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Hemophagocytic lymphohistiocytosis of indeterminate cause: a fatal adult case

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ABSTRACT

Hemophagocytic lymphohistiocytosis (HLH) is an uncommon life-threatening disorder characterized by wide spread non-neoplastic proliferation and inappropriate activation of mature macrophages resulting in hypercytokinemia. This uncontrollable and ineffective systemic immune response causes fever, hepatosplenomegaly, cytopenias and subsequently multiorgan failure. The authors report a case of a 41-year-old male patient with a 30-day history of weight loss, fever, icterus, hepatomegaly, and cytopenias. The diagnostic workup disclosed hypertriglyceridemia, hypofibrinogenemia, and elevated ferritin. Bone marrow examination and clinical course raised the suspicion of HLH and treatment was started with high-dose corticosteroids and immune globulin. The patient underwent multi-organ failure and expired after 58 days of hospitalization. The autopsy finding included massive bone marrow infiltration by non-neoplastic histiocytes, many of them showing hemophagocytosis, which immunohistochemical study revealed diffuse CD68-positive histiocytes, which were negative for S100 protein. Hemophagocytosis was also observed in the lungs, lymph nodes and liver. The immediate cause of death was attributed to a massive intestinal bleeding due to extensive ischemic necrosis at the duodenum/jejunal transition area.

Keywords: Hemophagocytic syndrome; Hemophagocytic lymphohistiocytosis; Macrophage activation; Autopsy.

CASE REPORT

A 41-year-old male patient sought medical attention complaining of daily high-grade fever accompanied by night sweats and 20 kg of weight loss during the last month. He reported that he was experiencing anorexia, asthenia, and progressive lower-limb weakness and recently noted jaundice. His past medical history included hypertension. He used to drink a lot of alcohol in the past, still smokes and was taking captopril regularly. Physical examination upon admission showed an apparently healthy man, febrile, slightly dehydrated, and icteric. His blood pressure = 120 / 75 mmHg, pulse rate = 106 beats per minute, respiratory rate = 18 respiratory movements per minute, axillary

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body temperature = 38 °C, body mass index = 21.6. Peripheral lymph node enlargement was not detected. Thorax examination showed the presence of a mild systolic murmur in the mitral valve area, and the lung examination was normal. Abdominal examination showed a palpable liver 1 cm below the right costal margin, as well as painful splenomegaly 5 cm below the left costal margin. The remainder of the physical examination was unremarkable.

Initial laboratory workup is shown in Table 1 and Table 2 summarizes the etiologic investigation.

The upper gastrointestinal endoscopy disclosed an enanthematic pangastritis. Echocardiography was normal. Abdominal ultrasonography showed a splenomegaly with hypoechoic areas within the splenic parenchyma, confirmed by the abdominal computed tomography.

The bone marrow aspiration showed hypercellularity at the expense of the granulocytic series, confirmed on the bone marrow biopsy, which also showed hyperplasia of the megakaryocytic series. On this biopsy, the presence a micro granuloma was also depicted. The Ziehl-Neelsen, Grocott and PAS staining failed to show the presence of acid-fast bacilli and fungi. The bone marrow immunophenotyping did not detect any evidence of lymphoma.

During hospitalization, the patient remained febrile, presented worsening hepatic function, and renal failure demanding hemodialysis. Clinical status was complicated even more with respiratory failure related to presumed pulmonary infection requiring vasopressors and mechanical ventilation. Supportive care involved frequent red cell, platelets, and plasma transfusions. The revision of the bone marrow aspirate hemophagocytosis was detected, which raised the possibility of a diagnosis of hemophagocytic lymphohistiocytosis (HLH). High-dose methylprednisolone (1 g/day for 3 days) was started in conjunction with gamma globulin therapy 30 g/day for 5 days as well as broad-spectrum antibiotics. A slight clinical improvement was observed. On day 25 of hospitalization, the patient underwent a splenectomy and liver biopsy. The procedures were undertaken to confirm the diagnosis as well as to definitively exclude the diagnostic possibility of lymphoid malignancy.

The splenic pathologic examination revealed massive infiltration of the splenic sinusoids by plump phagocytic histiocytes, associated with 95% of ischemic necrosis of the splenic parenchyma and atrophy of the residual white pulp (Figure 1). The liver biopsy revealed Kupffer cell hyperplasia as well as hemophagocytosis.

