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Case report

Macrophage activation syndrome in a patient with systemic juvenile idiopathic arthritis

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ABSTRACT

Machrophage activation syndrome (MAS) is a rare and potentially fatal disease, commonly associated with chronic rheumatic diseases, mainly juvenile idiopathic arthritis. It is included in the group of secondary forms of haemophagocytic syndrome, and other causes are lymphoproliferative diseases and infections. Its most important clinical and laboratorial manifestations are non-remitting fever, splenomegaly, bleeding, impairment of liver function, cytopenias, hypoalbuminemia, hypertriglyceridemia, hypofibrinogenemia and hyperferritinemia. The treatment needs to be started quickly, and the majority of cases have a good response with corticosteroids and cyclosporine. The Epstein–Barr virus is described as a possible trigger for many cases of MAS, especially in these patients in treatment with tumor necrosis factor (TNF) blockers. In these refractory cases, etoposide (VP16) should be administered, associated with corticosteroids and cyclosporine. Our objective is to describe a rare case of MAS probably due to EBV infection in a subject with systemic-onset juvenile idiopathic arthritis, which achieved complete remission of the disease after therapy guided by 2004-HLH protocol.

Síndrome de ativação macrofágica em paciente com artrite idiopática juvenil sistêmica

Palavras-chave:
Síndrome hematofagocítica
Vírus Epstein-Barr

RESUMO

A síndrome de ativação macrofágica (SAM) é uma doença rara e potencialmente fatal, normalmente associada às doenças reumáticas crônicas, em especial a artrite idiopática juvenil. É incluída no grupo das formas secundárias de síndrome hemofagocítica, cujas

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Artrite idiopática juvenil forma sistêmica
Protocolo de tratamento HLH-04

outras causas podem ser as doenças linfoproliferativas e infecções. As manifestações clínicas e laboratoriais mais importantes são a febre não remitente, esplenomegalia, hemorragias, disfunção hepática, citopenias, hipoalbuminemia, hipertrigliceridemia e hiperferritinemia. O tratamento deve ser iniciado rapidamente, e a maioria dos casos responde bem aos corticosteroides e à ciclosporina (CSA). O vírus Epstein-Barr (EBV) é descrito como possível gatilho para muitos casos de SAM, especialmente naqueles em tratamento com bloqueadores do fator de necrose tumoral (TNF). Nos casos refratários ao tratamento convencional, etoposide (VP16) deve ser administrado, em associação com corticosteroides e CSA. Nosso objetivo foi descrever um caso raro de síndrome hematofagocítica provavelmente secundária à infecção pelo vírus Epstein-Barr (EBV), em paciente com artrite idiopática juvenil sistêmica, confirmada pelas manifestações clínicas e laboratoriais típicas, mielograma e sorologia positiva contra o EBV, que atingiu remissão completa após inclusão no protocolo de tratamento HLH-04.

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a rare and potentially fatal disease. Its annual incidence is 1:50,000 live-born infants. It can be divided into two groups: primary and secondary.

Macrophage activation syndrome (MAS) is a severe complication of rheumatic diseases that occurs much more frequently in patients with systemic juvenile idiopathic arthritis (SJIA). It is characterized by fever, hepatosplenomegaly, cytopenias, liver dysfunction, bleeding diathesis and neurological symptoms, revealing a heterogeneous syndrome, which makes its detection harder. The presence of macrophages actively phagocytosing hematopoietic cells in the liver, spleen, bone marrow or lymph node confirms the diagnosis.[1,2] The criteria formulated for HLH diagnosis (Table 1) may not be useful to define MAS.[2] The great challenge is to differentiate it from the exacerbation of the underlying disease.[1,3,4] The clinical manifestations of both showed 40% similarity.[5] The pathogenesis of MAS consists of cytokine overproduction and exuberant inflammation, leading to uncontrolled macrophage phagocytosis, antigen presentation and persistent activation of T lymphocytes.[6,7] Prevalence is more often studied in SJIA patients, estimated to be between 7% and 13%.[3]

MAS is included in the group of secondary forms of HLH, whose causes are lymphoproliferative diseases, infections (viral, bacterial, parasitic and fungal) and rheumatic diseases. Genetic mutations, which compromise secretion of perforins, are the main trigger in the primary form.

Our objective was to describe a case of MAS probably due to Epstein–Barr virus (EBV) infection and show how the appropriate treatment was essential for a favorable outcome.

Table 1 – Diagnostic criteria for hemophagocytic lymphohistiocytosis (HLH).

A. Molecular diagnosis compatible with HLH: pathological mutations of *PRF1*, *UNC13D*, *Munc 18-2*, *Rab27a*, *STX11*, *SH2D1A*, or *BIRC 4*
OR
B. 5 of the 8 criteria listed below:
1. Fever (temperature greater than 38.3 °C);
2. Splenomegaly;
3. Cytopenias (involvement of at least 2 lineages)
   3.1. Hemoglobin < 9 g/dL or <10 g/dL in newborns
   3.2. Platelets < 100,000 mL
   3.3. Neutrophils < 1000 mL;
4. Hypertriglyceridemia (>265 mg/dL) or hypofibrinogenemia (<150 mg/dL);
5. Hemophagocytosis in the bone marrow, spleen, lymph nodes or liver – no evidence of malignancy;
6. Reduced or absent activity of NK cells;
7. Serum ferritin > 500 ng/dL;
8. Increase soluble CD25 (>2.400 U/mL)

Source: Histiocyte Society – Treatment Protocol of The Second International HLH Study 2004.

Case report

The patient is a 9-year-old girl diagnosed with SJIA since 2007, taking prednisolone 9 mg/day (0.3 mg/kg/day), methotrexate (MTX) 20 mg/week (0.6 mg/kg/week) and etanercept (ETN) 25 mg/week (0.8 mg/kg/week), with partially controlled disease. In December 2011, she presented fever, vomit, abdominal pain, diarrhea and jaundice, evolving with impairment of liver function, mucocutaneous bleeding, bicytopenia and hepatosplenomegaly. Upon hospital admission, she presented anemia (Hb 8.1 g/dL), thrombocytopenia ($57 \times 10^3/\mu L$), elevated serum liver enzyme levels (aspartate aminotransferase – AST – 518 U/L and alanine aminotransferase – ALT – 121 U/L), hypoalbuminemia (2.8 g/dL), coagulopathy (RNI 1,29), reduced serum levels of fibrinogen (94 mg/dL), increased triglycerides (353 mg/dL) and ferritin (>1000 ng/mL). Serology for viral and autoimmune hepatitis was negative. She received transfusions of fresh frozen plasma that controlled the bleeding. A bone marrow examination revealed hemophagocytosis (Fig. 1).

She was diagnosed with MAS and treated with 3 pulses of methylprednisolone 30 mg/kg/day, followed by oral prednisone (PDN) 2 mg/kg/day and cyclosporine (CSA) 2 mg/kg/day. MTX and ETN were suspended. Her symptoms and clinical signs did not improve despite the increase in CSA dose to 6 mg/kg/day. Fever was sustained and she maintained abnormal laboratory findings: bicytopenia (Hb 7.8 g/dL and platelets