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CLINICAL CASE

Hemophagocytic syndrome in children: a case report

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Summary

Introduction: Hemophagocytic syndrome is a group of clinical signs and laboratory findings that seriously and negatively compromise children's health, with an incidence of 1.2 cases/million/year. It can be underdiagnosed and confused with sepsis with a non-specific focus.

Case: A 4-year-old boy with an unremarkable medical history was admitted from the emergency service due to fever and abdominal pain for 20 days. He required intubation due to frank respiratory failure and admission to the Pediatric Intensive Care Unit with hypotension, liver failure, pancytopenia, and splenomegaly.

Evolution: Bacterial infections were ruled out using polycultures, and the SARS-CoV-2 test result was negative. Congenital and acquired immunodeficiencies were also ruled out. Toxoplasmosis, rubella cytomegalovirus, herpes simplex and Venereal disease research laboratory were negative. The Epstein–Barr virus test result was positive for IgM. Endocarditis with global pericardial effusion was observed. A medullary biopsy study showed normochromia, normocytosis, pancytopenia, and blasts.

Conclusion: Diagnosis of hemophagocytic syndrome is unusual, and because of its limited frequency, it is underestimated during clinical evaluation. However, the characteristics that are presented in this case report are consistent with the detailed information.

Key words: Lymphohistiocytosis, Hemophagocytic; Herpesvirus 4, Human; Epstein-Barr, Virus Infections; Perforin, Case Reports.

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Introduction

Hemophagocytic syndrome was described in 1939, and it was later recognized as a set of clinical signs and laboratory findings that are used to establish a diagnosis. It is characterized by prolonged fever, spinal cord failure, acute liver failure, pulmonary dysfunction, and neurological compromise [1].

Hemophagocytic syndrome has an incidence in children of 1.2 cases/million/year, and it is classified as primary or secondary hemophagocytic syndrome. Primary hemophagocytic syndrome, which is related to genetic alterations that are associated with the perforin enzyme that is responsible for macrophage apoptosis, while secondary hemophagocytic syndrome is related to infections where the Epstein–Barr virus is most frequent [2].

The secondary forms are also associated with autoimmune diseases and neoplasms. The diagnosis is made according to the diagnostic criteria that were established in the "hemophagocytic lymphohistiocytosis study" (HLH 2004). Its treatment has two phases, as follows: the first phase is an induction phase and the second is a maintenance or continuation phase. Both of these phases include corticosteroid therapy (dexamethasone), etoposide, and occasionally cyclosporine. We present the case of a patient with hemophagocytic syndrome because it has a low incidence in the pediatric population.

Clinical case

A 4-year-old male patient who was born and resided in Ambato, Mestizo, had Rh-positive type O blood and no significant pathological history. The child was admitted to hospital because he presented with a fever and abdominal pain of 20 days' duration. He had visited several doctors privately who had prescribed general analgesics and antibiotics with no improvement in his condition. His mother noticed changes in the oral mucosa and dyspnea, so she brought him to the emergency room. Upon admission, a deterioration of consciousness, hemiparesis, hypotension, and respiratory failure signs were observed, which required orotracheal intubation and mechanical ventilation to protect the patient's airway. Specialists from the pediatric intensive care unit (PICU) were consulted, who recommended starting vasoactive support due to the presence of hypotension, and the patient was admitted to the PICU.

Diagnostic workshop

The patient was admitted to the PICU with a diagnosis of sepsis due to an increase in temperature, severe pancytopenia, and positive biomarkers, for which broad spectrum antibiotic therapy was started. Hepatic failure, dyslipidemia, and splenomegaly were also observed. For severe pancytopenia, congenital and acquired immunodeficiencies were ruled out because the patient had normal immunoglobulin levels for his age and HIV test results were negative. The tests that were requested by the Infectology service showed negative results, as follows: toxoplasmosis, rubella cytomegalovirus, herpes simplex and HIV. (TORCH) non-reactive, Venereal disease research laboratory negative, negative blood cultures, negative urine culture, and negative nasopharyngeal swab for SARS-CoV-2. The Epstein–Barr virus test result was positive for IgM.

The Cardiology service evaluation included an echocardiogram, which showed the presence of a global pericardial effusion and collapse of the inferior vena cava, and the presence of congestion that was suggestive of endocarditis was reported.

