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Infection-Associated Hemophagocytic Syndrome: a Rare Potentially Fatal Complication of Systemic Infection. Report of Three Cases

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Infection-associated hemophagocytic syndrome is a rare, potentially fatal complication of systemic infection. It occurs most often in immunocompromised patients associated with a viral infection but the spectrum of conditions have been broadened to include virtually every type of infectious pathogen, malignancy and immunosuppressive therapy (1,2). We present three pediatric patients with a similar clinical history of pancytopenia, hepatosplenomegaly, and acute liver failure, and discuss the autopsy findings.

Key words: Hemophagocytic, Infection, Syndrome

Infection-associated hemophagocytic syndrome (IAHS) is a rare, potentially fatal complication of systemic infection in immunocompromised patients characterized by a proliferation of benign hemophagocytic histiocytes, fever, cytopenias, hepatosplenomegaly, deranged liver function and frequently coagulopathy (3,4). Skin rashes, lymphadenopathy and pulmonary infiltrates may be seen in some patients. The clinical syndrome is strongly associated with viral infections especially Ebstein-Barr virus (EBV), however herpes virus, hepatitis B, hepatitis C, Human Immunodeficiency Virus (HIV), cytomegalovirus (CMV), and adenovirus, as well as bacterial, fungal, and parasitic infections, malignancy and even immunosuppressive therapy have also been implicated (3-8). The pathogenesis of IAHS is unclear, although abnormal activation or regulation of the immune response, with resultant overexpression of inflammatory and macrophage activating cytokines have been proposed (3). Patients may recover spontaneously, but many die from complications of their underlying diseases. We present three patients presenting similar clinical findings of pancytopenia, hepatosplenomegaly, and acute liver failure and discuss the pathology.

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Case Reports

Case 1

A three month old boy was born at term to a 19 year-old G2P1A0 female with history of drug abuse, negative prenatal tests for VDRL, HIV, and Hepatitis B, and history of a urinary tract infection few days prior to delivery.

Patient was born by sterile vaginal delivery and discharged home from the Nursery after 48 hours. Three weeks prior to hospitalization, she developed an upper respiratory tract infection with fever after his immunizations at two months of age. However, a cell blood count revealed pancytopenia prompting patient's hospitalization for further evaluation.

Upon admission, cultures were negative, but aseptic meningitis was suspected due to an increased white blood cell count with predominance of lymphocytes on the spinal fluid. He was started on antibiotherapy and was transferred to the Pediatric Intensive Care Unit due to tachypnea, worsening anemia, and hepatosplenomegaly.

Clinical workup for EBV, HIV, Hepatitis B, CMV, TORCH and blood cultures were negative. He had elevated EBV and Parvovirus IgM. A bone marrow biopsy was reactive, and pancytopenia persisted despite several blood transfusions.

The patient persisted tachypneic, in respiratory distress, bleeding through all puncture sites and with signs of hypotension. He presented esophageal candidiasis, a pericardial effusion and ventricular dysfunction. Chest X-rays revealed a bilateral pneumonia and right upper lobe atelectasis. The Hematology Service evaluated the patient and a hemophagocytic syndrome was considered as a

diagnostic possibility. The patient continued deteriorating until death ensued 10 days after hospitalization.

Case 2

A five month old girl was hospitalized to our institution due to massive hepatosplenomegaly, liver dysfunction, and pancytopenia. She was transferred for liver biopsy and further management.

Past medical history was remarkable for two hospitalizations; one at 15 days of age due to respiratory problems and another at the age of one month due to septic shock. A third hospitalization was documented in the medical record at 4 months of age due to fever and pancytopenia.

An initial diagnosis of Dengue fever was considered but subsequently the patient was noted with hepatosplenomegaly, progressive deterioration, respiratory compromise and hepatic dysfunction.

Workup to establish the etiology of progressive hepatic dysfunction included Hepatitis A IgM which was borderline, HIV that was negative, an unremarkable bone marrow biopsy, negative blood and urine cultures, and non-contributory CMV, TORCH, and alpha-1-antitrypsin panel.

A quantitative amino acid profile in plasma had no evidence of aminoacidopathy. Organic acids in urine revealed a markedly elevated 4-hydroxyphenylacetic acid level; a finding that has been associated with small bowel disease and bacterial overgrowth syndromes.

Other clinical studies included a liver/spleen scan that revealed moderate hepatocellular dysfunction and moderate to marked splenomegaly, and a hepatobiliary scan that presented hepatomegaly with hepatocellular dysfunction and delayed visualization of the gallbladder raising the possibility of chronic cholecystitis. An abdominopelvic computerized scan also revealed hepatosplenomegaly and ascites. An abdominal sonogram showed ascites and a right pleural effusion.

