molecules and MHC I and II molecules on monomacrophages,¹² and an expansion of inflammatory monocytes (ie, an increase in CD14/CD16 expression).¹³ These mediators are secreted by the activated histiocytes and T lymphocytes, which infiltrate different tissues. This exaggerated inflammatory response is responsible for necrosis and organ failure and results in uncontrolled proliferation and phagocytic activity of histiocytes.

Diagnosis

Diagnosis of haemophagocytic syndrome relies on clinical, laboratory, and histopathological findings. Diagnostic guidelines were proposed by the Histiocyte Society in 1991¹⁴ and updated in 2004 (panel 2).¹⁵ Since therapy can be life saving and some of the clinical criteria occur late in disease, it is not necessary to fulfil all criteria before initiating therapy. Main symptoms of haemophagocytic syndrome are fever and splenomegaly. Jaundice, hepatomegaly, lymphadenopathy, rash, and neurological signs are also common (table 1). The hallmark laboratory finding is cytopenia, which can be profound. There is also

marked liver dysfunction; an elevated ferritin level is characteristic (table 2). Two highly diagnostic parameters are an increased plasma concentration of the alpha chain of the interleukin-2 receptor (sCD25) and impaired NK-cell activity. The elevation of interleukin-2 receptor in haemophagocytic syndrome suggests the activation of T lymphocytes and correlates with prognosis.¹⁶

On histopathology, activated macrophages with engulfed leucocytes, erythrocytes, platelets, and their precursor cells are the typical finding. The haemophagocytosis can be seen in any organ, particularly in the bone marrow, lymph nodes, liver, and spleen. If haemophagocytosis is absent in an initial biopsy specimen, the biopsy needs to be repeated.

Once a diagnosis of haemophagocytic syndrome is established, searches for an underlying genetic, rheumatological, or malignant disease and a possible infectious trigger should be undertaken.

Treatment

Haemophagocytic syndrome is a highly fatal disease if untreated. Since haemophagocytic syndrome is rare, no randomised controlled clinical trials testing potential treatments have been done. The immediate aim of therapy is suppression of the increased inflammatory response and control of cell proliferation using immunosuppressive or immunomodulatory agents and cytotoxic drugs. Treatment differs in children and adults and depends on the underlying disease, the presence of a trigger, and the severity of symptoms. For patients with reactive haemophagocytic syndrome associated with an infectious pathogen other than leishmaniasis, supportive care should be initiated since pathogen-direct therapy is not sufficient by itself to control the disease. Apart from cases of EBV, treatment of the underlying infection alone in reactive haemophagocytic syndrome is associated with recovery in 60–70% of patients.⁷

Chemotherapy using dexamethasone, cyclosporin, and etoposide was adopted by the Histiocyte Society in 1994^{17,18} (updated in 2004)¹⁵ and is used for severe (particularly familial and EBV-associated haemophagocytic syndrome) cases. For patients with genetic haemophagocytic syndrome and severe or refractory haemophagocytic syndrome, bone marrow transplantation should be considered. In a review of 122 patients, Arico and co-workers¹⁹ found that bone marrow transplantation recipients had a superior outcome compared with non-transplanted patients (66% vs 10% recovered, respectively). The HLH-94 study, which combined the chemotherapy protocol with bone marrow transplantation in 113 children, showed a probability of survival at 3 years of 56% for all cases (63 of 113 children survived) and 52% for proven familial cases (13 of 25 children survived).¹⁸ Reports of spontaneous regression have been described.²⁰

Monoclonal antibodies (anti-CD20 [rituximab] and anti-interleukin-2R α receptor [daclizumab]) have been used in the setting of rheumatic disease or malignancy

associated with haemophagocytic syndrome.²¹ The role of intravenous immunoglobulin for treating haemophagocytic syndrome is not fully understood, but if used early has some chance of success.²² However, intravenous immunoglobulin combined with steroids is thought to be inferior to an etoposide-containing regimen. The use of growth factors such as granulocyte-colony stimulating factor or GM-CSF can exacerbate haemophagocytic syndrome.²³

Infection-associated haemophagocytic syndrome

Haemophagocytic syndrome has been associated with a variety of viral, bacterial, fungal, and parasitic infections. Viral infections associated with the syndrome include EBV, cytomegalovirus, human herpesvirus 8 (HHV8), HIV, influenza virus, parvovirus, hepatitis virus, and enterovirus; however, EBV is the most common triggering agent.

