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Unexpected macrophage activation syndrome in a healthy young woman: a case report

A. SAVIANO, M. PETRUCCI, P. TILLI, G. PIGNATARO, C. PETRUZZIELLO, G. GIULIANO, V. OJETTI, M. COVINO, F. FRANCESCHI, M. CANDELLI

Department of Emergency Medicine, Fondazione Policlinico A. Gemelli IRCCS, Rome, Italy

Abstract. – Macrophage activation syndrome (MAS) is a life-threatening condition and a medical emergency with a high-risk of mortality. It belongs to a group of diseases known as "hemophagocytic lymphohistiocytosis", characterized by a cytokine storm, with secretion of tumor necrosis factor, interleukins and interferon-gamma, and an inappropriate activation of macrophages and T-lymphocytes. Some inflammatory and systemic autoimmune diseases, such as systemic juvenile idiopathic arthritis, Still's disease and systemic lupus erythematosus, can develop into macrophage activation syndrome. This is the first episode of macrophage activation syndrome (MAS) in a young healthy woman. She arrived at the Emergency Department complaining of four days of weakness and fever not responsive to paracetamol. She had no significant past medical history, her mother suffered from rheumatoid arthritis. In the Emergency Department, we performed laboratory exams, autoimmune and infectious disease screening, bone marrow biopsy. The final diagnosis was of macrophage activation syndrome. Macrophage activation syndrome, in extremely rare cases, can arise independently years before the manifestation of an autoimmune disease. Persistent fever, high level of inflammatory markers and pancytopenia should raise suspicion in healthy people, especially when associated with a family history of autoimmune disease. Early diagnosis and consequent early treatment are fundamental to avoid progressive tissue damage that can lead to organ failure and death.

Key Words:
Macrophage activation syndrome, Cytokine storm, Ferritin, Rheumatoid arthritis, Still's disease.

Introduction

Macrophage activation syndrome (MAS) is a life-threatening complication of several inflammatory and autoimmune diseases[1-4]. It is frequently associated[1,5,6] with systemic juvenile idiopathic arthritis (So-JIA), Still's disease, systemic lupus erythematosus, antiphospholipid syndrome, juvenile dermatomyositis, and connective tissue diseases. It belongs to a group of diseases known as hemophagocytic lymphohistiocytosis (HLH). It is characterized by a cytokine storm and inappropriate activation of macrophages and T-lymphocytes[7]. These cells usually destroy infected cells but they can also attack healthy cells in case of inappropriate activation. This condition is characterized by an overproduction of macrophage colony-stimulating factor, tumor necrosis factor (TNF), interleukin (IL)-1, IL-6, IL-10, IL-12, IL-18, IL-33 and w-gamma (IFNγ)[8].

Literature data[9] reported the presence of an autosomal recessive inheritance pattern that favors the onset of this disease. Some identified genes are perforin 1 (PRF1), syntaxin (STX)-11, syntaxin-binding protein (STXBP)-2[8]. This disease can be triggered by rheumatic diseases, bacterial or viral infections[1] (Epstein Barr virus, Cytomegalovirus, Dengue, Ebola, Herpes virus etc.), drugs or malignancies[9].

The symptoms of MAS include high fever, hepatomegaly, splenomegaly, swollen lymph nodes, hemorrhagic manifestations (epistaxis, hematemesis, petechiae, purpura) and a sepsis-like condition[7]. Some patients develop neurological symptoms (headaches, seizures, encephalopathy, altered mental status and coma), liver dysfunction (elevation of transaminase and bilirubin, hypoalbuminemia), renal failure, respiratory infiltrates and distress. All these symptoms can rapidly lead to multiple organ failure (MOF).

In 2016[10], criteria for MAS in patients with So-JIA were updated. Laboratory alterations included ferritin higher than 684 ng/ml plus two of the following: platelets less than 181000/mmc, aspartate aminotransferase (AST) higher than 48 U/L, triglycerides higher than 156 mg/dL and

Corresponding Author: Marcello Candelli, MD; e-mail: mcandelli@gmail.com

fibrinogen less than 360 mg/dL. Ferritin is the most characteristic laboratory parameter because it is released in the blood by macrophages. There are no specific criteria for MAS linked to other inflammatory and autoimmune diseases. Some possible findings are leukopenia, thrombocytopenia and anemia. Finally, bone marrow aspirate shows hypercellularity, hemophagocytosis, erytrophagocitosis[1] with positive soluble receptor alpha chain sCD25 and sCD163[8].

First-line therapy includes high dose corticosteroids (dexamethasone, methylprednisolone, and prednisolone) and immunosuppressive agents like cyclosporine or cyclophosphamide. In addition, etoposide has been recommended in the HLH treatment protocol[11]. Promising response was also obtained with an IL-1 inhibitor[4]. Immunoglobulins and anti-thymocyte globulins could be intravenous alternatives[7]. However, supportive measures (plasma exchange, red blood cells, platelet pools, vasopressors and fluid support) and the treatment of the underlying pathology (autoimmune, rheumatological, and infectious) are fundamental. To date, the most effective treatment seems to be the specific cytokine therapy[8] (for example, IL-1 blockade or IFNγ blockade or IL-6 blockade) with biological antibodies. Further studies and clinical trials are needed to assess and prove the effectiveness of these therapies.