Cyclosporine could not be started once the patient developed septicemia. The patient died on day 58 of hospitalization. An autopsy was performed.

AUTOPSY

Among the autopsy findings, histopathological examination revealed massive bone marrow infiltration by non-neoplastic histiocytes, many of them showing hemophagocytosis (the presence of red blood cells, granulocytes and their precursors,

Table 1 – Initial laboratory examination work up

Exam	Result	RV	Exam	Result	RV
Hemoglobin	14.8	12.3-15.3 g/dL	AST	443	10-31 U/L
Hematocrit	43.7	36.0-45.0%	ALT	404	9-36 U/L
Leukocytes	4.78	4.4-11.3.10³/mm³	Alkaline phosphatase	719	10-100 U/L
Rods	0	1-5%	γGT	368	2-30 U/L
Segmented	55	46-75%	Total bilirubin	9.6	0.3-1.2 mg/dL
Eosinophil	0	1-4%	LDH	1274	120-246 U/L
Basophil	2	0-2.5%	INR	1.69	1
Lymphocyte	31	18-40%	Fibrinogen	67	175-400 mg/dL
Monocyte	12	2-9%	Triglycerides	617	<150 mg/dL
Platelet	91.7	150-400.10³/mm³	Ferritin	>16500	22-322 ng/mL

ALT = alanine aminotransferase; AST = aspartate aminotransferase; γGT = gamma-glutamyl transferase; INR = international normalization ratio; LDH = lactate dehydrogenase; RV = reference value.

platelet debris as well as lymphocytes encompassed into the cytoplasm of the activated histiocytes) (Figure 2). The immunohistochemical study revealed diffuse CD68-positive histiocytes, which were negative for S100 protein. Other markers were used to evaluate the hematopoietic series and to rule out the presence of lymphomatous infiltration. CD20 was positive in small clusters of B-lymphocytes and rare in interstitial lymphocytes; CD3, CD2, and CD5 were positive in interstitial small T-lymphocytes. No other malignancy was present. The histological and immunohistochemical findings observed in the bone marrow were similar to the previous bone marrow biopsy performed during hospitalization.

Table 2 – Serologic investigation

Exam	Result
Anti-HIV	Negative
Anti-CMV (IgG and IgM)	Negative
Syphilis (VDRL and TPHA)	Negative
Anti EBV	IgG+/IgM–
Hepatitis B	Negative
Anti-HCV	Negative
Toxoplasmosis	IgG+/IgM–
Anti-*S. mansoni* (IgM)	Negative
Rheumatoid Factor	<15 UI/mL
ANF (Hep 2)	Negative

Hemophagocytosis was also observed in the lungs where the histiocytes were detected in the alveolar lumen (Figure 3). The lymph nodes exhibited hemophagocytosis associated with lymphoid depletion (Figure 4).

The examination of the liver also showed the diffuse presence of hemophagocytic histiocytes throughout the hepatic sinusoids (Figure 5). Extensive areas of ischemic centrilobular necrosis, probably related to the septic shock, were also observed.

The examination of the remaining organs revealed pathological changes associated with