The patient continued critically ill, in mechanical ventilation, on broad spectrum antibiotic coverage and with marked abdominal distention and anasarca. She had laboratory parameters consistent with chronic disseminated intravascular coagulation. An abdominal sonogram revealed liver and renal parenchymal disease but due to her clinical condition, a liver biopsy was contraindicated. She also had thrombocytopenia, anemia and a coagulopathy requiring multiple blood component transfusions. A therapeutic paracentesis was then performed and a liver transplant was recommended as a therapeutic alternative.

The Hematology service evaluated the patient and considered a hemophagocytic syndrome as a diagnostic possibility. The patient continued deteriorating, presenting metabolic acidosis, hypotension and oliguria until death ensued 3 days after hospitalization.

Case 3

A two month old girl was hospitalized with a diagnosis of clinical sepsis, anemia and thrombocytopenia. The patient developed hepatomegaly and continued pancytopenic requiring multiple platelets, packed red blood cell transfusions, and immunoglobulins.

The Hematology and Infectious Diseases Services recommended a workup for viral infection (TORCH, CMV, and Parvovirus). Initially, the patient was started in antibiotics, and was found with hepatosplenomegaly. An abdominal ultrasound with Doppler and abdominal CT scan showed no evidence of thrombosis or Budd-Chiari malformation. Tests for viral infections were negative. A bone marrow biopsy was performed to rule out a familial erythrophagocytic lymphohistiocytosis (FEL), but this biopsy showed mostly cortical bone and bone spicules with few marrow particles that were normocellular with a moderate number of nonspecific histiocytes, negative for S-100 inmunostain. A repeated bone marrow biopsy presented 100% cellularity, marrow elements mostly composed of histiocytes and markedly decreased marrow elements. This biopsy was diagnosed as histiocytosis.

Since the patient continued with hepatosplenomegaly, transfusion-dependent pancytopenia and a definite diagnosis could not be rendered in spite of workup performed, including metabolic workup, the case was discussed at Tumor Board and a liver biopsy was recommended. After liver biopsy, patient complicated hemodynamically. Patient died 23 days after hospitalization. The liver biopsy presented atypical histiocytosis within sinusoids.

Pathology findings

Autopsy findings were similar in all three patients and confirmed the clinical diagnosis of an infection-associated hemophagocytic syndrome.

These three patients were mildly icteric and presented marked abdominal distention and hepatosplenomegaly. Cases 1 and 2 presented anasarca and case 2 in addition to anasarca, also presented marked nephromegaly.

Histologically, almost all tissues examined were affected by a lymphohistiocytic infiltrate characterized by mature lymphocytes and benign histiocytes. Within these infiltrates, but more prominent in the bone marrow, lungs and spleen, hemophagocytosis was observed (Figure 1). Grocott stains for fungi and Ziehl Neelson stain for acid-