The Onco-Hematology service was consulted due to pancytopenia. The specialists performed a spinal cord aspirate that showed normochromia, normocytosis, moderate leukopenia with topical granulation, and severe thrombocytopenia. The blood cell test results showed leucoblasts at less than 5% and white blood cell levels were very low. The bone marrow was severely depressed with large megaloblastic changes. There was no evidence of tumor infiltration into the bone marrow.

Thus, because the patient's condition had been ongoing for 20 days, including fever, splenomegaly, severe pancytopenia, and hypertriglyceridemia, and because of the elevated ferritin and lactate dehydrogenase levels as well as the positive Epstein–Barr virus Ig M test result, the patient was diagnosed with hemophagocytic syndrome. Cyclosporine administration and corticosteroid therapy were started.

Clinical evolution

In the PICU, the patient required sedoanalgesic support, from which he was progressively weaned. These infusions, however, were required because the patient did not adequate wake and had no knowledge of his surroundings. This, coupled with evidence of right hemiparesis was the basis for the decision to perform a computed tomography study with the presence of three intraparenchymal hematomas. The neurosurgery specialist concluded that the patient did not have neurosurgical resolution. The patient required invasive mechanical ventilation support for 20 days. On day 10, the patient had an episode of sudden desaturation, with an oxygenation index greater than 15 and an arterial oxygen pressure-to-inspired oxygen fraction (PaFi) ratio <200, which was classified as severe acute respiratory distress syndrome (ARDS). The patient was, thus, placed into the prone position for 30 hours. The patient was then repositioned in the supine position, and he showed good clinical respiratory results, with a progressive decrease in ventilatory parameters, and radiological improvement. He was extubated on day 20.

Since admission, the patient had received parenteral nutrition that was adjusted to his clinical and metabolic conditions, which included liver failure with elevated liver enzyme levels, hyperbilirubinemia, altered clotting times, elevated pancreatic enzymes, hypoalbuminemia, and splenomegaly; this required special attention to his nutrition.

Outcome

After discharge from the PICU, the patient was transferred to a hospital ward, where the enteral nutrition route was resumed. The patient was discharged with immunosuppressive treatment on an outpatient basis. He was closely observed at monthly visits for the following 3 months.

Discussion

Hemophagocytic syndrome or hemophagocytic lymph histiocytosis was first described in 1939 as a condition that is characterized by fever, lymphadenopathy, pancytopenia, and histiocytic proliferation in the bone marrow [1]. In 1952, this syndrome was called hemophagocytic familial reticulosis, and it was described as either a hereditary disorder based on genetic alterations (primary) or it was associated with infections or malignant or autoimmune diseases (secondary) [1-2].

Epidemiology

The incidence of hemophagocytic syndrome in children is 1.2 cases/million/year, but these figures are thought to be largely underestimated. In Poland, hemophagocytic syndrome is diagnosed less frequently in the pediatric population (0.82/million/year) than in Western Europe, and it is believed that a reasonable number of patients are undiagnosed 2. This syndrome has a high mortality rate (approximately 50–60%), although it is believed that these figures are underestimated due to the difficulty of making a diagnosis and because the symptoms are non-specific. Studies in Japan and the USA revealed an incidence of up to 1 case per 80,000 children per year while another series of studies revealed autosomal recessive inheritance with an incidence of 1:50,000 children who were born alive3. In Latin American, no studies have been conducted to define the incidence of hemophagocytic syndrome. However, a study that was performed in Argentina between 2004 and 2016 to examine the clinical characteristics and mortality of hematophagocytic syndrome identified 20 confirmed hematophagocytic syndrome cases secondary to immunosuppression and infections [3, 4].

Classification

The following two classifications of hemophagocytic syndrome are recognized: 1) the primary (genetic) form, which is caused by mutations that affect the cytotoxicity of lymphocytes and immune regulation; and 2) the secondary form, which is associated with infections or malignant or autoimmune diseases. The primary form usually occurs in childhood or typically between the 1 to 6 months of age (70–80% of cases). However, the first episode can occur at any time during a person's lifetime [2-5]. The primary form is related to the presence of mutations in the perforin, syntaxin, and syntaxin gene bound to protein 2 or the presence of mutations in lysosome transport [5].

