

Hemophagocytic syndrome: a dilemma chasing the intensivists

Adriana Façanha Queiroz^a, Gabriel Nuncio Benevides^a,
Iracema de Cassia Oliveira Ferreira Fernandes^b, Patricia de Freitas Goes^b,
Albert Bousso^b, Cristiane Rubia Ferreira^c

Queiroz AF, Benevides GN, Fernandes ICOF, Goes PF, Bousso A, Ferreira CR. Hemophagocytic syndrome: a dilemma chasing the intensivists. Autopsy Case Rep [Internet]. 2015; 5(1):11-19. <http://dx.doi.org/10.4322/acr.2014.044>

ABSTRACT

Hemophagocytic lymphohistiocytosis or hemophagocytic syndrome is represented by an uncontrolled inflammatory response characterized by marked histiocyte activation and a cytokine storm. The entity may present a primary or genetic type, and the secondary type is usually triggered by infectious diseases of any kind, autoimmune disease, or neoplasia. This entity, although well described and with definite diagnostic criteria, still remains misdiagnosed because of the overlap presentation with other inflammatory processes. The authors present the case of a 13-year-old girl who was submitted to an appendectomy complicated with a pericolic abscess, which required a second operation in order to be drained surgically. During the postoperative period of this second surgical procedure, the patient remained febrile, developing cytopenias, and multiple organ failure. Unfortunately, she died despite the efforts of the intensive care. The autopsy findings were characteristic of hemophagocytic syndrome. The authors report the case to call attention to this diagnosis whenever unexpected outcomes of infections are experienced.

Keywords

Hemophagocytic Syndrome; Hemophagocytic Lymphohistiocytosis; Appendectomy; Autopsy

CASE REPORT

A 13-year-old girl was brought to medical attention complaining of fever and loss of appetite for 3 days, soon after she had been discharged after an appendectomy. On physical examination she was dehydrated, presenting tachycardia, tachypnea, and fever (axillary temperature was 38.8 °C). Blood pressure was 120/70 mmHg. Cardiac and pulmonary examination was normal, but the abdomen was diffusely tender; the rebound test was painful; intestinal sounds were present and normal. The surgical scar was

hyperemic. The abdominal ultrasound examination showed a pericolic image consistent with abscess, which was surgically drained. The abdominal secretion culture was positive for multisensitive *E. coli* and group G, β -hemolytic *Streptococcus sp.* Ceftriaxone and metronidazole were prescribed.

On the third post-operative day, the patient still referred abdominal pain, and the fever relapsed. Antibiotics were changed to vancomycin, ceftazidime and amikacin, but fever remained intermittently

^a Pediatrics Department - Hospital das Clínicas - Universidade de São Paulo, São Paulo/SP - Brazil.

^b Pediatrics Division - Intensive Care Unit - Hospital Universitário - Universidade de São Paulo, São Paulo/SP - Brazil.

^c Anatomy Pathology Service - Hospital Universitário - Universidade de São Paulo, São Paulo/SP - Brazil.



present. Abdominal computed tomography (CT) ruled out any surgical complication and the patient remained on a broad-spectrum antibiotic regimen, to which fluconazole was added. On the twelfth post-operative day (from the second surgery) the patient became hypotensive and tachycardic, and her temperature rose to 39.4 °C, reason why she was referred to the ICU. Vasoactive drugs were required for hemodynamic stabilization. The laboratory work-up is shown in Table 1. Blood and urine cultures were negative, and the transthoracic echo Doppler cardiogram was normal. The patient outcome worsened with progressive respiratory failure.

Another abdominal CT was done, which ruled out the presence of abscesses. Serologies are shown in Table 2.

A thorough microbiological examination was repeated. The blood, urine, catheter, and abdominal fluid cultures were negative. At the twentieth post-operative day, the blood cell count showed thrombocytopenia, hyperbilirubinemia, enlarged prothrombin time, and altered liver enzymes. On the twenty-second post-

operative day, the patient underwent an exploratory laparotomy in the pursuit of an abscess not evidenced by CT, which could explain the septic shock. On this third surgical procedure, loose peritoneal adhesions were present, but neither purulent secretion, nor intestinal perforation or bowel necrosis was found. The patient's outcome was worse and troublesome with multiple organ failure, requiring hemodialysis and frequent blood transfusions. Despite all efforts, she died on the twenty-fourth post-operative day. An autopsy was performed.

AUTOPSY FINDINGS

The corpse ectoscopy showed a Bogota bag closing the peritoneotomy. At the cavity overture, mild serohemorrhagic effusion was drained and non-dehiscent surgical sutures were revealed joining the distal ileum with the ascending colon. Neither signs of peritonitis nor intra-abdominal purulent collection were found.

Table 1. Laboratory work-up

Exam	Result	RV	Exam	Result	RV
Hemoglobin	8.9	12.3–15.3 g/dL	ALT	16556	9–36 IU/L
Hematocrit	24.6	36.0–45.0%	AST	6126	10–31 IU/L
Leukocytes	7.2	4.4–11.3 × 10 ³ /mm ³	AP	926	10–100 IU/L
Bands	14	1–5%	γGT	202	2–30 IU/L
Segmented	64	45–70%	TB	7.6	0.3–1.2 mg/dL
Eosinophil	0	1–4%	INR	4.66	1
Basophil	0	0–2.5%	Fibrinogen	98	175–400 mg/dL
Lymphocyte	8	18–40%	Triglycerides	105	< 150 mg/dL
Monocytes	1	2–9%	Ferritin	1287	22–322 ng/mL
Platelets	26.9	150–400 × 10 ³ /mm ³			

ALT = alanine aminotransferase; AP = alkaline phosphatase; AST = aspartate aminotransferase; γGT = gamma-glutamyl-transferase; INR = international normalized ratio; RV = reference value; TB = total bilirubin.