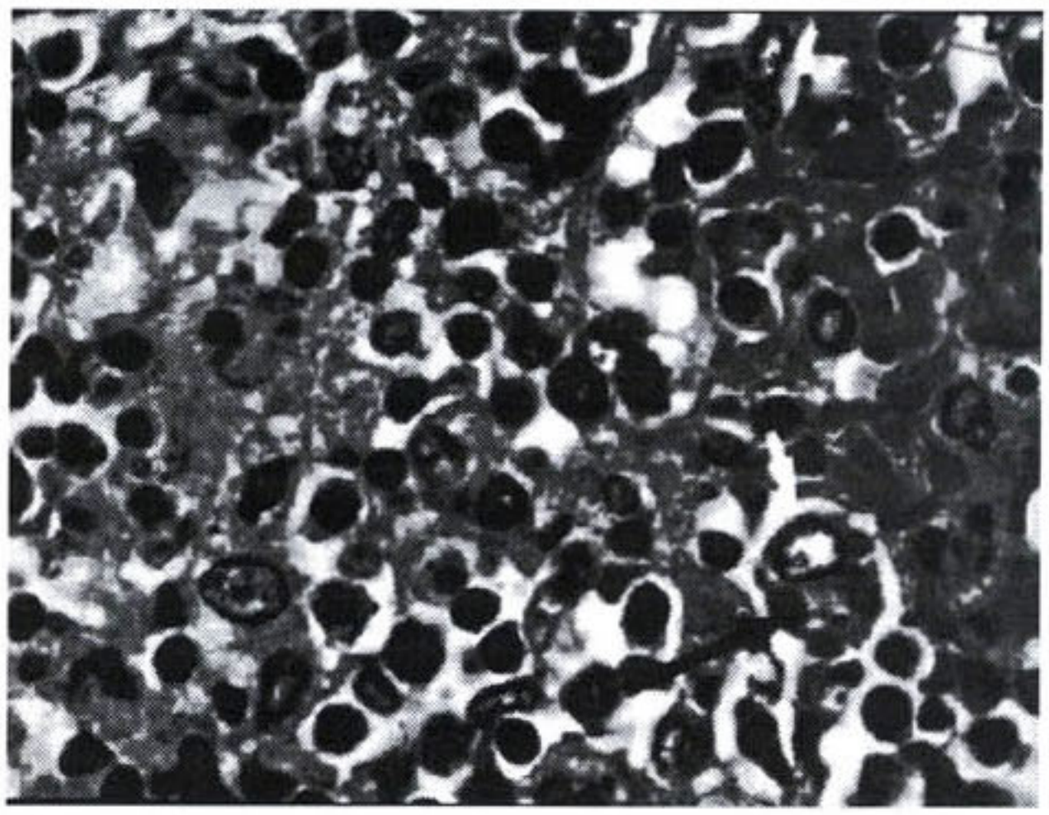

Figure 1. Spleen. Note benign histiocytes with hemophagocytosis.(Oil inmersion).

fast bacilli performed in bone marrow sections failed to reveal any organisms. Immunohistochemistry showed positive immuno-expression for CD68 highlighting an increased number of histiocytes within the bone marrow (Figure 2). Case 3 disclosed similar lymphohistiocytic infiltrates in the meninges. The liver revealed moderate steatosis and cholestasis.

Unfortunately, these three patients died of complications of their underlying disease. The first patient died of diffuse alveolar damage with acute bronchopneumonia, edema,

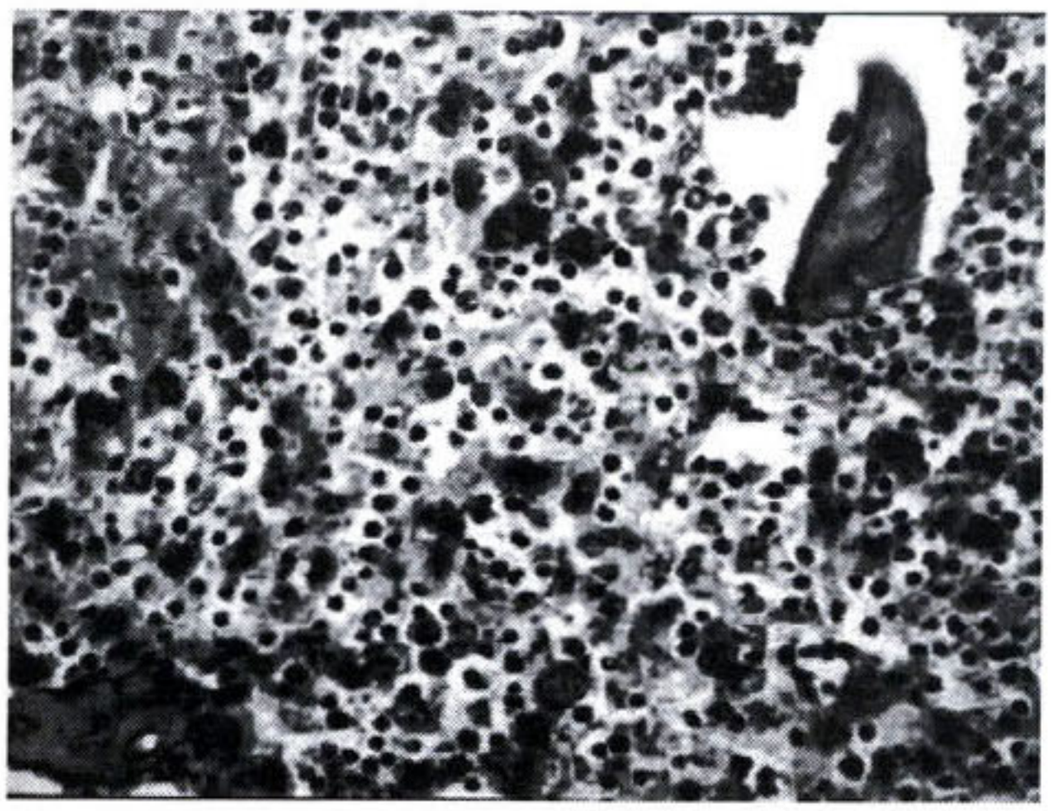

Figure 2. Bone marrow. CD68 immunostain highlights increased number of histiocytes. (40X)

and pulmonary hemorrhages. The second patient died of diffuse alveolar damage with prominent pulmonary hemorrhages. The third patient died of hypovolemic shock after liver needle biopsy in an attempt to establish a definitive diagnosis.