Virus-associated haemophagocytic syndrome

EBV: epidemiology, diagnosis, and treatment

Most EBV-associated haemophagocytic syndrome cases occur in apparently immunocompetent children and adolescents;²⁴ however, EBV-associated haemophagocytic syndrome can also occur in the setting of familial²⁵ (eg, familial haemophagocytic lymphohistiocytosis) and non-familial (eg, X-linked lymphoproliferative syndrome)²⁶ immune deficiencies as well as in infectious mononucleosis,²⁷ chronic active EBV infection,²⁸ and lymphoproliferative disorders (eg, NK T-cell leukaemia/lymphoma).²⁹ EBV-associated haemophagocytic syndrome has a high incidence in Asian countries, possibly because of the presence of a pathogenic EBV strain, but it has also been described in other countries, such as the USA and in Europe. In Japan, there are at least 25 cases of EBV-associated haemophagocytic syndrome per year in the paediatric population, with a peak incidence occurring between 1 and 2 years and a slightly higher frequency in girls than boys.²⁴ EBV-associated haemophagocytic syndrome occurs more commonly in the setting of reactivation.²⁴

During primary infection, EBV typically infects and replicates in B cells, and EBV-specific cytotoxic T cells are usually required to regulate the infected B cells and produce memory cells. In a limited number of individuals, EBV infects NK T cells and induces EBV-persistent infection with monoclonal or oligoclonal proliferation. In EBV-associated haemophagocytic syndrome, EBV infects primary CD8+ cells³⁰ with a failure to produce a sufficient number of EBV-specific cytotoxic T cells, suggesting a NK T-cell dysfunction.³¹ The typical cytokine storm seen in haemophagocytic syndrome is more pronounced in EBV-associated disease,³² causing haemophagocytosis and organ dysfunction.

Serological methods can help determine if the EBV-associated haemophagocytic syndrome has occurred in the setting of acute infection or is the result of a reacti-

	Percentage of patients affected
Fever	70–100%
Splenomegaly	70–100%
Hepatomegaly	40–95%
Lymphadenopathy	15–50%
Skin rash	5–65%
Neurological findings	20–50%

Adapted from reference 7.

Table 1: Clinical findings in haemophagocytic syndrome

	Percentage of patients affected
Anaemia	90–100%
Thrombocytopenia	80–100%
Neutropenia	60–90%
Hypertriglyceridaemia	60–70%
Hypofibrinogenaemia	65–85%
Hypertransaminasaemia	35–90%
Bilirubinaemia	35–75%
Elevated lactate dehydrogenase	45–55%
Hyperferritinaemia	55–70%

Adapted from reference 7.

Table 2: Laboratory abnormalities in haemophagocytic syndrome

vation process; however, these methods carry some diagnostic limitations, such as delay in positivity, difficulty in result interpretation, no variation with treatment, and absence of quantification of EBV. The detection and quantification of EBV nucleic acid by PCR³³ is therefore important for assessing the EBV load in patients with EBV-associated haemophagocytic syndrome, helping to determine not only the diagnosis, but also prognosis and efficacy of therapy.

