Hemophagocytic syndrome: a dilemma chasing the intensivists

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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 appendicectomy 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; Appendicectomy; 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

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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 × 103/mm3	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).
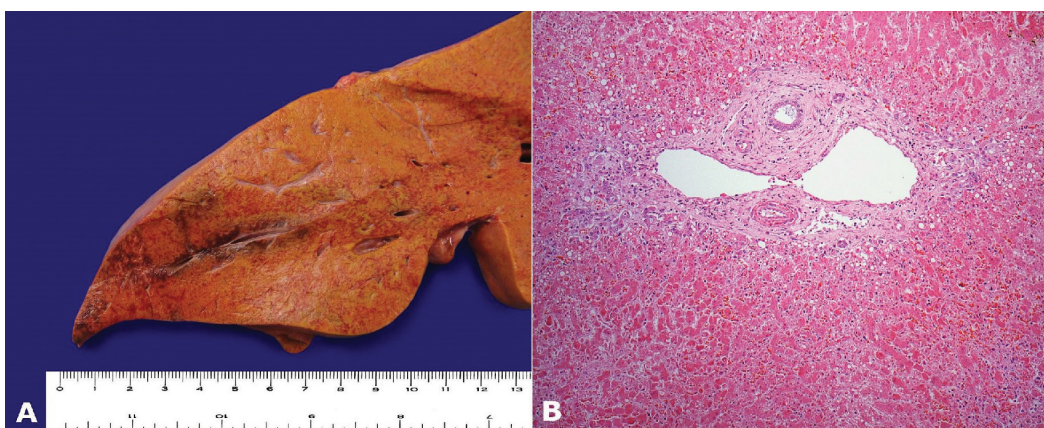
Figure 1. Gross view of the liver cutting surface showing a wide yellowish-brown area of ischemic infarction intermingled by winy-colored areas; **B** - Photomicrography of the liver showing extensive ischemic infarction of the hepatic lobule, zone 1 macro and microvesicular steatosis and preserved portal triad (HE, 100X).
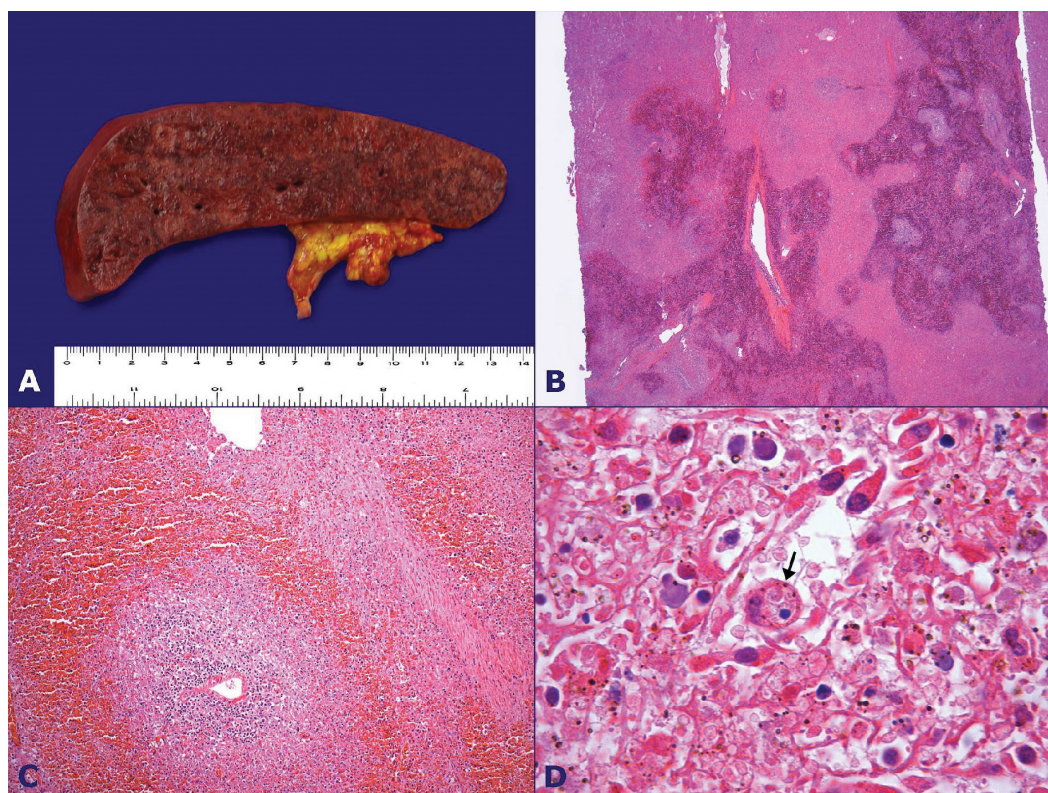

Figure 2. A - Gross view of the cutting surface of the spleen showing a reactive winy-colored parenchyma intermingled by ill-defined brown and friable areas. Photomicrography of the spleen in **B -** panoramic view showing areas of ischemic infarction and red pulp congestion (HE, 25X); **C -** white pulp lymphocytic depletion (HE,100X); **D -** the presence of macrophage phagocyting 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.