Table 2. Serologic investigation

Exam	Result	Exam	Result
Anti-HIV	Negative	Hepatitis B	Anti HBs+/HBsAg–/HBC–
Anti-CMV	IgG+/IgM–	Anti-HCV	Negative
Anti-EBV	IgG+/IgM–	Rubella	IgG+/IgM–
Hepatitis A	IgG+/IgM–	Aslo	< 80 UI/mL

CMV = cytomegalovirus; EBV = Epstein-Barr virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IgG = immunoglobulin G; IgM = immunoglobulin M.

The liver was enlarged and weighed 1280 g (mean reference value [mRV]: 1275 g); the capsular surface exhibited winy-colored areas. At the cut surface, extensive poorly defined yellowish parenchyma areas were evident intermingled with winy-colored areas consistent with infarction. At microscopy, extensive ischemic lobular necrosis was present as well as macro and microvesicular steatosis (Figure 1).

The spleen was enlarged and weighed 271 g (reference value [RV]: 112 g). The cut surface was winy, friable, and consistent with a reactive pattern. At microscopy, the white pulp was depleted and the red pulp was congested, and both were intermingled with ischemic infarction areas. Numerous histiocytes, phagocytizing red blood cells, and lymphocytes were present (Figure 2).

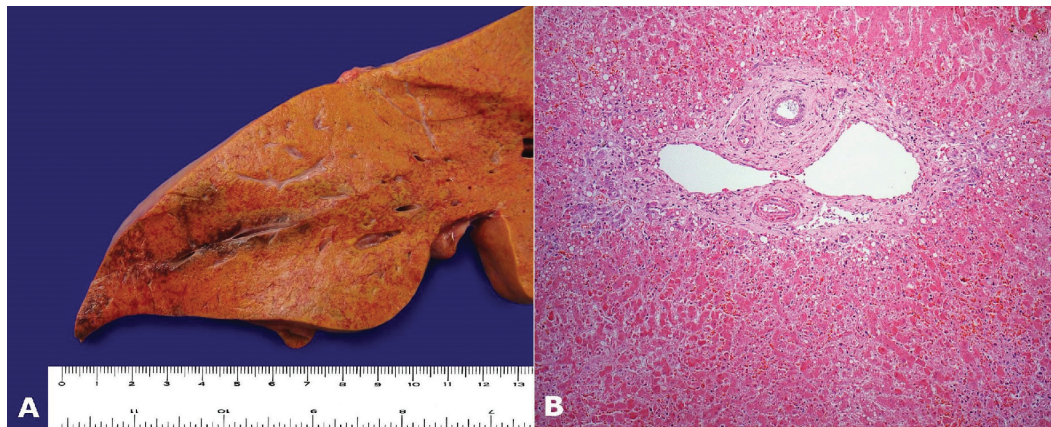


Figure 1. Gross view of the liver cutting surface showing a wide yellowish-brown area of ischemic infarction intermingled by winy-colored areas; **B** - Photomicrography of the liver showing extensive ischemic infarction of the hepatic lobule, zone 1 macro and microvesicular steatosis and preserved portal triad (HE, 100X).

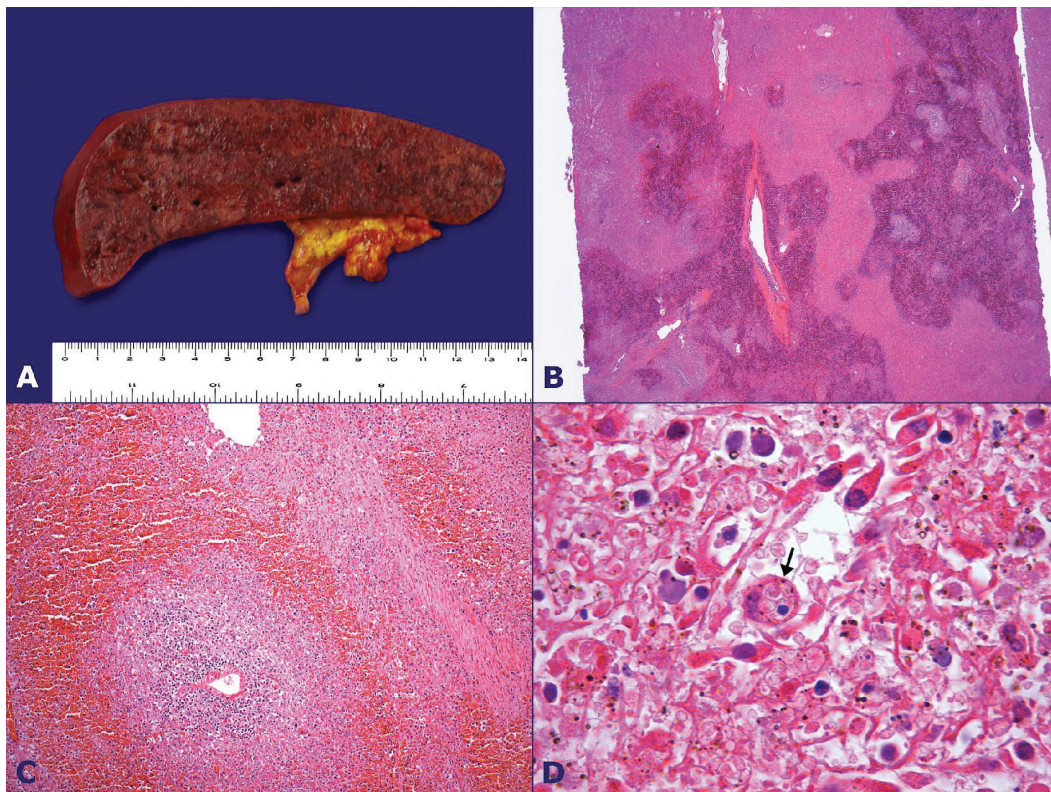


Figure 2. **A** - Gross view of the cutting surface of the spleen showing a reactive winy-colored parenchyma intermingled by ill-defined brown and friable areas. Photomicrography of the spleen in **B** - panoramic view showing areas of ischemic infarction and red pulp congestion (HE, 25X); **C** - white pulp lymphocytic depletion (HE, 100X); **D** - the presence of macrophage phagocytizing an erythrocyte and a lymphocyte in the red pulp (arrow) (HE, 1000X).