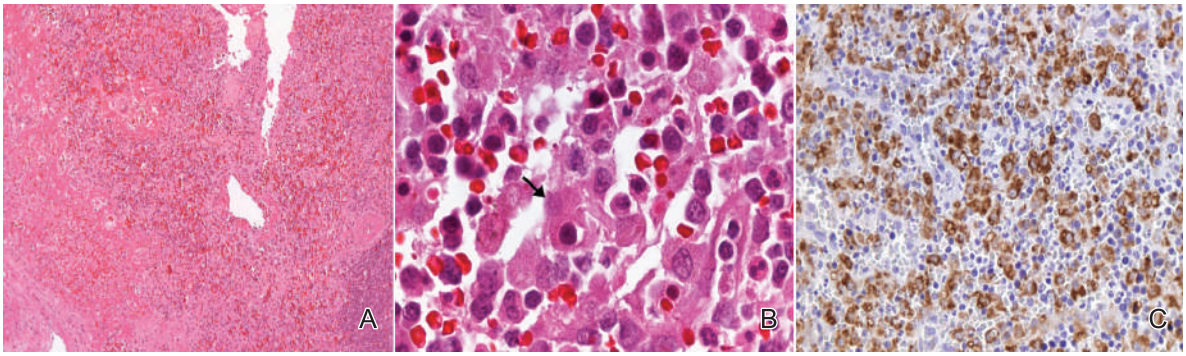

Figure 1 – Photomicrography of the spleen. **A -** Ischemic necrosis of the splenic parenchyma and atrophy of the residual white pulp (HE, 100X); **B -** Massive infiltration of the splenic sinusoids by phagocytic histiocytes (arrow, with a hematologic precursor cell inside the cytoplasm) (HE 400X); **C -** Immunohistochemical reaction reveals the CD68 positive histiocytes (Immunoperoxidase for CD 68).

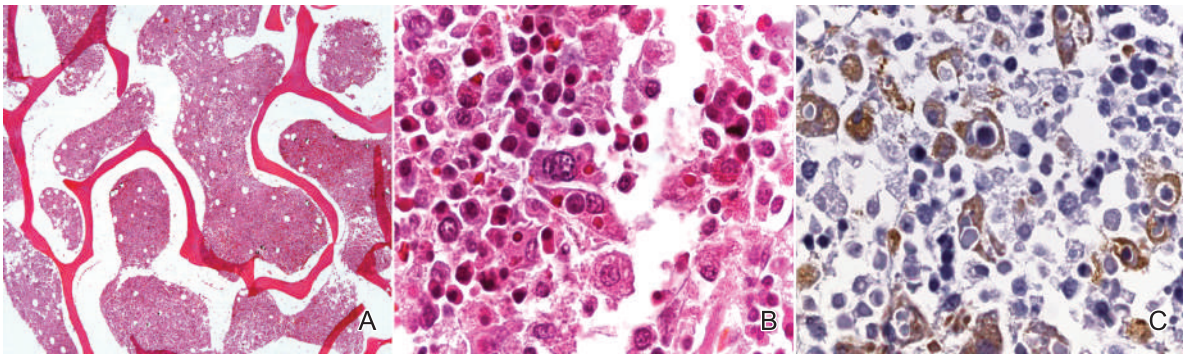

Figure 2 – Photomicrography of the bone marrow. **A -** Panoramic view of bone marrow shows hypercellularity (HE 100X); **B -** Massive bone marrow infiltration by non-neoplastic histiocytes, many of them showing hemophagocytosis (HE, 400X); **C -** Immunohistochemical reaction reveals the CD68 positive histiocytes (Immunoperoxidase for CD 68).

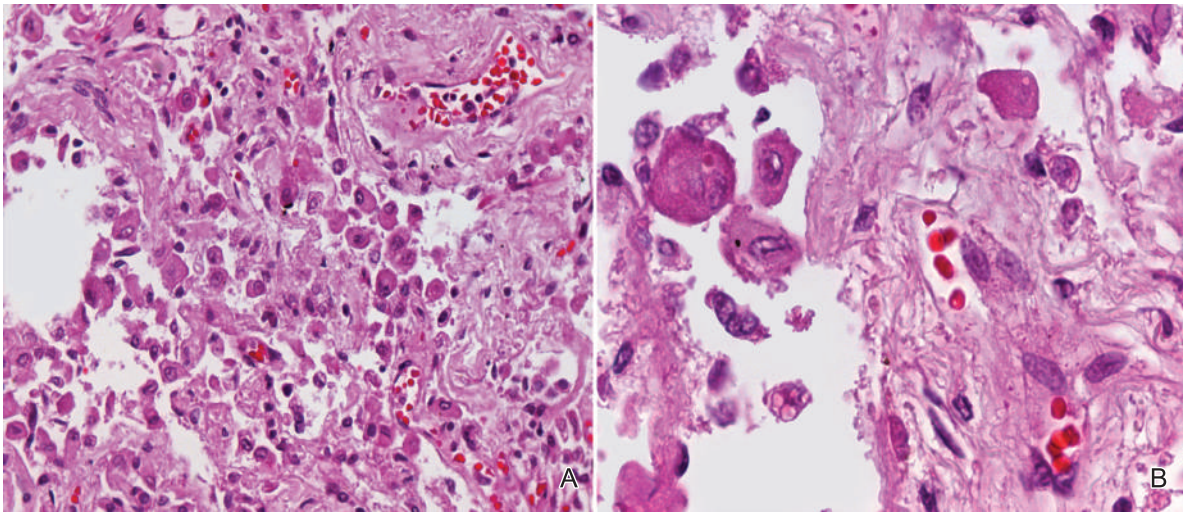

Figure 3 – Photomicrography of the lung. **A -** The alveolar lumen shows many histiocytes. (HE, 200X); **B -** Hemophagocytosis (arrow) (HE, 1000X).

