Macrophage activation syndrome in a child with unclassified systemic vasculitis probably triggered by Parvovirus B19 infection.

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ABSTRACT: Macrophage activation syndrome (MAS) is a life threatening complication of chronic rheumatic diseases of childhood and especially of systemic juvenile idiopathic arthritis. Infections, particularly viral, have been suggested to play a triggering role. We describe a case of systemic unclassified ANCA positive vasculitis complicated with fatal MAS triggered probably by Parvovirus B19 infection.

Key Words: Macrophage activation syndrome, Reactive hemophagocytic lymphohistiocytosis, Parvovirus B19 infection, Unclassified systemic vasculitis, Anakinra.

INTRODUCTION

Macrophage activation syndrome (MAS) is a life threatening complication of chronic rheumatic diseases in childhood[1-2]. Although it is seen most commonly in systemic juvenile idiopathic arthritis, it has also been described in association with systemic lupus erythematosus, juvenile dermatomyositis and Kawasaki disease[3-5]. It is characterized by an uncontrolled activation of T lymphocytes and macrophages, which leads to a systemic inflammatory response inducing multiorgan infiltration and dysfunction[5]. MAS can present as fever of unknown origin, cytopenias, organ failure (respiratory, cardiovascular, hepatic, renal) or encephalitis[1,3]. Diagnosis of MAS can be difficult, because there are no pathognomonic clinical or laboratory findings and it is based on decreed diagnostic criteria: two clinical, fever and splenomegaly and three of the five laboratory ones, cytopenia, hyper-triglyceridemia and/or hypofibrinogenemia, hyperferritinemia, hemophagocytosis in bone marrow, absent or low NK cell activity and increased CD25 levels[2-5]. Infections, particularly viral, have been suggested to play a triggering role[6]. We describe a case of systemic vasculitis complicated with MAS triggered by Parvovirus B19 infection a long time after the disease onset.

CASE REPORT

A 7 year old female patient, diagnosed with an unclassified vasculitic syndrome 6 years previously, was admitted with a week's history of non remitting fever of up to 39,5°C, diffuse maculopapular rash, paleness, fatigue and malaise. Her main disease started at the age of 9 months when a systemic ANCA positive vasculitis of unclassified type was diagnosed[7].

The disease was refractory to conventional therapeutic regiments. Persistent fever, rash and/or pericarditis recurred three or more times per year. During the 6-year period of the disease course she had taken steroids (peros or pulses), cyclosporine, intravenous immunoglobulin (IVIG), methotrexate, azathioprine, cyclophosphamide and anti-TNF (etanercept) without succeeding long-term remission. Lastly, she was put

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on anakinra, a recombinant IL-1 receptor antagonist and she responded dramatically getting into remission for about a year.

On admission's clinical examination the patient was in no acute distress. Her temperature was 38°C, heart rate 90 beats per minute and blood pressure 100/60 mmHg. Moreover, hepatomegaly (3 cm), splenomegaly (4 cm) and mild generalized lymphadenopathy (1-1.5cm) were ascertained. Laboratory evaluation revealed a leucocytosis with neutrophilia (11.5 x 10^9/L with 83% neutrophils), with normal hematocrit (36%) and platelet count (409 x 10^9/L). Acute face reactants were moderately elevated (ESR: 53 mm/hr and CRP: 9.29 mg/dl) as well as liver enzymes (AST: 115 U/l, ALT: 57 U/l, LDH:2374 U/l) while renal function (urea, creatinine and urine analysis) was normal. Her chest radiograph showed dense bilateral alveolar infiltrates, abdominopelvic ultrasonography revealed mild enlargement of the abdomen lymph nodes and heart ultrasonography was consistent with mild pericarditis. Bone marrow aspiration was normal but her serum immunologic profile showed a raised count of activated B cells (CD23: 28%, normal: 0-1.5) and low CD4/CD8 ratio (0.6, normal: 1-2.5).