Even though EBV in peripheral blood is highly associated with leucocytes, both EBV PCR in whole blood and serum need to be measured so that the EBV load in terms of viral replication can be established. A greater viral load is seen in patients with EBV-associated haemophagocytic syndrome compared with patients with infectious mononucleosis.³⁴ At onset of infectious mononucleosis, the EBV load measured by real-time PCR is 100–1000 copies per µg of peripheral blood mononuclear cell (PBMC) DNA. EBV load then disappears within 4–5 weeks after a normal increase in EBV-cytotoxic T cells. However, in EBV-associated haemophagocytic syndrome, the EBV load is usually more than 1000–1000000 copies per µg of PBMC DNA.³⁴ The quantitative analysis of cell-free EBV genome copy number at 4 months after therapy for EBV-associated haemophagocytic syndrome can assess the response to treatment and carries prognostic value.³⁵ EBV load has also been found to be associated with the severity of disease in other EBV-related diseases.

Genetic testing needs to be done to rule out or confirm the presence of an underlying immunodeficiency

(eg, familial haemophagocytic lymphohistiocytosis or X-linked lymphoproliferative syndrome), especially if haemophagocytic syndrome occurs early in life, has a relapsing pattern, or when there is consanguinity between the parents or the presence of haemophagocytic syndrome in another sibling.

Of all the viruses associated with haemophagocytic syndrome, EBV-associated syndrome carries the worst prognosis. However, aggressive therapy for this condition has yielded good results. A longitudinal follow-up of 78 patients in Japan³⁶ treated for EBV-associated haemophagocytic syndrome with a median follow-up of 43 months showed a 75% survival; 66 patients (85%) received an etoposide-based regimen, 12 patients (15%) required bone marrow transplantation, and clinical reactivation was seen in around 20% of cases.

EBV-specific therapy is ineffective in treating EBV-associated haemophagocytic syndrome, possibly because EBV responds poorly to aciclovir, as shown in studies using this drug for the treatment of infectious mononucleosis. Larger trials are needed to assess the effectiveness of specific anti-EBV therapy in EBV-associated haemophagocytic syndrome. Etoposide-containing regimens seem to have a crucial role in cure; etoposide has a high activity in histiocytic diseases and inhibits EBV nuclear antigen in EBV-infected cells. Mortality was found to be 14 times higher in patients with EBV-associated haemophagocytic syndrome who did not receive etoposide within the first 4 weeks after diagnosis³⁷ compared with those who received early therapy with etoposide. Bone marrow transplantation is necessary for patients with EBV-associated haemophagocytic syndrome in familial haemophagocytic lymphohistiocytosis, X-linked lymphoproliferative syndrome, chronic active EBV infection, and refractory disease.

Other herpes viruses

Cytomegalovirus has been associated with haemophagocytic syndrome in healthy patients³⁸ as well as patients with inflammatory bowel diseases,³⁹ rheumatological diseases,⁴⁰ and transplant recipients.⁴¹ Outlook for patients with cytomegalovirus-associated haemophagocytic syndrome is poor; between 1986 and 2002, four out of five patients less than 1-year-old with the condition died, according to the haemophagocytic lymphohistiocytosis Japanese registry.⁴² However, recent reports have shown that the use of specific anticytomegalovirus therapy, such as cytomegalovirus immunoglobulin, foscarnet, and ganciclovir, is curative^{38–41} for the disorder.

13 patients with HHV8-associated haemophagocytic syndrome have been described in the literature. Most of these cases occurred in the setting of Kaposi's sarcoma or multicentric Castleman's disease, and in immunocompromised hosts (eight patients were HIV positive and two patients were renal transplantation recipients).^{43–45} Nine of the 13 patients recovered; five had been treated

with an etoposide-containing regimen and four had been treated with ganciclovir and foscarnet.^{43–45}

HIV

HIV alone or in the presence of other opportunistic and non-opportunistic infections or malignancies has been associated with haemophagocytic syndrome. Although the association between HIV and haemophagocytic syndrome is rare, it is likely that the condition is underdiagnosed since HIV and haemophagocytic syndrome share many clinical and laboratory similarities. Around 10% of bone marrow biopsies in HIV patients before initiation of highly active antiretroviral therapy (HAART) showed haemophagocytosis.⁴⁶ In one autopsy study, haemophagocytosis was found in 20% of 56 HIV patients.⁴⁷