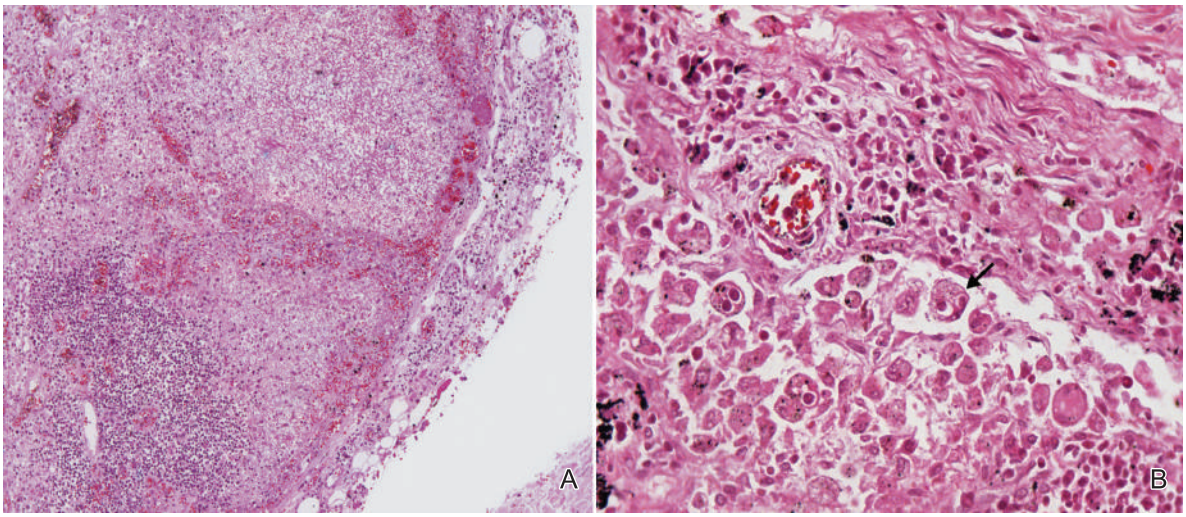

Figure 4 – Photomicrography of the lymph nodes. **A -** Lymphoid depletion. (HE, 200X); **B -** Histiocytes in the lymph node sinuses show hemophagocytosis (arrows) (HE, 400X).

infection and septic shock. The lungs were congested; the right lung weighted 639.0 g (reference value RV = 450.0 g) and the left lung weighted 432.0 g (RV = 375.0 g). Microscopically, intra-alveolar edema and massive congestion were present, as well as hemophagocytic histiocytes into the alveolar lumen. Ischemic injuries were found in many organs, very likely due to the septic shock. The duodenum/jejunal transition area showed extensive mucosal injury and diffuse bleeding, with a large amount (estimated at 500 g) of clots in the small intestine lumen. Its microscopic examination showed ischemic necrosis of the mucosa exhibiting massive intestinal bleeding, which was interpreted as the immediate cause of death (Figure 6). The autopsy also revealed acute renal tubular necrosis, infarction, and hemorrhage of the adrenal gland cortex, foci of ischemic necrosis of pancreatic acini, ischemic pituitary infarct, and skin ulcerations.

DISCUSSION

The term hemophagocytosis describes the pathologic finding of activated macrophages, engulfing erythrocytes, leukocytes, platelets, and their precursor cells. This phenomenon is an important finding in patients with hemophagocytic syndrome (HS), also known as hemophagocytic lymphohistiocytosis (HLH). This rare and frequently fatal disorder is characterized by unregulated

activation of the immune system, resulting in a systemic inflammatory response syndrome (SIRS).[1] Although rare, increased awareness of these conditions has led to more frequent diagnoses.