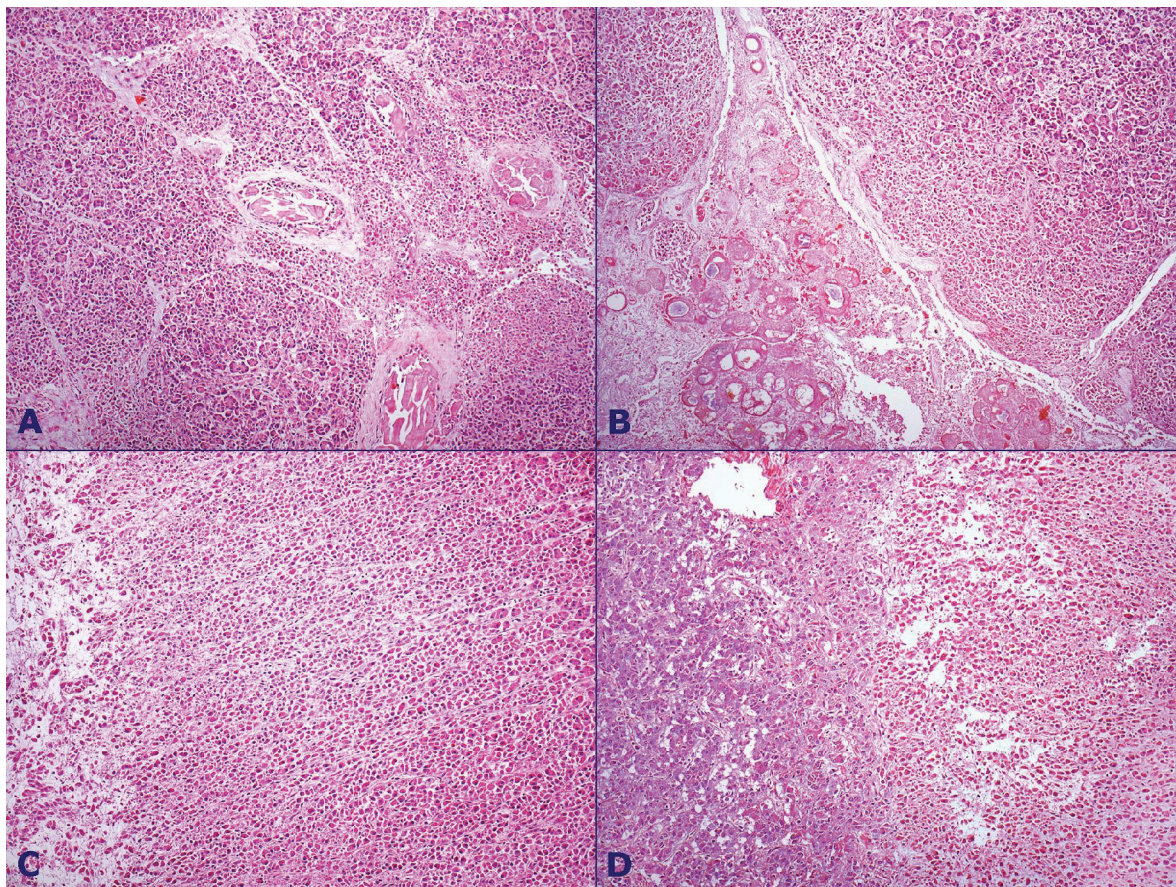
Figure 3. Photomicrography of the pancreas, in **A -** presence of ischemic infarcted areas (HE, 100X); in **B -** steatonecrosis in the pancreatic parenchyma (HE, 100X). Photomicrography of adrenal glands, in **C -** extensive cortical ischemic infarction (HE, 100X); **D -** corticomedullary transition showing a cortical coagulative necrosis (HE, 100X).