Case Report

A 39-years-old woman arrived at the Emergency Department (ED) complaining of four days of weakness and fever not responsive to paracetamol. She had no significant past medical history and did not take drugs. Her mother was affected by rheumatoid arthritis. One month prior to her access to the ED, she remembered having fever, sore throat and a blotchy rash. All symptoms disappeared after treatment with antibiotics and antipyretics. On physical examination, she was febrile (T 38.2°C) but alert and oriented in time and space. Respiratory rate was 17 breaths per minute, blood pressure was 110/70 mm/Hg, and heart rate was 98 beats per minute. She had no skin dyschromia, purpura or petechiae.

The laboratory evaluation revealed a hemoglobin level of 6.3 g per deciliter (normal range 12 to 16), a platelet count of 19.000 per cubic millimeter (normal range 150.000 to 350.000), an alanine aminotransferase of 1337 U/ml, total bilirubin 4 mg/dl, lactate dehydrogenase 5764 U/l, and triglycerides 899 mg/dl. In addition, the level of ferritin resulted more than 16500 ng/ml (normal range, 13-150 ng/ml). International normalized ratio (INR) was 2.83, D-dimer was 7989 ng/ml, and antithrombin III was normal. The autoimmune antibodies screening (lupus anticoagulant antibodies, anti-nucleus antibodies, extractable nuclear antibodies, anti-neutrophil cytoplasmic antibodies, rheumatoid factor, anti-citrulline antibodies) was normal. Hematological diseases (as disseminated intravascular coagulation or thrombotic thrombocytopenic purpura) were excluded.

The chest X-Ray revealed diffuse interstitial alveolar involvement with bilateral basal pleural effusion. The echocardiogram showed normal-sized heart chambers and mitral valve prolapse with mild insufficiency.

During her stay in the ED, the left ventricular contractility worsened to 20%. A thorax and abdomen computed tomography (CT) scan described intestinal edema, submucosal edema of the stomach and of the descending tract of the colon, mild sub-hepatic, sub-splenic and peri-cholecystic fluid collection. Liver and kidneys were normal. Spleen was mildly enlarged. The blood screening for infectious diseases [Hepatitis B, Hepatitis C, Immunodeficiency virus, Cytomegalovirus, Epstein Barr Virus (EBV), Herpes viruses, Influenza viruses, Syphilis, Salmonella, Proteus OX19, Proteus OX2, Proteus OXK, Rickettsia, Chlamydia pneumoniae, Leishmania] resulted negative. The bone marrow biopsy revealed normal cellularity, activated monocytes and initial hemophagocytosis. A small amount of immature cellular components was found. We diagnosed MAS. The patient was treated with immunoglobulins and cyclosporine. She received concentrated red blood cells, platelet pools, intravenous fibrinogen and fresh frozen plasma to treat low fibrinogen levels, anemia, thrombocytopenia and coagulation deficiency. In addition, she was treated with antibiotics, vasopressors (noradrenaline), and inotropic support (dobutamine) in continuous infusion for marked hypotension. The patient's condition did not improve. She received non-invasive, and then, invasive ventilation (tracheostomy). She progressively developed multiple organ failure and died in the Intensive Care Unit.

Conclusions

MAS is a severe disease with a mortality rate of 8-22%[12]. Both adults and children can develop

it[13]. In rare cases, it can be the initial presentation of an autoimmune disease. When this happens, the diagnosis can be very difficult. In literature, it was described as the initial manifestation of juvenile systemic lupus erythematosus in a 4-years-old child and as the initial manifestation of HLH in a 15-years-old male[14]. In adults, it was described as the onset of systemic lupus erythematosus[15] or Still's disease[16]. The young woman in our case report was healthy and without a significant past medical history. Persistent fever, inflammatory markers and pancytopenia should suggest this condition in healthy people, when associated with a family history of autoimmune disease, (in our case rheumatoid arthritis). Randomized controlled trials are necessary to design new strategies for treatment. Intravenous corticosteroids, cyclosporine and immunoglobulins (after exclusion of sepsis) are the first-line therapy. Etoposide is usually used as a treatment for HLH; when it is not well tolerated, it is possible to use anti-thymocyte globulin. Other emerging option are a recombinant IL-1 receptor antagonist[4], an anti-IL1b and an anti-IL6 receptor. Another possibility is rituximab, an anti-CD20, in case of MAS triggered by an EBV infection. In addition, recent research studies showed a promising role of anti-INF_{γ} blockers. Early diagnosis and targeted and timely therapy are essential to improve the survival rate and avoid progressive tissue damage, organ failure, and death.

Conflict of Interest

The authors declare that they have no conflict of interests.

Authors' Contribution

All the authors give their significant contribution to this manuscript; they have read and approved the final version of it.

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