HLH occurs in all age groups and is classified in two major forms: genetic or primary, and acquired or secondary. Farquhar and Claireux from the University of Edinburgh are credited with the first description of genetic HLH in 1952, which they named after "familial hemophagocytic reticulosis."[2] This genetic or primary HLH is inherited in an autosomal recessive or x-linked manner and is divided into a) familial HLH (FHLH) in which the clinical syndrome of HLH is the only manifestation; and b) the immune deficiencies like Chédiak-Higashi syndrome, Griscelli syndrome, and x-linked proliferative syndrome, in which the HLH may develop.[3] In FHLH, the onset of the disease occurs in 70-80% of cases below 1 year of age, although several late-onset cases have been reported.[4,5] The acquired, or secondary HLH was first described by Risdall in 1979 and occurs in all age groups.[6] The leading triggering agents in secondary HLH are viruses of the herpes group, especially Epstein-Barr virus (EBV) and cytomegalovirus (CMV). Other examples include varicella zoster virus,[7] human herpesvirus (HHV)-6,[8] and HHV-8,[9] HIV,[10] Rubella,[11] adenovirus,[12] parvovirus,[8] hepatitis B virus,[13] and avian influenza.[14] The latter is a particularly potent stimulus for hemophagocytic reactions in Asia, probably associated with the high mortality observed in that infection. Other microbial pathogens include Mycobacterium tuberculosis,[15] Serratia marcenses,[16] Burkholderia cepacia,[17] and fungal infections such as candidiasis,[18] aspergillosis,[19] and histoplasmosis.[20] The identification of an infectious organism does not necessarily discriminate between the genetic and acquired form of HLH, since most episodes in genetic HLH may also be triggered by infections.[21]

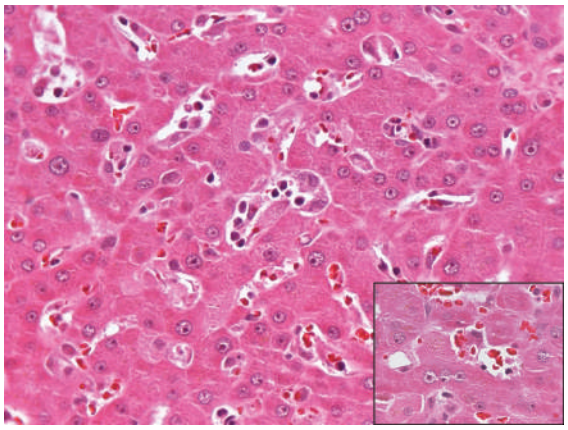

Figure 5 – Photomicrography of the liver. **A -** Diffuse presence of hemophagocytic histiocytes throughout the hepatic sinusoids (HE, 400X); **B -** Detail (HE, 1000X).

Acquired HLH has also been reported, mostly in adults, in association with malignant diseases especially lymphomas, lymphoma-associated hemophagocytic syndrome (LAHS). In Japan, the EBV genome was detected in more than 80% of patients with T/NK cell lymphoma.[22] The EBV-infected T/NK cells seem to play a major role in the development of LAHS, as well as in EBV-associated HLH without lymphoma.[23] The HLH that occurs in association with autoimmune diseases is called macrophage-activation syndrome (MAS) and is