Table 1 Causes of hemophagocytic syndrome

Infectious Viruses
Epstein–Barr virus; cytomegalovirus; hepatitis A, B, or C; herpes simplex virus; HIV
Bacteria
Mycobacteria tuberculosis, Coxiella burnetti, Mycoplasma pneumoniae, Rickettsia conorii
Spirochetes
Borrelia burgdorferi, Leptospira, Treponema pallidum
Fungi
Aspergillus, Candida albicans, Cryptococcus neoformans, Histoplasma capsulatum
Parasites
Babesia microti, Leishmania, Plasmodium falciparum, Toxoplasma gondii
Autoimmune diseases
Macrophage activation syndrome, systemic lupus erythematosus, rheumatoid arthritis, mixed connective tissue disease, systemic sclerosis, Sjogren's syndrome, polyarteritis nodosa, DRESS syndrome (Drug reaction with eosinophilia and systemic symptoms).
Other conditions
malignant diseases, such as lymphomas or leukemias T or natural killer, lymphomas anaplastic, large cell lymphomas, type B leukemias, late-stage Chediak Higashi Syndrome, use of antiretroviral therapy, Kawasaki disease, metabolic diseases

For the secondary form of hemophagocytic syndrome, several infectious conditions cause 50% of the cases, which are mostly associated with viral infections, followed by neoplasia, rheumatological diseases, and immunodeficiency syndrome [6-7]. The most frequent etiology that was reported in the pediatric group was secondary to infection, mainly a primary infection with the Epstein–Barr virus [8] (see Table 1).

Pathophysiology

The perforin gene was first described in 1999 by Stepp [9]. Currently, more than six genetic alterations are known to be associated with hemophagocytic syndrome, which are found on chromosomes 6, 9, 10, and 17 [10]. Under normal conditions macrophage activity is regulated by CD8+ T cells and NK cells, which, through the perforin/granzyme pathway, induce apoptosis of activated macrophages through the caspase pathway. This controlled cytotoxicity occurs by utilizing a complex cell–cell binding system that activates the movement of vesicles with granzymes through microtubules. Failure to control macrophage activation and the absence of their apoptosis are characteristic of hemophagocytic syndrome [10]. In these patients, NK cells and cytotoxic T lymphocytes (CTL) are unable to lyse antigens due to the mutation of perforin, so the inflammatory response is perpetuated with excessive production of cytokines such as interferon γ (IFN-γ). IFN-γ stimulates macrophages to produce interleukin (IL)-12 and other cytokines such IL-2, tumor necrosis factor α (TNF-α), IL-1, IL-6, IL-10, IL-18, and macrophage-colony stimulating factor, which perpetuate the activation of an uncontrolled immune response [9].

Clinical manifestations

Clinical manifestations of hemophagocytic syndrome include particular signs and symptoms. This section assesses our patient's clinical findings that were compatible with the clinical case.

Prolonged fever

Fever of unknown origin is a common diagnosis in general pediatric wards. In a case series, patients who were diagnosed with hemophagocytic syndrome had a fever above 38.9°C for a median of 19 days (range, 4–41 days) [10-12].

Liver disease and coagulopathy

Most patients had variable evidence of acute liver failure at the time of presentation, and thus, it should be considered in the differential diagnosis [10]. Almost 95% of patients have characteristics of disseminated intravascular coagulation and are at high risk of acute bleeding.

Bone marrow failure

Anemia and thrombocytopenia are present in over 80% of patients at presentation. The cellularity of bone marrow aspirates varies from normocellular to hypocellular or hypercellular, and the prevalence of hemophagocytosis varies between 25% and 100%, with 1–10 hemophagocytes per 500 cells [13]. Despite the hemophagocytic syndrome nomenclature, a diagnosis should never be made or be excluded solely due to the presence or absence of hemophagocytosis.

Cutaneous manifestations

The incidence of cutaneous manifestations ranges from 6% to 65%, including generalized rashes, erythroderma, panniculitis, morbilliform erythema, petechiae, and purpura.

Pulmonary dysfunction

Patients may develop pulmonary dysfunction leading to an urgent admission to the intensive care unit. In a review of radiographic abnormalities in 25 patients, 17 had acute respiratory failure syndrome, with a fatal outcome in 88% of these cases [14, 15].

Neurological symptoms

Over one-third of patients present with neurological symptoms, including seizures, meningism, decreased level of consciousness, cranial nerve palsy, psychomotor retardation, ataxia, irritability, or hypotonia [16].

Diagnosis

Since 1991, the Histiocytosis Society has published the six diagnostic criteria that were subsequently revised in 2004, and three additional criteria were added to standardize and not underestimate the disease [17].