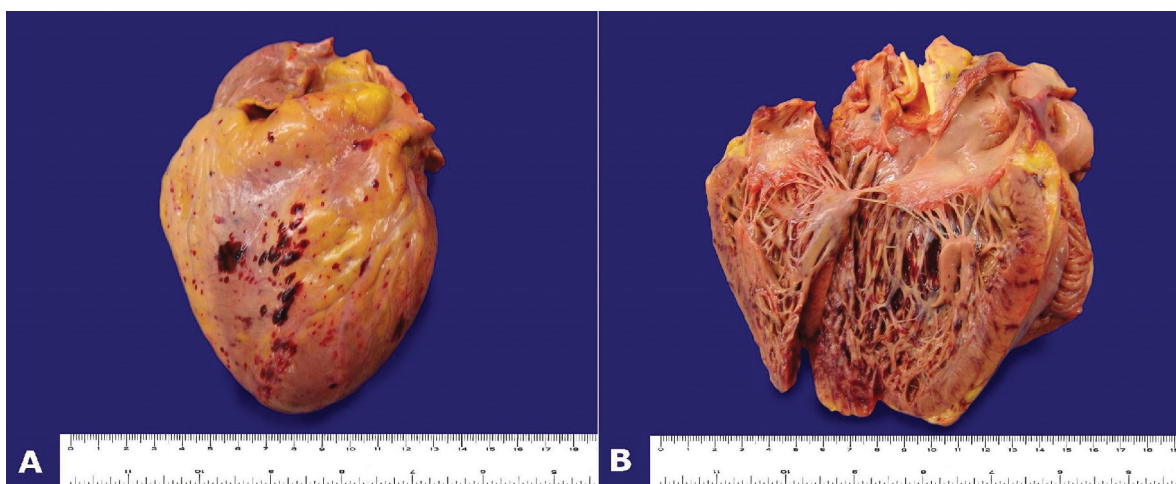
Figure 4. Gross view of the heart showing petechiae and hemorrhagic suffusions on the pericardial surface in **A** and in the myocardium and endocardium in **B**.

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-Smith[1] 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 1944[2] and Asher in 1946[3], 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
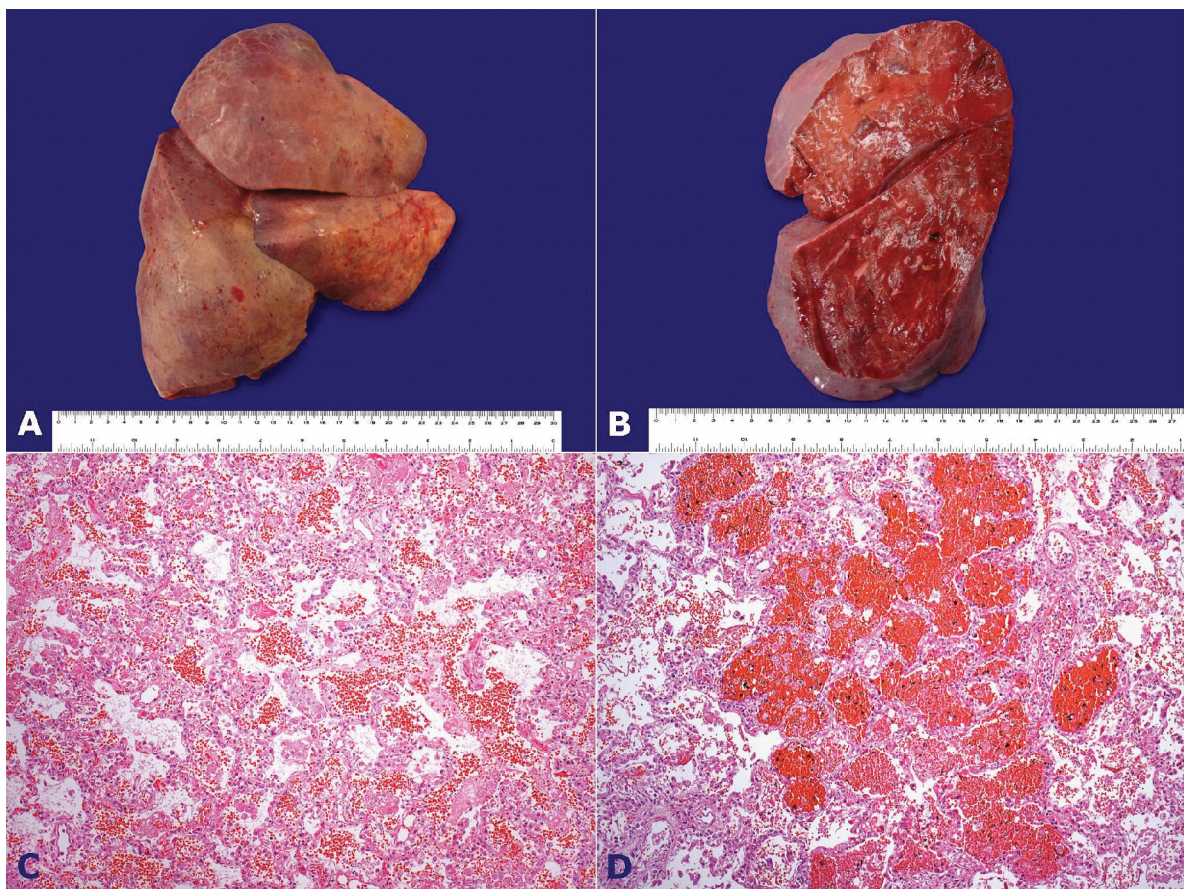

Figure 5. A and **B -** Gross view of the right lung with petechiae on the pleural surface in A and left lung in B, showing winy-colored firm parenchyma, without friable areas; photomicrography of the lung showing in **C** - alveolar spaces filled by macrophages, erythrocytes and fibrin deposits (HE, 100X); **D -** alveolar hemorrhage (HE, 100X).
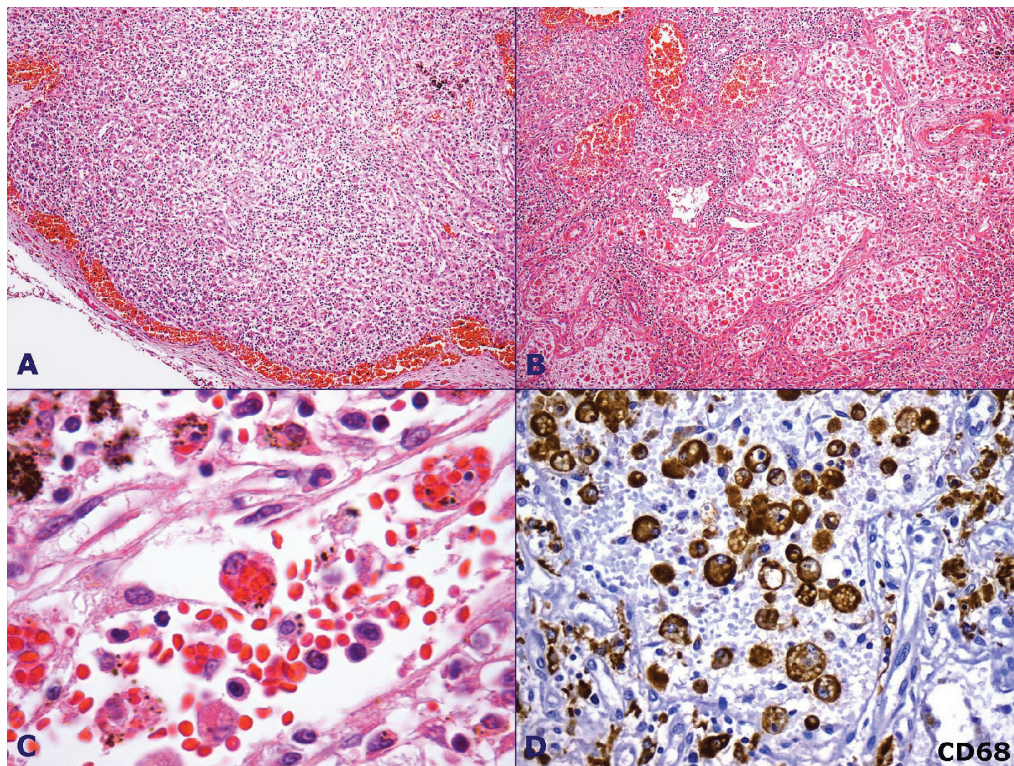
Figure 6. Photomicrography of the lymph node showing in **A -** marked lymphocytic depletion and subcapsular sinus congestion and the presence of numerous histiocytes (HE, 40X); **B -** dilated medullary sinus histiocytosis (HE-100X); **C -** (HE-1000X) detail of the histiocyte phagocyting numerous erythrocytes (hemophagocytosis) (HE, 1000X); **D -** presence of numerous histiocytes with hemophagocytosis, positive immunophenotype for CD68 in the medullary sinus (immunohistochemistry, 400X).