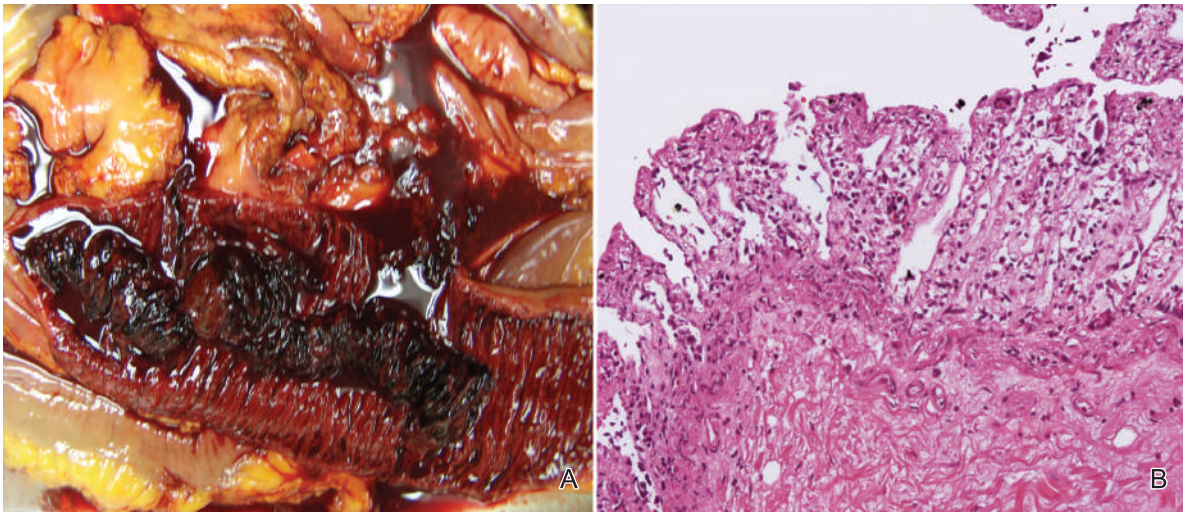

Figure 6 – Duodenum/jejunal transition. **A -** Gross examination reveal extensive mucosal injury with diffuse bleeding, with large amount of clots into the small intestine lumen; **B -** Photomicrography of the small intestine showing ischemic necrosis of the mucosa (HE, 200X).

now considered a special form of HLH occurring in patients with juvenile rheumatoid arthritis, systemic erythematous lupus, Behcet's syndrome and other entities. The MAS has many characteristic features of HLH, but cytopenias may be less severe, cardiac impairment appears to be more common and coagulopathy more pronounced.[24,25] In the case reported here, the laboratory workup failed to point out a triggering etiological agent, and the autopsy failed to reveal evidence of a lymphoma.

The differential diagnosis of non-neoplastic proliferation of histiocytes, regarding histopathological features, includes (Table 3).

Sinus histiocytosis with massive lymphadenopathy (SHML), also known as Rosai-Dorfman Disease deserves special attention in the differential diagnosis of this case. This disorder is characterized by massive bilateral enlargement of cervical lymph nodes, which show, in the histological examination, sinuses expansion by large histiocytes, lymphocytes and plasma cells. The histiocytes show intracytoplasmic vacuoles with the presence of lymphocytes and plasma cells, a process called emperipolesis, as well as erythrophagocytosis.[26] Unlike the HLH, however, the histiocytes in the SHML express S-100, what was negative in the present case, permitting the exclusion of this diagnostic possibility. HLH, mainly in the familial form, occurring in early life, can mimic SHML. The pathologic features of the HLH are characterized by lymphoid depletion and massive sinusoidal infiltration by histiocytes. Contrasting with SHML, hemophagocytic syndromes present as a disseminated disease of aggressive clinical course [26], occasionally seen in the SHML[27].

The Histiocytic Sarcoma (HS), a malignant proliferation of cells with morphologic and immunophenotypic features of mature tissue histiocytes[28] could be consider in the differential diagnosis of the case presented here. This disorder was previously called true Histiocytic Lymphoma or Malignant Histiocytosis, but as they were subsequently shown to be lymphomas, generally of T-cell origin, these terms were no longer used. In contrast to HLH, patients with HS present tumoral skin lesions (solitary or multiple), bone lytic lesions and primary tumors in the central nervous system. On the other hand, HLH is characterized by diffuse, rather than localized, histiocytic infiltration. The histopathology of HS shows lymph node involvement by malignant cells similar to histiocytes and the visceral organ involvement may exhibit a sinusal pattern. Hemophagocytosis is seldom seen in the tumor cells, which show large pleomorphic nuclei and variable mitotic activity[26].

Table 3 – Non-neoplastic histiocytic proliferations[26]

(1) Reactive sinus histiocytosis
(2) Sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman)
(3) Hemophagocytic syndromes: 3.a - Familial hemophagocytic lymphohistiocytosis 3.b - Secondary hemophagocytic syndromes
(4) Storage disorders 4.a - Niemann-Pick disease 4.b - Gaucher's disease 4.c - Tangier disease

The incidence of HLH in adults is unknown. The disorder is believed to be underdiagnosed, and most reported studies are related to children. In the case of the primary autosomal recessive form, also known as familial hemophagocytic lymphohistiocytosis (FHL), the incidence is estimated at 1:50,000 live born children.[29]