Treatment

The Histiocytosis Society performed the first international treatment protocol for hemophagocytic syndrome in 1994 with an overall survival rate of 55%, and there was an average follow-up of 3.1 years. In 2004 (Table 2), the treatment guidelines were updated, and they were divided into the following two phases: 1) induction, which has as its main objective to suppress the inflammatory process using dexamethasone, etoposide, or cyclosporine for 8 weeks; and 2) treatment continuation, which is administered in children with a family history of the disease or with a diagnosis that was verified by molecular biology, children without a family history but with severe and persistent disease, and patients with reactivation of the disease. This continuation treatment consists of pulses of dexamethasone and etoposide from the weeks 9 to 40 [18–20] (see Table 2).

Table 2 Diagnostic criteria for hemophagocytic syndrome according to the HLH 2004 study

A: Molecular alterations that are consistent with hemophagocytic syndrome are verified using the following test results: pathological mutation of PRF1, UNC13D, Munc 18-2, Rab27a, STX11, SH2D1A, and BIRC4.
B. Five of the following criteria must be met: 1) Fever >38.5°C 2) Splenomegaly 3) Cytopenia (at least two of three cell lines in the peripheral blood), as follows: hemoglobin <9 g/dL, platelets <100,000/μL, and neutrophils <1,000/μL. 4) hypertriglyceridemia (fasting triglycerides >265 mg/dL) and/or hypofibrinogenemia (500 IU/L) 5) Hemophagocytosis demonstrated in bone marrow, spleen, lymph nodes, liver 6. Absent or decreased NK cell activity 7. Ferritin> 500 IU / L 8 High soluble CD 25.
These criteria (called Criterion A) are sufficient to make a diagnosis. In the absence of clinical symptoms, the clinical criteria that are listed above are used

Conclusions

Diagnosis of hemophagocytic syndrome is unusual, and because of its limited frequency, it is underestimated during clinical evaluation. However, the characteristics that are presented in this case report are consistent with the detailed information. Where there is evidence that this pathology usually occurs in pediatric patients, hemophagocytic syndrome is linked to genetic and infectious causes, such as the Epstein–Barr virus, such as in this case, and there are clinical and laboratory characteristics that are essential for establishing its diagnosis and treatment according to the criteria proposed by the HLH-2004.

Abbreviations

HLH: hemophagocytic lymphohistiocytosis study 2004.

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Authors' contributions

EETP: Research idea, article writing, critical analysis, editorial corrections.
FPPC: Data compilation, Bibliographic review.
JMMM: Research Idea, Article Writing, Critical Analysis.
MFGM: Critical Analysis, editorial corrections.
All authors read and approved the final version of the manuscript

Availability of data and materials

Data sharing is not applicable.

Ethical statements

Protection of persons

The authors declare that the procedures followed were in accordance with the ethical standards of the responsible human experimentation committee and in accordance with the World Medical Association and the Declaration of Helsinki.

Confidentiality of the data

The authors declare that they have followed the protocols of their work center on the publication of patient data.

Consent for publication

The authors have obtained the informed consent from the guardians of the patient referred to in the article. This document is in the possession of the corresponding author. The parents have signed the authorization for publication of this case.

Competing interests

The authors have no competing interests to declare.

References

1.Karla Adriana Espinosa Bautista, P. G. Síndrome hemofagocítico. Conceptos actuales. Gaceta Médica de México, (2013) 149:431-7.

2. Malinowska I, Machaczka M, Popko K, Siwicka A, Salamonowicz M, et- - Adamska B. Hemophagocytic syndrome in children and adults. Arch Immunol Ther Exp (Warsz). 2014 Oct;62(5):385-94. DOI:10.1007/s00005-014-0274-1. Epub 2014 Feb 9. PMID:24509696; PMCID: PMC4164855.

3. Santidrian, Rosso D, Elena G. Síndrome Hemofagocítico en Pediatría. Revista Pediatrica Elizalde, 2012;4(1): 18- 22.

4. De La Cruz-Armijo F, Povea-Palomino JC, Javier-Najarro R, Altamirano-Molina M, Abarca- Salazar S. Tratamiento exitoso de Síndrome Hemofagocítico secundario a infección de virus de Epstein Barr. Reporte de Caso. Acta Med Peru. (2019) 36(3):227-30

5. Allen M, De Fusco C, Legrand F, Clementi R, Conter V, Danesino C, Janka G, Aricò M. Familial hemophagocytic lymphohistiocytosis: how late can the onset be? Haematologica. 2001 May;86(5):499-503. PMID: 11410413.