The pancreas weighed 70 g (mRV: 97.5 g), and presented purplish areas at the cut surface, which microscopy disclosed to be consistent with steatonecrosis and ischemic necrosis (Figure 3A and 3B). Both adrenal glands exhibited extensive cortical ischemic necrosis (Figure 3C and 3D).

At the opening of the thoracic cavity, petechiae were evident on both lung surfaces and pericardium. The heart weighed 191 g (mRV: 221 g) and exhibited myocardial hemorrhagic suffusions mainly on the left ventricle (Figure 4). Recent pericardial and myocardial hemorrhage were found at the necropsy.

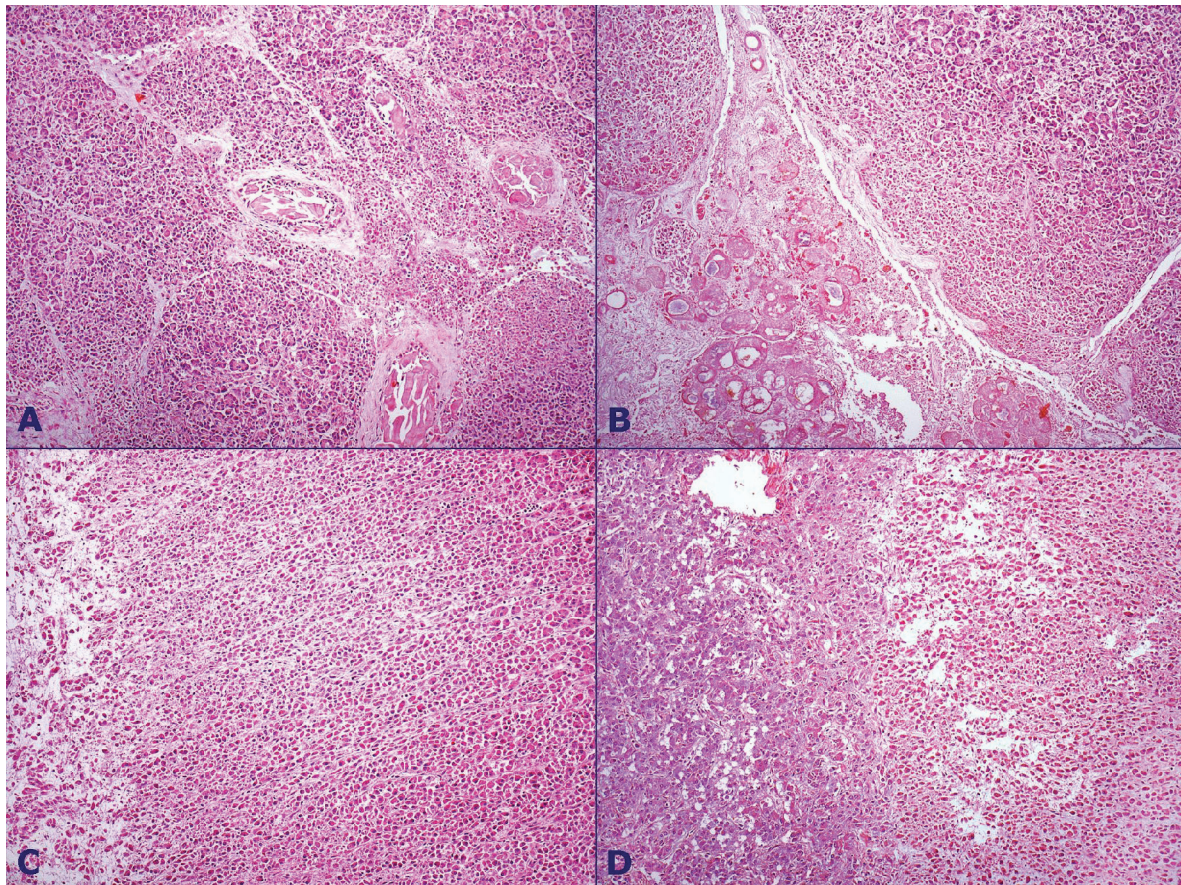


Figure 3. Photomicrography of the pancreas, in **A** - presence of ischemic infarcted areas (HE, 100X); in **B** - steatonecrosis in the pancreatic parenchyma (HE, 100X). Photomicrography of adrenal glands, in **C** - extensive cortical ischemic infarction (HE, 100X); **D** - corticomedullary transition showing a cortical coagulative necrosis (HE, 100X).