In a recent review of 39 patients with HIV-associated haemophagocytic syndrome,⁴⁸ 82% were male, median age was 38 years (range 26–59 years), and 11 patients had no opportunistic infection or malignancy, suggesting a possible role of HIV itself in triggering haemophagocytic syndrome. 90% of patients had fever, 67% hepatomegaly, and 55% splenomegaly. Pancytopenia was very common. 80% of patients had a CD4-cell count of less than 200 cells per μL (mean 132 cells per μL). Recovery was noted in only 28% of patients. A worse outcome was seen in patients with a CD4-cell count of less than 200 cells per μL . In 15 patients where information regarding treatment was available, only three received antiretroviral drugs and one responded to HAART.⁴⁹ Two patients received chemotherapy that did not consist of the haemophagocytic lymphohistiocytosis protocol. Intravenous immunoglobulin (in six patients), steroids (five patients), and splenectomy (two patients) were occasionally used.

Haemophagocytic syndrome was the initial presentation of HIV infection in eight patients^{50,51} with acute HIV-associated haemophagocytic syndrome reported in the literature. Even though only one patient received HAART,⁵¹ all eight patients survived. HIV-associated haemophagocytic syndrome has also been described in the setting of immune reconstitution inflammatory syndrome.⁵²

Influenza

Influenza-associated haemophagocytic syndrome is very rare. The condition has been described with different influenza viruses—eg, human influenza,^{53,54} avian influenza,⁵⁵ and swine influenza⁵⁶—and is seen in both immunocompromised⁵³ and in immunocompetent hosts.⁵⁴

Patients with severe avian influenza (H5N1) infection have symptoms and laboratory findings similar to those seen in haemophagocytic syndrome—mainly encephalitis, organ dysfunction accompanied by haemophagocytosis, pancytopenia, and cytokine storm. Reactive haemophagocytosis is the most common pathological finding.^{57,58} A recombinant haemagglutinin (H5) from an H5N1 virus may suppress perforin

expression in human CD8+ T cells and may reduce the cytotoxicity of these cells, preventing them from killing H5-bearing cells. The resulting persistence of H5-bearing cells leads to a marked lymphoproliferation and interferon- γ hyperproduction with macrophage over-activation.⁵⁹ Since mortality caused by H5N1-associated haemophagocytic syndrome is high (around 50%) and antiviral drugs can be ineffective, some authors suggest treatment with a modified HLH-94 protocol⁶⁰ with a shorter course of etoposide and dexamethasone. However, in a randomised study from Vietnam, all patients with H5N1-associated haemophagocytic syndrome died despite receiving steroids.⁶¹

Other viruses

In 28 patients⁶²⁻⁶⁷ with parvovirus-associated haemophagocytic syndrome, the most common underlying disease was hereditary spherocytosis. More than half the patients were women and older than 15 years of age. Despite the fact that 16 patients did not receive any specific therapy, 22 patients survived, suggesting that parvovirus B19-associated haemophagocytic syndrome carries a better prognosis compared with other virus-associated haemophagocytic syndromes.

A fulminant hepatitis can mimic haemophagocytic syndrome. Hepatitis A virus (HAV) has been found to be more commonly associated with haemophagocytic syndrome than other hepatitis viruses. Eight of 11 patients⁶⁸⁻⁷⁰ with HAV and haemophagocytic syndrome survived when steroids were given frequently.

Enterovirus-associated haemophagocytic syndrome has been described in nine paediatric patients,⁷¹ of whom five had no underlying illness and five died despite therapy. Intravenous immunoglobulin was used in seven patients with a variable success rate.⁷¹

Other viruses found to be associated with haemophagocytic syndrome include adenovirus, measles, mumps, rubella, dengue, hantavirus, and severe acute respiratory syndrome.