Discussion

In 1979, Risdall and associates described 19 patients with a clinical syndrome characterized by fever, hepatosplenomegaly and progressive pancytopenia in which a benign histiocytic proliferation and hemophagocytosis were the main pathologic findings (5). Lymphadenopathy, pulmonary infiltrates, and skin rash were often present, and many patients had elevated transaminases, high bilirubin levels, increased alkaline phosphatase, prolonged partial thromboplastin time, hypofibrinogenemia, elevated lactate dehydrogenase and triglicerides. This syndrome was mainly observed in a setting of viral infection and immunosuppression, and has been strongly associated with Epstein-Barr virus, herpes virus, hepatitis B, hepatitis C, HIV, CMV, and adenovirus. Afterwards, many similar cases have been described and it has been proven that many other causes besides the ones described above contribute to the development of this condition. It has been shown that bacteria, parasites, fungi and even malignancies, most lymphomas, may also induce it. However, in some patients, an infectious agent could not be found by serology, but only by in situ hybridization.

Hemophagocytic lymphohistiocytosis (HLH) includes the frequently indistinguishable secondary hemophagocytic syndromes which include infection and malignancy-associated hemophagocytic syndrome, and familial hemophagocytic syndrome. We have presented three pediatric patients with infection-associated (secondary) hemophagocytic syndrome, in which pancytopenia, hepatosplenomegaly and deranged liver function were the main clinical findings. A tertiary care hospital is our setting, and other studies have also demonstrated that this is where this condition is most commonly observed (8).

The clinical features of this condition have been well characterized, however, the pathogenesis is not quite clear. It is strongly suggested that these patients have an underlying problem of immune regulation, mainly a dysfunction of cellular cytotoxicity. Many patients show a deficiency in natural killer (NK) cell activity sometimes during the course of the disease, although some patients may have normal function (7). In another set of patients NK cell activity becomes negative during the course of the disease and remains so throughout. Possible mechanisms leading to NK deficiency could be nonexpression of effector molecules of cellular cytotoxicity such as granzymes which could be inherited in the familial form or transient in IAHS, or target-induced NK-cell anergy. Activated lymphocytes also play a role in the pathogenesis as well as large amounts of macrophage inflammatory protein (MIP)-1α, which blocks hematopoietic progenitor

differentiation and induces monocyte hyperactivation and a profound inflammatory response to viral infections (7). There are also large amounts of cytokines including gamma interferon, tumor necrosis factor alpha, macrophage colony stimulating factor, soluble interleukin IL-2 receptor, and interleukins 1 and 6. Nevertheless, it is still not clear whether the NK-cell activity is a constitutional or secondary feature of hemophagocytic lympho-histiocytosis. Genetic studies have suggested a role of certain HLA alleles on susceptibility of the disease, and the many clinical variations may be due in turn to many genetic variations (8).

The pathology shows marked benign histiocytic hyperplasia with hemophagocytosis, which is essential but not specific for this condition. This may be encountered in virtually every organ, but most commonly in spleen, lymph nodes, bone marrow and liver. In the cerebrospinal fluid, a moderate pleocytosis is frequently seen, predominantly due to small lymphocytes (9).

As stated before, this syndrome is usually seen as a complication of common infection. Infection-associated hemophagocytic syndrome by bacterial infection has been linked to a high recovery rate; the worst prognosis has been found with EBV infection (7). However, many patients develop disseminated, multisystemic disease and die of their underlying diseases. Children below 3 years of age show the highest mortality rate, and prognosis is especially poor in children below one year of age (7).

There is still no effective means of distinguishing secondary hemophagocytic syndrome from familial hemophagocytic histiocytosis. The clinical and pathophysiologic findings are identical in both conditions. The latter is an autosomal recessive disease, hence a negative family history does not rule out the disease. Additionally, positive identification of an infectious agent does not rule out the familial form. Detection of a specific genetic lesion at a molecular level will provide the means to establish it as a genetic disease (7-9).

Resumen

El síndrome hemofagocítico asociado a infección es una complicación rara de una infección sistémica con consecuencias potencialmente fatales. Frecuentemente ocurre en pacientes inmunosuprimidos asociado a una infección viral pero el espectro de condiciones incluye virtualmente cualquier patógeno infeccioso, malignidad, incluso terapia immunosupresiva. Presentamos tres pacientes pediátricos con un cuadro clínico similar de pancitopenia, hepatosplenomegalia y fallo agudo hepático y discutimos los hallazgos de autopsia.

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