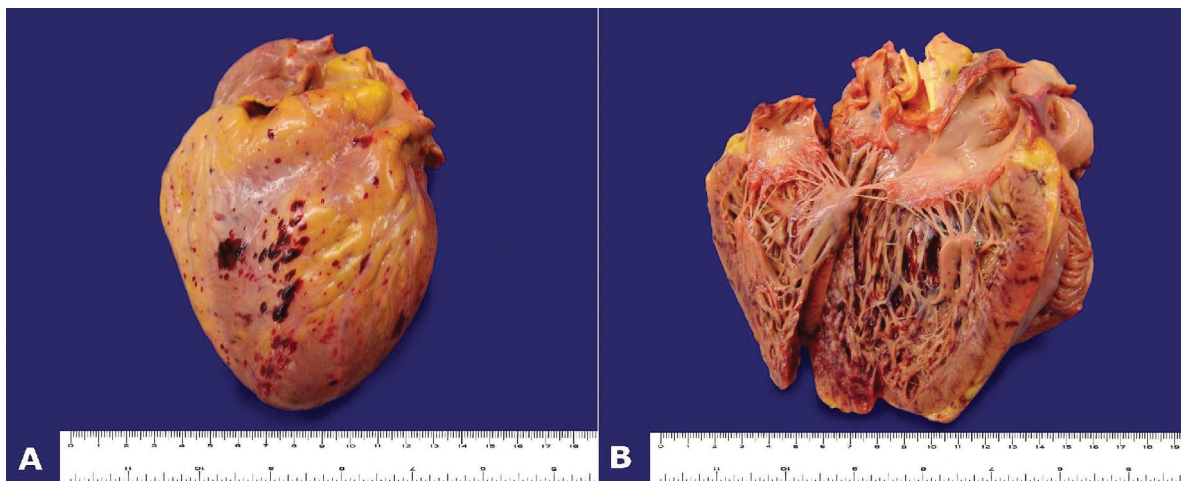


Figure 4. Gross view of the heart showing petechiae and hemorrhagic suffusions on the pericardial surface in **A** and in the myocardium and endocardium in **B**.

Both lungs presented increased volume; the cut surface was winy-colored, and the parenchyma was not friable, which was consistent with shock lung. At microscopy, the alveolar spaces were filled by numerous macrophages, fibrin, and red blood cells; no hemophagocytosis was found at this site (Figure 5).

Numerous mediastinal and intra-abdominal lymph nodes were detected showing a sinusal histiocytosis lymphadenitis pattern with associated lymphocytic depletion and histiocytes with erythrocytes phagocytosis (intracytoplasmic erythrocytes). The histiocytes were phenotypically CD68-positive, S100-negative (Figure 6).

The bone marrow showed evident hypercellularity, predominantly represented by the granulocytic series elements associated with the presence of numerous histiocytes with hemophagocytosis (Figure 7).

Hypoxic-ischemic encephalopathy and acute tubular necrosis were evident and were attributed to the long-lasting hemodynamic shock.

The autopsy findings are consistent with hemophagocytic syndrome, which was probably triggered by acute appendicitis.

DISCUSSION

The hemophagocytic syndrome or hemophagocytic lymphohistiocytosis (HLH) is a rare and severe entity. In 1939, Scott and Robb-Smith¹ first described what they called histiocytic medullary reticulosis, a condition characterized by histiocytic proliferation with erythrophagocytosis throughout the lymphoreticular tissue. Similar cases were published by Anderson in 1944² and Asher in 1946³, but only in 1952 two Scottish pediatricians published the case of two 9-week-old twins with "hemophagocytic reticulosis."⁴ Since then, numerous cases have been reported widening the clinical presentation and proposing a diagnostic approach.^{5,6}

Initially, HLH was believed to be a syndrome of childhood, as most of the patients presenting this

