REVISTA BRASILEIRA DE REUMATOLOGIA

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SOCIEDADE BRASILEIRA DE REUMATOLOGIA

Case report

Macrophage activation syndrome in a patient with systemic juvenile idiopathic arthritis

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ARTICLE INFO

Article history:
Received 25 October 2012
Accepted 10 February 2014
Available online 28 November 2014

Keywords:
Hemophagocytic lymphohistiocytosis
Epstein–Barr virus
Systemic-onset juvenile idiopathic arthritis
HLH-04 treatment protocol

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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http://dx.doi.org/10.1016/j.rbre.2014.02.020

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

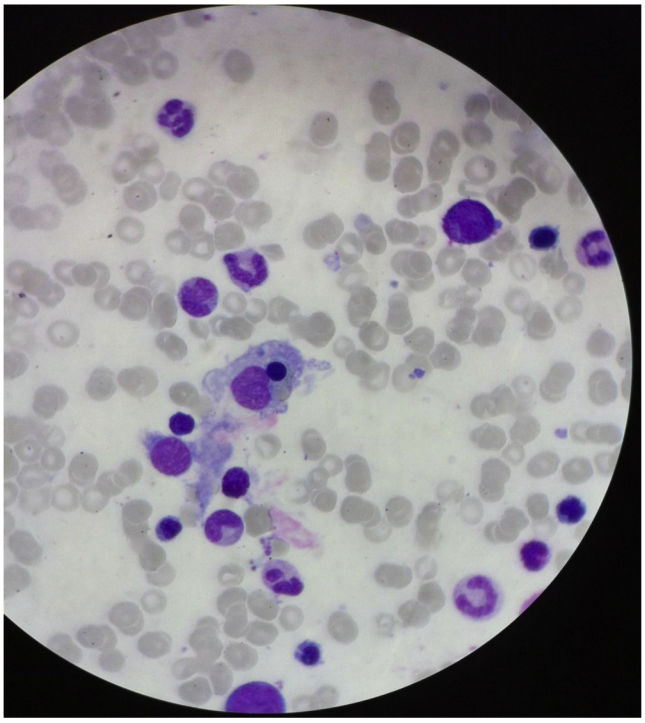

Fig. 1 – Hemophagocytosis in the bone marrow. *Credit*: Dr. Paulo do Val Rezende (Department of Pediatric Hematology of Hospital das Clínicas of Universidade Federal de Minas Gerais).

$94 \times 10^3/\mu L$), increased serum ferritin levels (>1.000 ng/mL), elevated triglycerides (445 mg/dL) and reduced fibrinogen (96 mg/mL).

She developed sepsis after the initial treatment, worsening her clinical and laboratory condition. In addition to antibiotics, intravenous human immunoglobulin (IVIG) 2 g/kg was administered, with no improvement.

After cytomegalovirus (CMV) and EBV serology results, the latter positive IgM and IgG, and a lumbar puncture, to rule out central nervous system (CNS) involvement, we decided in conjunction with the Hematology team, to start HLH-04 treatment protocol: dexamethasone, etoposide (VP 16), in addition to CSA, for eight weeks. After the fourth week of treatment protocol, there was febrile neutropenia (total leukocyte count $0.87 \times 10^3/\mu L$), and hair rarefaction, both complications that were already expected with this treatment.

The disease remitted after eight weeks. Her last laboratory assessment showed normalization of ferritin (270 ng/mL), triglycerides (78 mg/dL), hemoglobin (13.7 g/dL), fibrinogen (250 mg/mL), AST (23 U/L) and ALT (34 U/L). The patient is currently taking PDN 5 mg/day and CSA 6 mg/kg/day.

Discussion and conclusion

The purpose of this case report is motivating rheumatologists to consider MAS when faced with patients with fever, hepatosplenomegaly, impairment of liver function and cytopenias, so treatment can be quickly initiated. It is important to emphasize that the diagnosis of MAS is often a challenge as it may mimic a flare of the underlying disease. There are no validated criteria for diagnosis of MAS.[6] Ravelli et al.[2] proposed diagnostic guidelines for MAS complicating SJIA, based on expert consensus. Clinical and laboratory findings that were more sensitive to MAS differentiation from flares of the underlying disease were selected. The most frequent findings were thrombocytopenia, hyperferritinemia, elevated liver enzymes, leukopenia, bone marrow hemophagocytosis, persistent fever, drop in the erythrocyte sedimentation rate, hypofibrinogenemia and hypertriglyceridemia.[2] In our patient, the presence of bleeding, daily and non-remitting fever, pancytopenia and reduced fibrinogen serum levels stood out, which led us to consider a diagnosis other than SJIA activation.

We consider that there was a combination of triggers. Immunosuppression with synthetic and biological drugs, persistent disease activity, and EBV infection has contributed to a severe and life-threatening disease. The SJIA therapy, mainly MTX but also ETN,[5,6] might have been the trigger. Biological drugs have been described not only as a possible treatment for MAS, but also as syndrome triggering factors.[6]

Currently, the treatment for macrophage activation syndrome is based on corticosteroids and CSA. CSA has proved effective in patients with severe disease and corticosteroid resistant,[6,7] that is why it was introduced early in the treatment. Human intravenous immunoglobulin is an alternative therapy,[6,8] also ineffective in our patient. There are a few reports of effectiveness of interleukin-1 antagonists, particularly anakinra[9] (unavailable in our country) in those patients refractory to conventional treatment. Since the disease was refractory to the initial therapy, we were motivated to look for other causes, like the possible association with EBV infection, considered to be one of the major etiological agents and responsible for the most severe cases.[8,10,11] So we chose the treatment guided by the HLH-04 protocol. VP16 is important, mainly, in refractory cases,[6,8,11–13] and should be promptly initiated since it confers the most favorable prognosis in these situations.[11]

The HLH treatment protocol was proposed in 1994 and revised in 2004 for treatment of primary and secondary forms, related to infections and malignancies. The specific infectious treatment appears to have a result in cases of visceral leishmaniasis, cytomegalovirus and bacterial infections, but there is no benefit described in disease associated with EBV infection.[9,10] The treatment was based on the dexamethasone and VP16 association, in an eight-week induction period. In case of remission, treatment should be suspended after eight weeks.[1,3,12] Otherwise, these patients should be referred to stem cell transplantation.[6,12]

In summary, the importance of this report is, in addition to the extensive discussion of possible triggers, the successful treatment with etoposide, which was essential for induction of remission of MAS. We also emphasize how often MAS has been diagnosed nowadays and question whether the immunobiological therapy has implied an increase in the number of cases, since it makes our patients more vulnerable to opportunistic infections of any etiology that is also considered to be a predisposing factor for the disease.

Conflict of interest

The authors declare no conflicts of interest.

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