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Case report

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Cure of hemophagocytic lymphohistiocytosis triggered by Epstein–Barr virus infection after early diagnosis and appropriate treatment with etoposide, dexamethasone, and immunoglobulin

Abstract

Hemophagocytic lymphohistiocytosis (HLH) is an aggressive and life-threatening condition characterized by uncontrolled activation of T lymphocytes and inappropriate activation of mature macrophages secreting excessive cytokines leading to marked hypercytokinemia. It can also be secondary to neoplasms, rheumatologic diseases, or infections. This was a case report, described in Central Brazil, of a 17-year-old female patient diagnosed with HLH after infection by Epstein–Barr virus (EBV), which eventually improved after early diagnosis and treatment with etoposide, dexamethasone, and immunoglobulin. The early diagnosis and treatment of this condition are of utmost importance owing to its high mortality rate. Therefore, this is a case report of a young patient who developed HLH, after EBV infection, requiring transfer to a reference hospital for infectious diseases, with optimization of diagnosis and early initiation of specific treatment after discussion between a medical team made up of several specialists.

Keywords: hemophagocytic lymphohistiocytosis, Epstein–Barr virus infection, early diagnosis

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Introduction

Hemophagocytic lymphohistiocytosis (HLH) is an extremely aggressive and life-threatening condition characterized by uncontrolled activation of T lymphocytes and inappropriate activation of mature macrophages secreting excessive cytokines leading to marked hypercytokinemia.[1,2] HLH can be classified as primary (of genetic origin) or secondary caused by neoplasms, autoimmune diseases, or infections, such as cytomegalovirus or Epstein–Barr virus (EBV) infection.[2,3] The clinical symptoms include fever, hepatosplenomegaly, lymphadenomegaly, pancytopenia, liver dysfunction, hypertriglyceridemia, hyperferritinemia, and increased levels of interleukin-6, interferon alpha, and tumor necrosis factor, which can lead to multiple organ failure[4]. The term hemophagocytosis is used to describe the pathological findings in biopsies of bone marrow, lymph nodes, liver, or spleen, and refers to the phagocytosis of cells of the hematopoietic system by activated macrophages. This phenomenon is an important finding in patients with this syndrome; however, it is not pathognomonic and may be present in other disorders.[5]

The most used diagnostic criteria are the HLH-2004 criteria of the Histiocyte Society, characterized by the presence of eight awards (five of eight must be present). The criteria are fever, splenomegaly, cytopenias affecting at least two lineages (hemoglobin <9 g/dL, platelet count <100.000/ µL or absolute neutrophil count <1000/ µL), hypertriglyceridemia and/or hypofibrinogenemia (triglycerides ≥265 mg/dL and or fibrinogen ≤150 mg/dL), hemophagocytosis in bone marrow, spleen, or lymph nodes, low or absent NK cell activity, ferritin ≥ 500 µg/L and sCD25 (sIL2Rα) ≥ 2,400 U/ml.[6]

Treatment should not be delayed when there is clinical suspicion as it is a fatal syndrome, especially in patients diagnosed late. Corticosteroids can be administered as initial treatment; however, the primary treatment is epipodophyllotoxin derivatives (etoposide and teniposide) together with corticosteroids. These drugs can be combined with immunosuppressive drugs such as cyclosporine.[7,8] If patients are infected with an active virus, targeted treatments should be initiated, including rituximab for EBV and antiviral agents such as ganciclovir, cidofovir, oseltamivir, or others as indicated.[9]

Secondary HLH caused by lymphoma, autoimmune diseases, HIV, kala-azar, EBV and other causes have been described in several countries around the world.[4] In Brazil, cases of HLH secondary to kala-azar, HIV infection, EBV infection and others causes have already been reported in several regions.[10–13] This report describes a case of HLH in a young patient described in Central Brazil with confirmed previous EBV infection.

Case description

MLM was a 17-year-old female student, single, experiencing intense odynophagia, asthenia, and self-medicating with nimesulide and amoxicillin. As no clinical improvement was observed, the patient sought medical attention and was eventually diagnosed with tonsillitis. Azithromycin was administered as additional treatment; however, pruritic erythematous micropapules appeared all over the patient's body.

After 14 days, the patient experienced fever, sweating, nausea, vomiting, diffuse abdominal discomfort, jaundice, choluria, and fecal acholia, hence, she was admitted to the municipal emergency department. After admission, the severity of abdominal pain, nausea, jaundice, choluria, and fecal acholia improved; however, admission in the intensive care unit was required due to the onset of febrile neutropenia. Physical examination showed blood pressure 110/85 mmHg, heart rate 86 bpm, respiratory rate 18 bpm, afebrile, in good general condition, oriented, eupneic, hydrated, pale (3+/4+), conscious, and cooperative. On respiratory auscultation, vesicular murmur

preserved, without adventitious sounds. Cardiac auscultation revealed regular heart rhythm, normophonetic sounds, and systolic murmur (2+/6+, which was more audible in the mitral focus). Abdominal physical examination, pain upon palpation and visceromegaly were not noted. Lymphadenomegaly was also not observed.