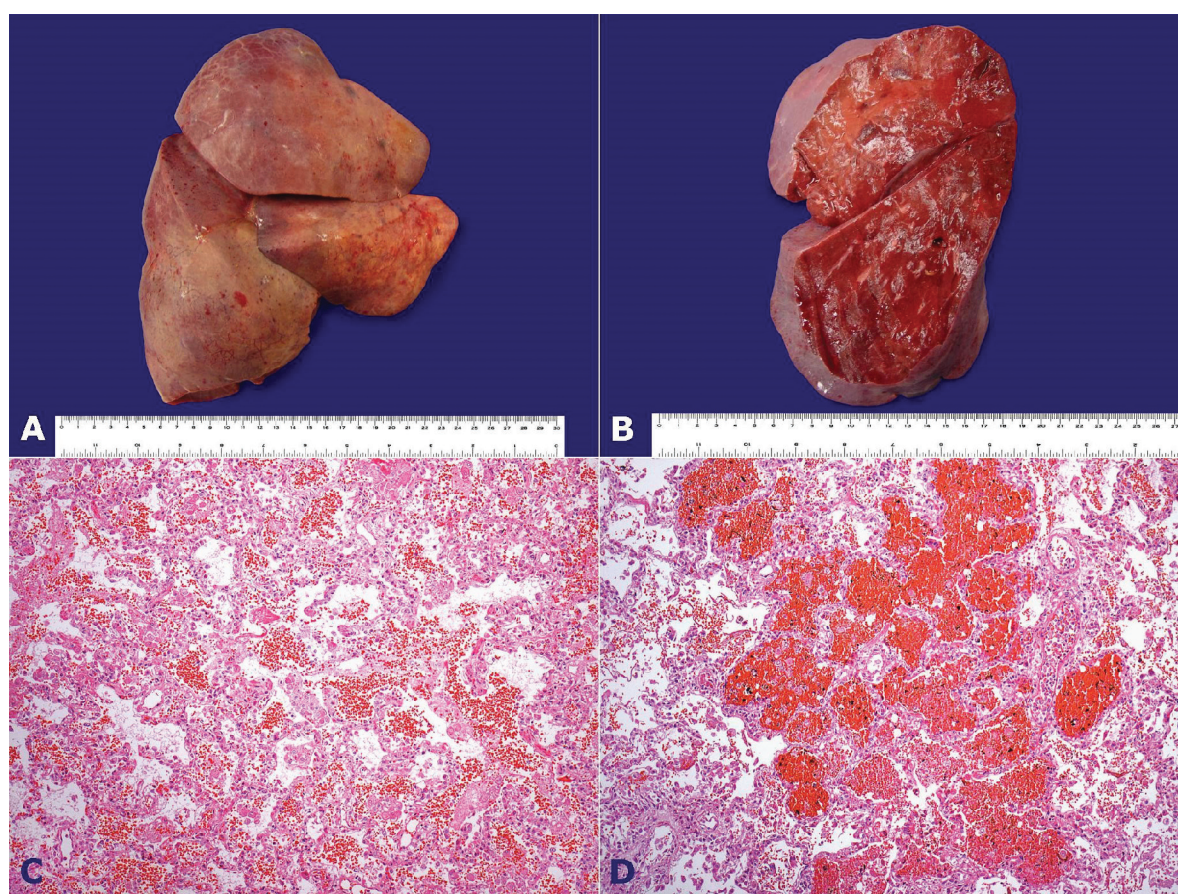


Figure 5. **A** and **B** - Gross view of the right lung with petechiae on the pleural surface in **A** and left lung in **B**, showing winy-colored firm parenchyma, without friable areas; photomicrography of the lung showing in **C** - alveolar spaces filled by macrophages, erythrocytes and fibrin deposits (HE, 100X); **D** - alveolar hemorrhage (HE, 100X).

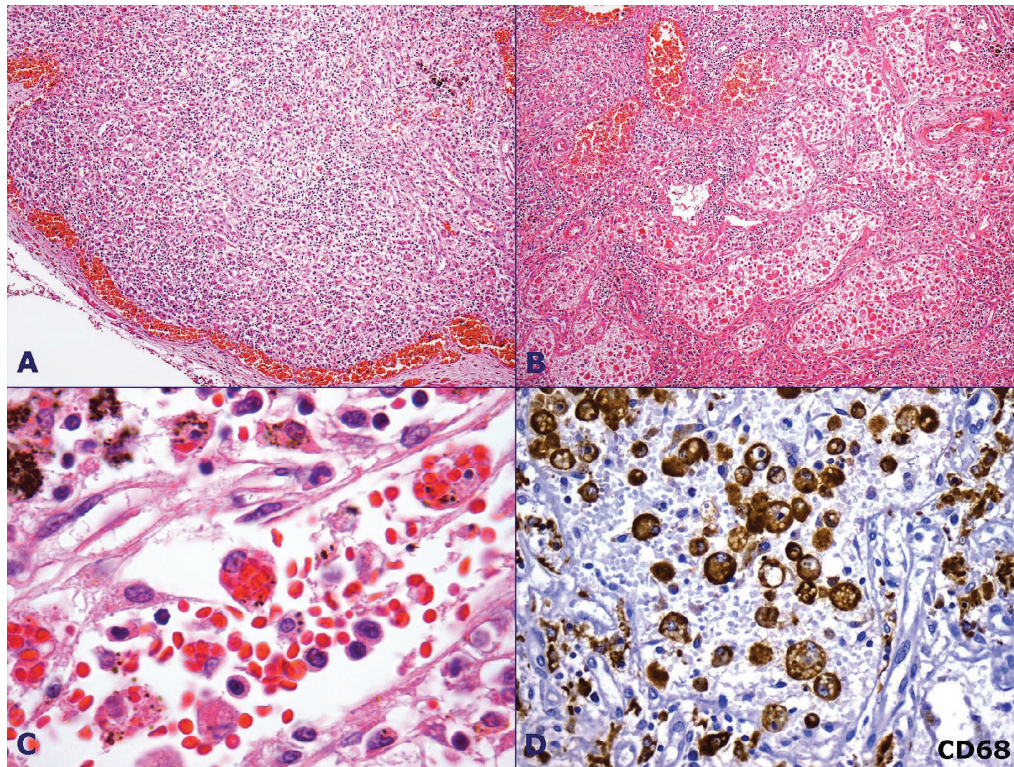


Figure 6. Photomicrography of the lymph node showing in **A** - marked lymphocytic depletion and subcapsular sinus congestion and the presence of numerous histiocytes (HE, 40X); **B** - dilated medullary sinus histiocytosis (HE-100X); **C** - (HE-1000X) detail of the histiocyte phagocytosing numerous erythrocytes (hemophagocytosis) (HE, 1000X); **D** - presence of numerous histiocytes with hemophagocytosis, positive immunophenotype for CD68 in the medullary sinus (immunohistochemistry, 400X).