According to these clinical and laboratory data, infection and/or flare of the disease was considered and broad-spectrum antibiotics (ceftazidime plus amikacin) were introduced after the collection of blood and urine cultures and serologic investigation for bacterial or viral infection. Furthermore, anakinra was interrupted and intravenous cyclophosphamide as well as IVIG was initiated. After this treatment fever and rash were slightly reduced but fatigue and malaise sustained. Ten days later the patient had a deterioration of her general condition with persistent high-grade fever (>40° C) resistant to anti-febrile drugs (paracetamol, mefenamic acid and ibuprofen) accompanied by hepatosplenomegaly, irritability and altered mental status. Laboratory work-up revealed neutropenia (1.2 x 10^9/L, normal: 1.5-8), anemia (8.2 g/dl), thrombocytopenia (45 x 10^9/L, normal: 150-400), hyperferritinemia (13000 ng/ml, normal: 10-140), high levels of LDH (4964 U/l), hypertriglyceridemia (600 mg/dl, normal: 0-150) and sudden fall of ESR (25 mm/1h) and fibrinogen (2.8 g/dl, normal: 3.5-5.2) in parallel with coagulation disturbances (D-dimmers 4615 μg/l, normal: 50-285, aPTT 50s, normal: 24-36 and PT 17s, normal: 10-14). These clinical and laboratory findings (fever, splenomegaly, pancytopenia, hypertriglyglyceridemia, hypofibrinogenemia and hyperferritinemia) fulfilled the proposed diagnostic criteria for MAS syndrome[3-5]. In addition, serological tests for viral infections revealed a probable Parvo B19 virus infection (positive IgM antibodies by ELISA in a title of 0.473, normal: cut off 0.3), while CMV, EBV, Coxsakie, Echo, HIV, HCV and HBV serology was negative as it was all cultures and serologic investigations for bacterial infections. Unfortunately, the further Parvovirus evaluation with DNA analysis by PCR and IgG antibody measurement was unworkable.

Treatment with intravenous pulse methylprednisolone (30mg/Kg/day) for 3 consecutive days in combination with intravenous cyclosporine (5 mg/Kg/day in 2 divided doses) was started and fresh frozen plasma, platelets, packed red blood cells, and albumin were added in order to correct coagulation defects and anemia. But despite this rigorous treatment the patient's condition was rapidly deteriorated. Thirteen days after admission she developed seizures, confusion and unconsciousness and was transferred to the intensive care unit. She further lapsed into coma with multiple organ failure and died 6 days later despite maximum intensive care support.

DISCUSSION

MAS is a rare and potentially fatal condition of rheumatic diseases. Unfortunately, diagnosis can be difficult at onset and confusable[8]. Our patient initially presented with clinical and laboratory features consistent with an infection and/or flare of the underlying disease. The presence of a Parvo B19 positive IgM antibodies support the hypothesis of a recent Parvovirus infection but it was impossible to confirm the diagnosis with DNA analysis by PCR. MAS was suspected about a week after admission but the bone marrow aspiration obtained at that time did not reveal elements of hemophagotytosis and a further bone marrow aspiration was not obtained due to the rapid deterioration of the patient's clinical condition. Unfortunately, although parvovirus B19 associated MAS carries a better prognosis compared with other viruses, in our case it was fatal[1,6,9,10].

The pathophysiology of MAS involves dysregu-

lation of T-cytotoxic lymphocytes and natural killer cells, which fail to clear infected cells resulting in persistent antigen activation of T cells and excessive production of cytokines. The cytokine storm leads to abnormal production and activation of macrophages which display an increased phagocytosis of blood elements[3-6]. This immunohaematological process of reticuloendothelial system is currently classified among the reactional histiocytoses and MAS is also named as autoimmune disease associated reactive hemophagocytic lymphoistiocytosis (ReHLH)[1,5,11].