Bacteria, parasite, and fungi-associated haemophagocytic syndrome

Bacteria-associated haemophagocytic syndrome and Mycobacteria spp

36 cases of haemophagocytic syndrome associated with tuberculosis have been published and recently reviewed.⁷² 60% of patients were male and median age was 44 years. Half the patients had underlying comorbidities. Fever was present in all cases and organomegaly in 75% of cases. 83% of patients had evidence of extrapulmonary tuberculosis. Pancytopenia, particularly thrombocytopenia, was common (89% of patients). 29 patients received therapy, either antituberculous drugs alone (nine patients) or a combination of antituberculous drugs with immunomodulatory therapy (20 patients). Immunomodulatory treatment mostly consisted of steroids but two patients underwent splenectomy and two

plasmapheresis. 12 of the 20 patients who received a combination of immunomodulatory and antituberculous treatment and seven of nine patients who received antituberculous treatment alone survived. All patients who received no treatment died.

Haemophagocytic syndrome has also been seen to develop after adjuvant intravesical BCG therapy⁷³ and BCG vaccination.⁷⁴ The incidence of bacteria-associated haemophagocytic syndrome varies between studies.^{9,46,75} Haemophagocytic syndrome associated with pyogenic bacteria can sometimes carry a better prognosis than virus-associated haemophagocytic syndrome. However, when associated with sepsis, bacteria-associated haemophagocytic syndrome can be fatal unless timely and appropriate supportive care and antibiotics are given.

Campylobacter, *fusobacterium*, *mycoplasma*, *chlamydia*, *legionella*, typhoid, *rickettsia*, *brucella*, *ehrlichia*, and Lyme disease, as well as other bacterial infections, have been identified in patients with haemophagocytic syndrome.

Parasites

Leishmania donovani can cause haemophagocytic syndrome and can also mimic the syndrome (organomegaly, cytopenia). A bone marrow aspirate determines the correct diagnosis. Treatment of leishmaniasis-associated haemophagocytic syndrome with amphotericin B results in cure.⁷⁶ Malaria⁷⁷ (*Plasmodium falciparum* and *Plasmodium vivax*), toxoplasma, babesiosis, and strongyloidiasis have also been described with haemophagocytic syndrome. A travel history is crucial to help determine the triggering agent in patients returning from endemic regions.⁷⁸

Fungi

Haemophagocytic syndrome can either be associated with yeast (eg, *Candida* spp, *Cryptococcus* spp,⁷⁹ *Pneumocystis* spp) or moulds (eg, *Histoplasma* spp,⁸⁰ *Aspergillus* spp, *Fusarium* spp). Haemophagocytic syndrome associated with fungal infection occurs most commonly in the setting of AIDS, lymphoma, chronic steroid use, and in transplant recipients.

Search strategy and selection criteria

Data for this Review were identified by searches of Medline and references from relevant articles for the period January, 1966, to September, 2006. Search terms included "hemophagocytic syndrome", "haemophagocytic syndrome", "hemophagocytosis", "haemophagocytosis", "histiocytic hemophagocytosis", "histiocytic haemophagocytosis", "hemophagocytic lymphohistiocytosis", "haemophagocytic lymphohistiocytosis", "histiocytosis", "viruses", "Epstein barr virus", "herpesvirus, human", "cytomegalovirus", "HIV infections", "influenza, human", "parvovirus", "hepatitis", "enterovirus", "bacteria", "parasites", "fungi". English and French language papers were reviewed.

Conclusion

Clinicians need to be aware of the occurrence of haemophagocytic syndrome in patients with persistent fever, organomegaly, and cytopenias in the setting of an infectious process, particularly EBV infection. Management of this syndrome relies on early diagnosis, identification of a triggering pathogen or an underlying disease, and control of the lymphocyte/macrophage proliferation and activation. Specific antimicrobial therapy can be beneficial in selected cases. Severe cases are treated with chemotherapy, generally an etoposide-containing regimen, and bone marrow transplantation is the treatment for familial, severe, and persistent non-familial cases.

Conflicts of interest

We declare that we have no conflicts of interest.

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