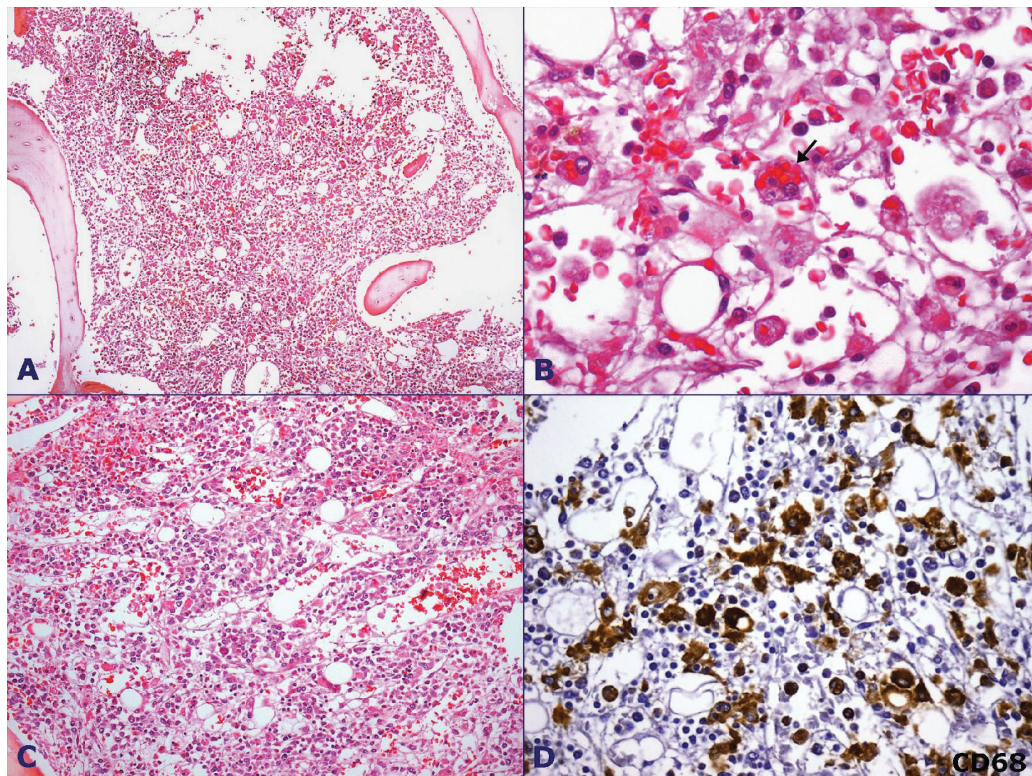


Figure 7. Photomicrography of the bone marrow showing in **A** - hypo cellularity for the age with the presence of interstitial histiocytes (HE, 100X); **B** - Detail of the histiocytes with numerous intracytoplasmic erythrocytes (arrow) (HE, 400X); **C** - delayed granulocytic maturation (HE, 200X); **D** - numerous interstitial histiocytes immunophenotypically positive for CD68 (immunohistochemistry, 400X).

disease were younger than 2 years; however, numerous cases in teenagers and adults have been reported. The incidence varies widely between geographic regions and different populations. In Turkey, an incidence of 7.5 cases in 10,000 live births has been reported, and three Texas (USA) academic centers reported 1 case in 100,000 live births.^{5,7-10}

HLH is classified in **two types**: **primary** or genetic, and **secondary** or **acquired**. Primary HLH is an autosomal recessive disease and may exhibit a familial form (FHL), which is rare and fatal without treatment. Other genetic forms include Chédiak-Higashi, Griscelli syndrome, and chromosome-X-linked lymphoproliferative disease, which present distinct phenotypic characteristics and may present the HLH syndrome in their clinical course.^{11,12}

HLH can be faced as a clinical condition caused by hypercytokinemia in a scenario where the **immune system is over activated** but **ineffective**. In a broad sense, HLH is currently understood as an **immune system's lack of ability to deal with trigger events**, which, in the **majority** of the cases, are **infectious**. The last decade has focused on the determination of HLH etiopathogenesis, especially the genetic and molecular bases of this entity.¹²

The mutations of perforin (PFR-1), hMunc13.4, and syntaxin-11 were implicated in the familial HLH. These genes are related to the NK-cells and T-cells cytotoxic granules exocytosis. The γ -interferon hypersecretion in conjunction with macrophage activation, the NK cells, and CD8 T-lymphocytes have a central role in the HLH physiopathology. The familial form is based on the mutation of the perforin-encoding gene, a key protein of cytotoxic granules. A recent study with a perforin-deficient murine model infected by lymphocytic choriomeningitis virus, produced the development of HLH.¹²⁻¹⁷

The secondary or acquired HLH form, in contrast to the familial form, is not associated with known mutations and is frequent among children and adults. **Infectious, autoimmune diseases and neoplasm may represent the trigger** events responsible for the uncontrolled immune system and inflammatory responses. **Viral** infections like Epstein-Barr virus (EBV), cytomegalovirus (CMV), type 8 herpes virus, HIV, influenza virus, parvovirus and **hepatitis A, B, and C virus**, as well as Gram-**negative bacteria**, **yeast**,

and **parasitic** infections are frequently associated with the HLH etiology. HLH may also be associated to **malignancy** mainly those of **hematologic** lineage, either as the initial presentation or during the course of chemotherapy.¹⁸ NK or T-cell **lymphomas** are the most common HLH-associated malignancies.⁷

HLH clinically presents as a **febrile illness associated with multiple organ involvement**. The commonest clinical finding is **hepatomegaly**, which has presented in **95%** of the patients, followed by **lymphadenopathy**, **edema**, **jaundice**, **rash**, and **neurological** symptoms. Unfortunately, the initial presentation of HLH may often be **misdiagnosed** and interpreted with hyper inflammatory diseases, like **severe sepsis** or diseases that require **surgical** treatment, challenging and delaying the diagnosis. Siminas et al.¹⁹ reported four pediatric cases of HLH that presented by masquerading as surgical diseases (neonatal abdominal distension, ileostomy closure, and Hirschsprung's disease; iatrogenic sigmoid perforation and Crohn's disease, and streptococcal toxic shock syndrome with primary peritonitis). HLH was suspected after several days of unexplained fever (average of 23 days), hepatomegaly, and **pancytopenia**. In 2014, Kassel et al.²⁰ reported the first case of HLH that clinically and radiologically mimicked acute appendicitis. Interestingly, during the laparoscopy, findings of diffuse plaque-like lesions in the small intestine required attention and were biopsied, showing HLH histological patterns.^{5,16,20-21}