Laboratory tests were carried out and yielded the following results: hemoglobin level 6.9g/dl, hematocrit count 20.8%, leukocyte count 1670/μL, neutrophil count 1100/μL, platelets 52.000/mm^3, prothrombin time 82.7%, international normalized ratio 1.24, glucose level 95mg/dL, urea level 11mg/dL, creatinine level 0.4mg/dL, albumin level 2.8g/dL; oxalacetic transaminase level 242U/L, pyruvic transaminase level 203U/L, and C-reactive protein level 1.9mg/L (normal: <0.5mg/L). Bone marrow immunophenotyping showed normoproliferative granulocytic series, slight increase in monocyte percentage, normal lymphocyte subpopulations, and absence of cell population with anomalous immunophenotype in the analyzed sample. Serological test showed presence of EBV immunoglobulin M (IgM). Sepsis caused by EBV was diagnosed, and ganciclovir therapy was initiated. Leukopenia continued to worsen, and ganciclovir was discontinued 2 days later. The patient was referred to the intensive care unit (ICU) and was under protective isolation. Filgrastim, acyclovir, meropenem, teicoplanin, fluconazole, and later polymyxin B were administered, however, no improvement was observed.

The patient was transferred to the semi-intensive ward of a university hospital within 9 days after ICU admission. Her clinical condition remained the same along with the occurrence of hyporexia, weight loss, burning epigastralgia, and vomiting.

Total abdominal tomography showed a slight increase in spleen size (12.8 cm in the longest axis), with a homogeneous texture and a small amount of perihepatic, perivesicular, and pelvic free fluid. Chest tomography showed laminar pleural effusion in the right lung base.

During this hospitalization, screening was performed to assess for infectious and rheumatological (anti-mitochondria, anti-smooth muscle, immunoglobulin G, antinuclear antibodies, lupus anticoagulant, perinuclear antineutrophil cytoplasmic antibodies ANCA, cytoplasmic ANCA, anti-deoxyribonucleic acid (DNA), anti-Sjögren's-syndrome-related antigen A, and anti-cardiolipin and oncological pathologies, including bone marrow aspirate, which were not noted.

During the investigation, the patient developed febrile neutropenia (neutrophil count: 488/μL), maintaining thrombocytopenia (platelet count: 52,000/μL), and hyperferritinemia (ferritin level: 11,100ng/mL). After discussing with numerous personnel with various fields of specialty, a diagnosis of hemophagocytic lymphohistiocytosis secondary to EBV was made, based on the following criteria: fever, pancytopenia, mild splenomegaly, hypertriglyceridemia, hyperferritinemia, previous history of EBV infection confirmed by serological test (reactive IgM), and viral DNA in the serum detected on polymerase chain reaction test.

The following specific treatments were initiated: 20 g/day of immunoglobulin for 7 days, 230 mg of etoposide twice a week for 2 weeks, and 16 mg/day of dexamethasone. Meropenem was also restarted. Linezolid, micafungin, acyclovir, and sulfamethoxazole/trimethoprim treatment was associated with clinical improvement and subsequent cure.

Discussion

This was a case in Brazil Central of a young patient with EBV infection causing severe and potentially fatal HLH. Multidisciplinary support and aggressive treatment were employed due to the lack of improvement after receiving corticosteroid therapy as initial treatment. HLH is associated with viral infections, malignancy, and certain chemotherapeutic agents, it may develop in all age groups and may be secondary to infection caused by some agents such as the herpes group, especially EBV and cytomegalovirus.[1–3]

This patient had difficult-to-control fever, marked hyperferritinemia, cytopenias, and splenomegaly, which are common clinical findings in patients with HLH and can lead to death if the clinical diagnosis is delayed. Although hemophagocytosis is an important finding in HLH, its absence should not interfere with the diagnostic and therapeutic decision if the other criteria are present.[5]

sCD25 is a diagnostic criterion for HLH, and although it was not measured in this case, dramatically elevated levels of CD25 appear to be relatively specific for HLH, and a relatively high CD25/soluble ferritin ratio is useful in differentiating of lymphoma-associated HLH from HLH associated with non-malignant etiologies.[14]

As soon as HLH is diagnosed, especially in patients with no clinical improvement following corticosteroid therapy, epipodophyllotoxin derivatives (etoposide and teniposide) should be administered in combination with corticosteroids and cyclophosphamide.[7,8] Ganciclovir was administered but was discontinued shortly thereafter due to the occurrence of adverse effects. However, acyclovir was initiated to treat EBV infection. Therefore, a specific antiviral should be used in patients with an active viral infection.[9]

Conclusion

Therefore, this is a case report of a young patient who developed HLH, after EBV infection, requiring transfer to a reference hospital for infectious diseases, with optimization of diagnosis and early initiation of specific treatment after discussion between a medical team made up of several specialists.

Acknowledgments

None.

Conflicts of interest

There was no conflict of interest in this case report.

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