The supposed pathophysiology of HLH is an uncontrolled stimulation of histiocytes (macrophages and dendritic cells), natural killer (NK) cells, cytotoxic T lymphocytes (CTLs) leading to persistent hypercytokinemia and systemic inflammatory response syndrome (SIRS).[25] In patients with hemophagocytic syndrome, splenic macrophages appear to be activated, as evidenced by increased expression of major histocompatibility complex Class I (MHC-I) and MHC-II molecules, as well as the macrophage colony-stimulating factor receptor.[30] Once triggered by an infectious agent, histiocytes (macrophages and dendritic cells), NK cells, and CTLs are activated and mutually stimulate each other. NK cells and CTLs kill their targets through cytolytic vesicles containing perforin and granzyme. The cytolytic vesicles are formed in the killer cells, fuse with the plasma membrane and release their content in the immunological synapse, which is formed upon contact between the killer and the target cells.[31] This sequence of events ends with the killing of the offending agent, removal of the antigen, and termination of the immune response. Deficient cytotoxic activity impairs the elimination of cellular targets, expressing antigens and the down-regulation of the immune response as well. This process may be compromised by defects caused by mutations and will be responsible for the inherited or primary HLH.

Currently, nine genetic disorders have been described as related to the diagnosis of HLH in children; many familial cases still await molecular definition.[25] Abnormalities in the function (but rarely in the quantity) of NK cells have been observed in patients with all forms of HLH.[25] Sustained immune activation with persistent high cytokine levels will be responsible for the clinical picture of HLH. Studies of cytokine levels in blood and tissues have indicated persistently elevated circulating levels of multiple proinflammatory cytokines during symptomatic disease.[25] It is not fully clear how apparently immunocompetent patients develop dysfunction of NK cells and CTLs following triggering events, such as viral infections. In the case of EBV infection, it is believed that instead of affecting B-lymphocytes, as usual, the virus infects NK-T cells, stimulating their proliferation with subsequent production of proinflammatory cytokines, particularly tumor necrosis factor-α (TNF-α) and interferon-γ, through the stimulation by EBV latent-membrane-protein 1 (LMP-1). This hypercytokinemia stimulates macrophages leading to the HLH. EBV infection has also been implicated in the pathogenesis of LAHS—the latter being a continuum of the natural progression of T-cell infection with EBV. Some patients diagnosed with EBV-associated HLH who survived have been observed to progress to T-cell lymphoma. Latent-membrane-protein 1 is believed to protect the EBV-infected T cells against the TNF-α-induced apoptosis. These cells are thought to survive and can later cause a relapse of the disease.[1] Chromosome analysis of EBV-infected T-cells in patients with HLH showed clonality early in the course of the disease, accounting for further progression to lymphoma.[32] Viruses may interfere with CTL function by specific proteins; high levels of cytokines may have the same effect. The high prevalence of EBV-associated HLH in Asia also suggests a genetic basis. In patients with lymphomas, secretion of cytokines by the malignant cells is a possible explanation.[3]

The clinical and laboratory findings of HLH consist in prolonged fever, hepatosplenomegaly, and cytopenias, and less frequently, lymphadenopathy, rash, icterus, and neurological symptoms, many of them observed in the patient reported here. Characteristic laboratory alterations include high levels of triglycerides, ferritin, liver enzymes, bilirubin, lactate dehydrogenase, and low fibrinogen due to endothelial activation/coagulopathy, as observed in our patient.[24,25] A hallmark of HLH, no matter if in genetic or acquired form, is the impaired or absent function of NK and cytotoxic-T cells. The number of NK cells may be normal or decreased.[33] The symptoms of HLH can be explained by high concentrations of cytokines and organ infiltration by activated lymphocytes and histiocytes.[30] Ongoing hypercytokinemia is a reflection of the failure of natural immune down-regulation due to defective NK and CTL function.[25] Fever is induced by interleukin-1 (IL-1) and IL-6, and pancytopenia is rather the consequence of high levels of TNF-α and interferon γ, than of hemophagocytosis. TNF-α inhibits lipoprotein lipase leading to elevated triglycerides. Activated macrophages not only secrete ferritin but also plasminogen activators, which results in high plasmin levels and hyper fibrinolysis, hepatosplenomegaly, increased liver enzymes and bilirubin.[3] The Histiocyte Society created diagnostic guidelines in 1991, based on common clinical, laboratory, and histopathological findings. This guideline was revised keeping the five criteria of the 1991 guidelines but introducing three additional criteria. The diagnostic criteria for HLH are summarized in Table 4.