Cytopenia is the commonest laboratory finding in HLH, particularly, **thrombocytopenia**, which presented in **97%** of the patients. Other laboratory abnormalities are **elevated ferritin** determination, **hypofibrinogenemia**, **hypertriglyceridemia**, liver dysfunction (elevated **lactate dehydrogenase**, serum **transaminases**, and **bilirubin**), impaired or absent NK cells, and T cell cytotoxicity (characteristic of FHL).^{5-7,21} Thrombocytopenia is a common finding in Pediatrics; in the intensive care setting it is quite often associated with severe diseases and poor prognosis. In children, immune thrombocytopenia is common, but the presence of **thrombocytopenia** should raise the suspicion of **hemolytic uremic syndrome (HUS)**, **thrombotic thrombocytopenic purpura (TTP)**, sepsis accompanied or not by disseminated intravascular coagulation (**DIC**) and **drug-induced thrombocytopenia** (like heparin adverse event).²²⁻²⁷

The diagnosis of HLH can be made following the diagnostic criteria proposed by the Histiocyte Society, which was revised in 2007.⁶ A molecular diagnosis consistent with HLH is enough to make the diagnosis of the familial form with known genetic abnormalities. In other cases, **five out of eight positive criteria is required**: fever, splenomegaly, cytopenias, hypertriglyceridemia and/or hypofibrinogenemia, evidence of hemophagocytosis, low/absent NK cell activity, hyperferritinemia, and high soluble interleukin 2 receptor levels.^{6,28}

Without treatment, HLH has a **dismal prognosis**, with less than **5%** having long-term survival, and a median **survival** time of 2 months. With newer **chemotherapy** regimens (**etoposide**, **dexamethasone**, and **methotrexate**) and protocols (HLH-94), the overall **survival** rate of **5 years has raised to 54%**, clinically relevant disease is still present in 28% of the survivors and **19% have late neurological effects**. For patients with the familial form of HLH, after the initial chemotherapy, or with recurrent or refractory disease a hematopoietic stem cell transplant is the definitive treatment.^{5,6,16,21,29}

The case reported herein presented sustained fever, cytopenias, hypofibrinogenemia, hyperferritinemia, and the findings of hemophagocytosis, which permitted the diagnosis of HLH (Table 1 and Table 2).

The HLH still remains a poor suspected entity in critical care patients, which invariably delays the proper treatment, and consequently increase the mortality. HLH may not be present at the beginning of an infectious, autoimmune, or neoplastic disease; however, it can be responsible for an unfavorable outcome in some cases. **When patients experience unexpected outcomes, despite** intensive care and appropriate and optimized **antibiotic** regimens, intensive care physicians should recall the hypothesis of **HLH** as a **differential diagnosis**.

REFERENCES

1. Scott RB, Robb-Smith AHT. Histiocytic medullary reticulosis. *Lancet*. 1939;234(6047):194-8. [http://dx.doi.org/10.1016/S0140-6736\(00\)61951-7](http://dx.doi.org/10.1016/S0140-6736(00)61951-7).
2. Anderson RG. Histiocytic medullary reticulosis with transient skin lesion. *BMJ*. 1944;1(4336):220-1. <http://dx.doi.org/10.1136/bmj.1.4336.220-a>. PMID:20785276
3. Asher R. Histiocytic medullary reticulosis: a case without lymphadenopathy. *Lancet*. 1946;1(6401):650. [http://dx.doi.org/10.1016/S0140-6736\(46\)90495-3](http://dx.doi.org/10.1016/S0140-6736(46)90495-3). PMID:21027953
4. Farquhar JW, Claireaux AE. Familial haemophagocytic reticulosis. *Arch Dis Child*. 1952;27(136):519-25. <http://dx.doi.org/10.1136/adc.27.136.519>. PMID:13008468
5. Trottestam H, Horne A, Aricò M, et al. Chemoimmunotherapy for hemophagocytic lymphohistiocytosis: long-term results of the HLH-94 treatment protocol. *Blood*. 2011;118(17):4577-84. <http://dx.doi.org/10.1182/blood-2011-06-356261>. PMID:21900192
6. Henter JI, Horne A, Aricò M, et al. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer*. 2007;48(2):124-31. <http://dx.doi.org/10.1002/pbc.21039>. PMID:16937360
7. Tothova Z, Berliner N. Hemophagocytic syndrome and critical illness: new insights into diagnosis and management. *J Intensive Care Med*. 2014 Jan 8. <http://dx.doi.org/10.1177/0885066613517076>. [Epub ahead of print] PMID:24407034
8. Gürgey A, Gözü S, Ozyürek E, et al. Primary hemophagocytic lymphohistiocytosis in Turkish children. *Pediatr Hematol Oncol*. 2003;20(5):367-71. <http://dx.doi.org/10.1080/08880010390203891>. PMID:12775534
9. Niece JA, Rogers ZR, Ahmad N, Langevin AM, McClain KL. Hemophagocytic lymphohistiocytosis in Texas: observations on ethnicity and race. *Pediatr Blood Cancer*. 2010;54(3):424-8. <http://dx.doi.org/10.1002/pbc.22359>. PMID:19953651
10. Ramos-Casals M, Brito-Zerón P, López-Guillermo A, Khamashta MA, Bosch X. Adult haemophagocytic syndrome. *Lancet*. 2014;383(9927):1503-16. [http://dx.doi.org/10.1016/S0140-6736\(13\)61048-X](http://dx.doi.org/10.1016/S0140-6736(13)61048-X). PMID:24290661
11. Janka GE. Hemophagocytic syndromes. *Blood Rev*. 2007;21(5):245-53. <http://dx.doi.org/10.1016/j.blre.2007.05.001>. PMID:17590250
12. Janka GE, Lehmborg K. Hemophagocytic syndromes: an update. *Blood Rev*. 2014;28(4):135-42. <http://dx.doi.org/10.1016/j.blre.2014.03.002>. PMID:24792320
13. Stepp SE, Dufourcq-Lagelouse R, Le Deist F, et al. Perforin gene defects in familial hemophagocytic lymphohistiocytosis. *Science*. 1999;286(5446):1957-9. <http://dx.doi.org/10.1126/science.286.5446.1957>. PMID:10583959
14. Feldmann J, Callebaut I, Raposo G, et al. Munc13-4 is essential for cytolytic granules fusion and is mutated in a form of familial hemophagocytic lymphohistiocytosis (FHL3). *Cell*. 2003;115(4):461-73. [http://dx.doi.org/10.1016/S0092-8674\(03\)00855-9](http://dx.doi.org/10.1016/S0092-8674(03)00855-9). PMID:14622600