6. Nicole Beffermann, Javier Pilcante, Mauricio Ocqueteau, Mauricio Sarmiento M. Síndrome hemofagocítico adquirido: reporte de casos de cuatro pacientes. Rev Med Chile, (2015) 143: 1172-1178

7. Fisman DN. Hemophagocytic syndromes and infection. Emerg Infect Dis. 2000 Nov-Dec;6(6):601-8. doi: 10.3201/eid0606.000608. PMID: 11076718; PMCID: PMC2640913.

8. Kazuhiro Kogawa, Hiroki Sato, Takeshi Asano, Shouichi Ohga, Kazuko Kudo, Akira Morimoto, Shigeru Ohta, Prognostic factors of Epstein Barr virus-associated hemophagocytic lymphohistiocytosis in children: Report of the Japan Histiocytosis Study Group, Pediatric Blood and Cancer 2014;61(7):1257-1262.

9. Tang YM, Xu XJ. Advances in hemophagocytic lymphohistiocytosis: pathogenesis, early diagnosis/differential diagnosis, and treatment. Scientific World Journal 2011;;11:697-708. DOI: 10.1100/tsw.2011.62.PMID: 21442147; PMCID: PMC5720059.

10. Jordan MB, Allen CE, Weitzman S, Filipovich AH, McClain KL. How I treat hemophagocytic lymphohistiocytosis. Blood. 2011;118(15):4041-52. DOI: 10.1182/blood-2011-03-278127. Epub 2011 Aug 9. PMID: 21828139; PMCID: PMC3204727.

11. Palazzi DL, McClain KL, Kaplan SL. Hemophagocytic syndrome in children: an important diagnostic consideration in fever of unknown origin. Clin Infect Dis 2003;36(3):306-312

12. Sandrock K, Nakamura L, Vraetz T, Beutel K, Ehl S, et-al. Zieger B. Platelet secretion defect in patients with familial hemophagocytic lymphohistiocytosis type 5 (FHL-5). Blood.2010;23;116(26):6148-50. DOI: 10.1182/blood-2010-08-302943. PMID: 21183701.

13. Gupta A, Weitzman S, Abdelhaleem M. The role of hemophagocytosis in bone marrow aspirates in the diagnosis of hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer. 2008;50(2):192-4. DOI: 10.1002/pbc.21441. PMID: 18061932.

14. Morrell DS, Pepping MA, Scott JP, Esterly NB, Drolet BA. Cutaneous manifestations of hemophagocytic lymphohistiocytosis. Arch Dermatol. 2002;138(9):1208-12. DOI: 10.1001/archderm.138.9.1208. PMID: 12224982.

15. Fitzgerald NE, MacClain KL. Imaging characteristics of hemophagocytic lymphohistiocytosis. Pediatr Radiol. 2003;33(6):392-401. DOI: 10.1007/s00247-003-0894-9. Epub 2003 Mar 21. PMID: 12768255; PMCID: PMC7100656.

16. Horne A, Trottestam H, Aricò M, Egeler RM, Filipovich AH, et-la. Gadner H, Imashuku S, Ladisch S, Webb D, Janka G, Henter JI; Histiocyte Society. Frequency and spectrum of central nervous system involvement in 193 children with haemophagocytic lymphohistiocytosis. Br J Haematol. 2008 Feb;140(3):327-35. DOI: 10.1111/j.1365-2141.2007.06922.x. Epub 2007 Dec 10. PMID: 18076710.

17. Henter JI, Horne A, Aricó M, Egeler RM, Filipovich AH, Imashuku S, Ladisch S, McClain K, Webb D, Winiarski J, Janka G. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer. 2007 Feb;48(2):124-31. DOI: 10.1002/pbc.21039. PMID: 16937360.

18. George MR. Hemophagocytic lymphohistiocytosis: review of etiologies and management. J Blood Med. 2014 Jun12;5:69-86. DOI:10.2147/JBM.S46255. PMID: 24966707; PMCID: PMC4062561.

19. Tamamyan GN, Kantarjian HM, Ning J, Jain P, Sasaki K, McClain KL, et al. Malignancy-associated hemophagocytic lymphohistiocytosis in adults: Relation to hemophagocytosis, characteristics, and outcomes. Cancer 2016 Sep 15;122(18):2857-66. DOI: 10.1002/cncr.30084. Epub 2016 May 31. PMID: 27244347; PMCID: PMC5014667.

20. Dávila D, de la Peña López I. Síndrome Hemofagocitico, Reporte de un caso y revisión de la literatura. Hematooncología. Fundación clínica Médica Sur 2018;62(2):15-21.

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