A recent review undertaken in a pediatric hospital concerning elevated ferritin results showed that ferritin levels greater than 10,000 mcg/dL were 90% sensitive and 96% specific for HLH diagnosis.[35] Although hemophagocytosis in biopsy specimens is the hallmark of HLH, the absence of this finding should not hinder the physician from starting treatment if other diagnostic criteria are met. It is not uncommon to require more than one biopsy specimen to demonstrate this microscopic evidence. On the other hand, the mere presence of hemophagocytosis in the reticuloendothelial system is not implied in the diagnosis, once it also occurs in other disorders.[1,21] Some valuable diagnostic and disease markers are: increased concentrations of IL-2 receptor (sCD25) and decreased NK cell function, b-2 microglobulin,[31] macrophage inflammatory protein-1a (MIP-1a)[36] and CD163.[37]

In the diagnostic work up for infectious agent, searching for EBV, CMV, herpes simplex virus, adenovirus, parvovirus B19, and others are recommended. The patient should be screened for underlying immune deficiency, autoimmune diseases, and malignancies.

Since HLH masquerades as a normal infection, the diagnosis is frequently challenging. Time may then be lost with extensive workup for an infectious disease and consequently prolonged antibiotic therapy. Ferritin, fibrinogen, and triglycerides are not routinely determined in patients with fever, and the absence of hemophagocytosis,

Table 4 – Revised diagnostic guidelines for HLH[34]

The diagnosis HLH can be established if one of either 1 or 2 below is fulfilled
(1) A molecular diagnosis consistent with HLH
(2) Diagnostic criteria for HLH fulfilled (5 out of the 8 criteria below)
(A) Initial diagnostic criteria (to be evaluated in all patients with HLH)
Fever
Splenomegaly
Cytopenias (affecting 2 of 3 lineages in the peripheral blood): Hemoglobin <9 g/dL (in infants <4 weeks: hemoglobin <10g/dL), Platelets <10,000/mm^3, Neutrophils <1,000/ mm^3
Hypertriglyceridemia and/or hypofibrinogenemia: Fasting triglycerides ≥265 mg/dl, Fibrinogen <150 mg/dL
Hemophagocytosis in bone marrow or spleen or lymph nodes
No evidence of malignancy
(B) New diagnostic criteria
Low or absent NK-cell activity (according to local laboratory reference)
Ferritin >500 mg/L
Soluble CD25 (i.e. soluble IL-2 receptor) ≥2,400 U/mL

in the early stage of the disease, is often the reason why the diagnosis is unwarranted.[3]

Because HLH can be rapidly fatal without specific intervention, treatment should be started when a clinical suspicion exists, even when the results of diagnostic studies are still pending.[25] High dose corticosteroids, which are cytotoxic for lymphocytes and inhibit expression of cytokines and differentiation of dendritic cells, are indicated for the treatment of HLH. Immunoglobulin has been used mainly in the treatment of adults. They act by cytokine and pathogen-specific antibodies. Cyclosporine A, which affects T-lymphocyte activation and macrophage function, has proved to be effective for maintaining remission in genetic HLH.[38] Etoposide is another option for HLH treatment. The HLH-2004 protocol was designed for patients with or without evidence of familial or genetic disease regardless of the presence of suspected or documented viral infections. In this protocol, patients under the age of 18 years at the onset of treatment who fulfill the diagnostic criteria are advised to receive dexamethasone, etoposide and cyclosporine A in an initial therapy scheme for eight weeks.[34]

The therapeutic effect of the splenectomy has not been extensively reported. Imashuku et al. reported five cases in which splenectomy was part of the treatment; three patients died after the procedure.[39] Zang et al. reported a case in which the splenectomy showed benefit and considered the splenectomy as a diagnostic aiding tool for HLH.[40]

HLH is still overlooked since the clinical symptoms are similar to infections found in immune competent patients. Hemophagocytosis does not have to be present in the initial diagnostic workup. Patients with prolonged fever, unresponsive to antibiotics, accompanied by pronounced hepatosplenomegaly and cytopenias should be highly considered in the differential diagnosis of HLH. Due to the severity of the disease, clinical suspicion has to be followed by exhaustive search for the precise diagnosis and early institution of therapy.

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