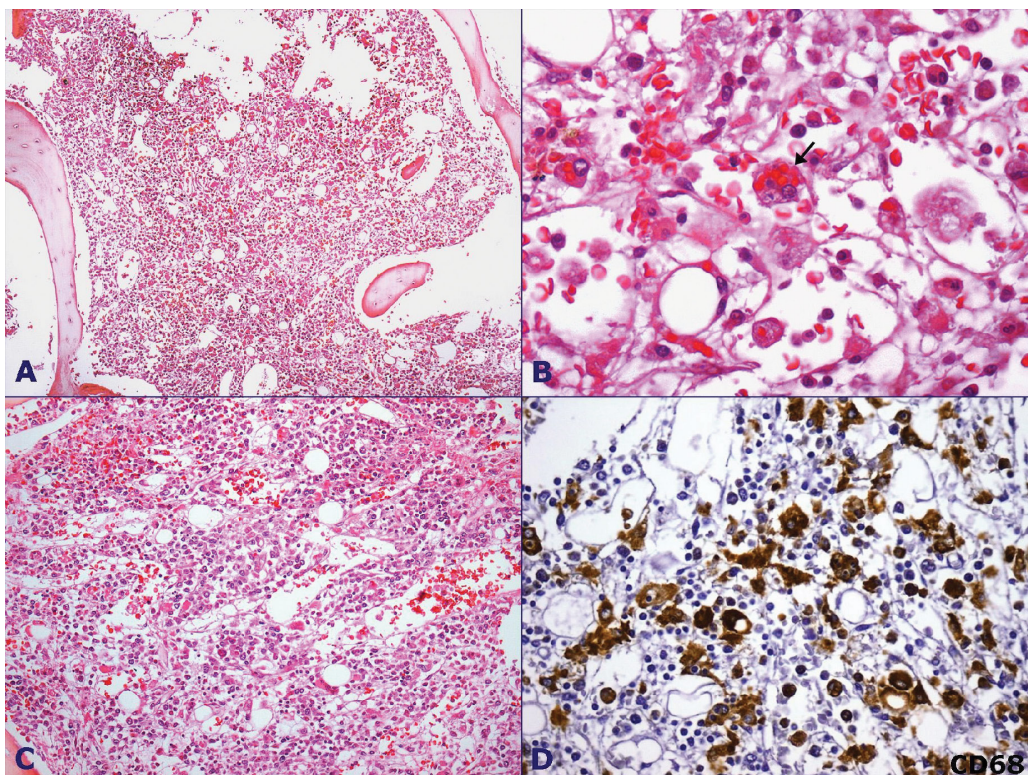
Figure 7. Photomicrography of the bone marrow showing in **A -** hypo cellularity for the age with the presence of interstitial histiocytes (HE, 100X); **B -** Detail of the histiocytes with numerous intracytoplasmic erythrocytes (arrow) (HE, 400X); **C -** delayed granulocytic maturation (HE, 200X); **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 detains 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.

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