Diagnosis of MAS/ReHLH can be difficult, especially in early phases, because there are no pathognomonic clinical findings and it must be differentiated by infections, sepsis, thrombotic thrombocytopenic purpura, disseminated intravascular coagulation or a flare up of an underlying disease. Diagnostic criteria were proposed in 1991 by a study group of histiocyte society and modified in 2004 [3-5,11]. They suggest that MAS diagnosis is established if five of eight diagnostic criteria are fulfilled: two clinical criteria, fever and splenomegaly and three laboratory ones, cytopenia, hyper-triglyceridemia and/or hypofibrinogenemia and evidence of hemophagocytosis in bone marrow, spleen or lymph nodes. Recently three new diagnostic criteria have been proposed, including hyperferritinemia, increased soluble CD25 levels and absent or low natural killer cell activity[3-5,12].

Our patient fulfilled 5 of the 8 criteria for diagnosis of MAS: fever, splenomegaly, cytopenias, hyperferritinemia and hypertriglyceridemia plus hypofibrinogenemia. Unfortunately, evaluation of soluble CD25 levels and natural killer cell activity was unworkable. Hemophagocytosis in bone marrow was not found probably due to the fact that aspiration was performed early in the disease course, so it does not exclude the diagnosis of MAS[3,13].

Early recognition of MAS and aggressive therapy are critical. Clinical differentiation from a typical flare of the underlying rheumatic disease is vital, as delay in administration of specific therapy may be followed by a rapidly fatal course[13-14]. High dose corticosteroid treatment is the suggested initial treatment of choice in MAS, which can be effective in almost half of patients with MAS. Second line agents used include cyclosporine, etoposide and IVIg[13]. Finally, anti-thymocyte globulin, anti-TNF, anti-interleukin-2Ra and other monoclonal antibodies (anti-CD20) have been used in the setting of rheumatic disease or malignancies associated with MAS[3-5, 12,13].

MAS can be fatal with a mortality of 8-22% in different reported series. Various prognostic factors have been suggested as delayed diagnosis, severe multiorgan failure, severe neutropenia and coagulopathy as well as the presence of CNS disease and poor response to therapy[1-5, 9]. In our patient, poor response to treatment of the underline disease and CNS involvement probably contributed to the fatal outcome of MAS despite the early administration of the specific therapeutic management with methylprednisolone pulse, cyclosporine and IVIg.

In conclusion, MAS is a rare and potentially lethal complication of childhood rheumatic diseases. Unfortunately diagnosis can be difficult at onset but is critical because prognosis is related to how early aggressive treatment is started. A better understanding of its pathophysiology can lead to further improvement in the management of MAS. At last, physicians should take into account that patients at high risk of developing MAS are not only those with Systemic onset Juvenile Idiopathic Arthritis, but with every other rheumatic diseases of childhood including vasculitic syndromes as well.

Abbreviations

MAS = Macrophage activation syndrome, ReHLH = Reactive hemophagocytic lymphohistiocytosis, ANCA = Antinuclear cytoplasmic autoantibodies, IVIG = Intravenous immunoglobulin

Σύνδρομο διέγερσης μακροφάγων σε παιδί με αταξινόμητη συστηματική αγγειΐτιδα πιθανόν λόγω λοίμωξης από παρβοϊό Β19.

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ΠΕΡΙΛΗΨΗ: Το σύνδρομο διέγερσης μακροφάγων (MAS) είναι μια δυνητικά θανατηφόρος επιπλοκή των χρόνιων ρευματικών νοσημάτων της παιδικής ηλικίας και συχνότερα της συστηματικής νεανικής ιδιοπαθούς αρθρίτιδας. Οι λοιμώξεις, ιδίως οι ιογενείς, πιθανολογείται ότι αποτελούν εκλυτικό παράγοντα στην πρόκληση του συνδρόμου. Περιγράφεται η περίπτωση ενός παιδιού με αταξινόμητη συστηματική αγγειΐτια με θετικά ANCA αντισώματα το οποίο ανέπτυξε θανατηφόρο MAS πιθανόν λόγω λοίμωξης από παρβοϊό Β19.

Λέξεις Κλειδιά: Σύνδρομο διέγερσης μακροφάγων, Αντιδραστική αιμοφαγοκυτταρική λεμφοϊστιοκύττωση, Λοίμωξη από παρβοϊό Β19, Αταξινόμητη συστηματική αγγειΐτιδα, Ανακίνρα.

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