15. zur Stadt U, Schmidt S, Kasper B, et al. Linkage of familial hemophagocytic lymphohistiocytosis (FHL) type-4 to chromosome 6q24 and identification of mutations in syntaxin 11. *Hum Mol Genet.* 2005;14(6):827-34. <http://dx.doi.org/10.1093/hmg/ddi076>. PMID:15703195
16. Jordan MB, Hildeman D, Kappler J, Marrack P. An animal model of hemophagocytic lymphohistiocytosis (HLH): CD8+ T cells and interferon gamma are essential for the disorder. *Blood.* 2004;104(3):735-43. <http://dx.doi.org/10.1182/blood-2003-10-3413>. PMID:15069016
17. Mahlaoui N, Ouachée-Chardin M, Saint Basile G, et al. Immunotherapy of familial hemophagocytic lymphohistiocytosis with antithymocyte globulins: a single-center retrospective report of 38 patients. *Pediatrics.* 2007;120(3):e622-8. <http://dx.doi.org/10.1542/peds.2006-3164>. PMID:17698967
18. Paes VR, Lima PP, Siqueira SAC. Hemophagocytic lymphohistiocytosis associated with hepatosplenic T-cell lymphoma: case report. *Autops Case Rep.* 2014;4(4):19-24. <http://dx.doi.org/10.4322/acr.2014.035>.
19. Siminas S, Caswell M, Kenny SE. Hemophagocytic lymphohistiocytosis mimicking surgical symptoms and complications: lessons learned from four cases. *J Pediatr Surg.* 2013;48(7):1514-9. <http://dx.doi.org/10.1016/j.jpedsurg.2012.12.024>. PMID:23895965
20. Kassel R, Robertson JO, Kung VL, et al. Small intestinal ulcers in hemophagocytic lymphohistiocytosis presenting as acute appendicitis. *J Ped Surg Case Reports.* 2014;2(6):325-7. <http://dx.doi.org/10.1016/j.epsc.2014.05.009>.
21. Gholam C, Grigoriadou S, Gilmour KC, Gaspar HB. Familial haemophagocytic lymphohistiocytosis: advances in the genetic basis, diagnosis and management. *Clin Exp Immunol.* 2011;163(3):271-83. <http://dx.doi.org/10.1111/j.1365-2249.2010.04302.x>. PMID:21303357
22. Recht M. Thrombocytopenia and anemia in infants and children. *Emerg Med Clin North Am.* 2009;27(3):505-23. <http://dx.doi.org/10.1016/j.emc.2009.04.009>. PMID:19646651
23. Sakr Y. Heparin-induced thrombocytopenia in the ICU: an overview. *Crit Care.* 2011;15(2):211. PMID:21457505.
24. Chaari A, Medhioub F, Samet M, et al. Thrombocytopenia in critically ill patients: a review of the literature. *Trends in Anaesthesia and Critical Care.* 2011;1(4):199-202. <http://dx.doi.org/10.1016/j.tacc.2011.05.003>.
25. Hui P, Cook DJ, Lim W, Fraser GA, Arnold DM. The frequency and clinical significance of thrombocytopenia complicating critical illness: a systematic review. *Chest.* 2011;139(2):271-8. <http://dx.doi.org/10.1378/chest.10-2243>. PMID:21071526
26. Parker RI. Etiology and significance of thrombocytopenia in critically ill patients. *Crit Care Clin.* 2012;28(3):399-411. <http://dx.doi.org/10.1016/j.ccc.2012.04.007>. PMID:22713614
27. Krishnan J, Morrison W, Simone S, Ackerman A. Implications of thrombocytopenia and platelet course on pediatric intensive care unit outcomes. *Pediatr Crit Care Med.* 2008;9(5):502-5. <http://dx.doi.org/10.1097/PCC.0b013e3181849af1>. PMID:18679144
28. Henter JL, Elinder G, Söder O, Ost A. Incidence in Sweden and clinical features of familial hemophagocytic lymphohistiocytosis. *Acta Paediatr Scand.* 1991;80(4):428-35. <http://dx.doi.org/10.1111/j.1651-2227.1991.tb11878.x>. PMID:2058392
29. Janka GE. Familial hemophagocytic lymphohistiocytosis. *Eur J Pediatr.* 1983;140(3):221-30. <http://dx.doi.org/10.1007/BF00443367>. PMID:6354720

Conflict of interest: None

Submitted on: January 28, 2015

Accepted on: February 21, 2015

Correspondence

Gabriel Nuncio Benevides

Divisão de Clínica Pediátrica – Hospital Universitário

Avenida Prof. Lineu Prestes, 2565 – São Paulo/SP – Brazil

CEP: 05508-000

Phone +55 (11) 97484-0708

E-mail: gnbenevides@gmail.com