

Case Report

J Ped. Nephrology 2017;5(1)
http://journals.sbmu.ac.ir/jpn

Macrophage Activation Syndrome as the Initial Manifestation of Systemic Lupus Erythematosus in a 7-Year-Old Girl – A Case Report.

How to Cite This Article: Begum A, MuslimaAkte AHM, Md. Rahman A, MuinUddin G. Macrophage Activation Syndrome as the Initial Manifestation of Systemic Lupus Erythematosus in a 7-Year-Old Girl – A Case Report. J Ped. Nephrology 2017;5(1)

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Received: Sep-2016

Revised: Oct-2016

Accepted: Oct-2016

Introduction

Autoimmune rheumatic diseases are rare in children. Children represent 15%–20% of patients with systemic lupus erythematosus (SLE), with an incidence of 0.3–0.9 per 100,000 and a prevalence of 3.3–8.8 per 100,000 children [1]. Unlike adults, children have more severe disease at diagnosis [2]. One of the complications observed in patients with SLE is macrophage activation syndrome (MAS).

Macrophage activation syndrome (MAS) is a potentially fatal condition. It occurs most commonly in association with systemic onset

Macrophage activation syndrome (MAS) is a potentially fatal complication of several chronic rheumatic diseases. Although it occurs most commonly with systemic onset juvenile idiopathic arthritis (SoJIA), it may also occur in association with systemic lupus erythematosus (SLE), Kawasaki disease, and adult onset Still's disease. It is usually triggered by infections or due to medication modification. Here we report a 7-year-old girl who presented simultaneously with features of MAS and SLE and responded with pulse methylprednisolone followed by oral prednisolone and pulse cyclophosphamide.

Keywords: Macrophage Activation Syndrome (MAS); Systemic Lupus Erythematosus (SLE); Child.

Running Title: Macrophage Activation Syndrome in SLE

juvenile idiopathic arthritis (SoJIA) [3-5]. However, this syndrome has been also described in patients with other pediatric inflammatory diseases such as Kawasaki disease, juvenile dermatomyositis, and periodic fever syndromes [6-10].

The incidence of MAS associated with SLE is about 0.9–4.6% [11]. It is a multisystemic disease, presenting with several signs and symptoms, including high fever, hepatomegaly, splenomegaly, hemorrhagic manifestations (e.g. purpura), dysfunction of the central nervous system like lethargy, and alterations in laboratory tests,

including pancytopenia, hypofibrinogenemia, hypertriglyceridemia, and hyperferritinemia. We report a rare case of MAS that occurred as the first manifestation of SLE and was treated with high dose intravenous methylprednisolone and cyclophosphamide.

Case Report

A 7-year-old girl, first issue of non-consanguineous parents, was admitted with the complaints of generalized convulsion followed by unconsciousness and bleeding from the gingiva and rectum for four days. On query, her mother gave a history of painful swelling of multiple joints which was not associated with morning stiffness, was non-migratory, and was additive in nature involving both large and small joints. She also had a history of swelling of the whole body which first appeared over the peri-orbital region and then became gradually generalized. She had a history of passing red colored urine and oral ulceration. For this illness, she received two units of blood transfusion. On examination, she was semiconscious and moderately pale with a GCS of 8/15. Bleeding marks were seen in the oral and nasal cavity. Her temperature was 100° F, pulse rate was 100b/min (regular, low volume), BP was 90/60 mmHg, and respiratory rate was 30b/min. She had edema but did not have lymphadenopathy or signs of meningeal irritation. Bed side urine for albumin was 3+. Her weight was 18 kg (5th percentile) and height was 128 cm (75th percentile) Fig. 1.

On systemic examination, she had hepatomegaly and ascites; other systemic examinations were unremarkable.

Her urinalysis showed 3+ proteinuria, plenty of red blood cells, and 0-2 pus cells, and 24-hour urinary protein was 0.6 gm/day. Hematological picture showed mild anemia (Hb-10.9 gm/dl), thrombocytopenia (PC-45,000/cumm), and leukocytosis (TC-15,000/cmm). Peripheral blood film showed mild normocytic normochromic anemia. Her ESR was 20 mm in the 1st hour. Direct coombs test was positive. Serum albumin level was 20gm/l, serum creatinine was 4.0 mg/dl, and blood urea was 194 mg/dl. Prothrombin and activated partial thromboplastin time were within the normal range. The ferritin level was very high (16,700 ng/ml), and the fibrinogen level was low (307 ng/dl). She had elevated liver enzymes (SGPT 250 U/L). Serum lactate dehydrogenase was increased (547u/l). She had low levels of complements (C30.44 gm/L, C4 0.34 gm/L). ANA

and anti dsDNA were positive (anti dsDNA: 100 mg/dl). Percutaneous renal biopsy was done, which was consistent with mesangial proliferative lupus nephritis (stage two). Immunofluorescence study showed fine granular deposits with IgG (+++) and C3 (++) in the mesangium. Electron microscopy was not done due to unavailability. She was managed with intermittent peritoneal dialysis and fresh frozen plasma transfusion. Immunosuppressive therapy was given in the form of six pulses of methylprednisolone (30 mg/kg/day) followed by oral prednisolone 2 mg/kg/day, and cyclophosphamide injection 750 mg/m²/dose monthly for 6 months. Other supportive managements like hydroxychloroquine and antihypertensive agents were also prescribed. She achieved complete remission after 15 days.



Fig. 1. Clinical manifestation of the patient

Discussion

Macrophage activation syndrome (MAS), first named in 1993, is a subcategory of hemophagocytic lymphohistiocytosis (HLH). This is a clinicopathological entity characterized by activation of histiocytes with prominent

hemophagocytosis in the bone marrow and other reticuloendothelial systems [12]. It has primary and secondary forms. The primary type includes a group of genetic disorders that results in an altered function of the immune cells. The secondary or acquired form may be associated with malignancy, infection, or autoimmune diseases [13]. In patients with autoimmune diseases, it is called MAS and can occur as the initial manifestation at the time of diagnosis or form part of an exacerbation or an infectious process [14].

It is caused by excessive activation and proliferation of T lymphocytes and macrophages. The etiology of this syndrome is not fully understood. In particular, a report of marked elevation of soluble cytokines in some children with MAS suggests that uncontrolled proliferation of cytotoxic T lymphocytes (CD8+) may underlie this disease [15].

The recognition that MAS is clinically similar to HLH has led many clinicians to use the diagnostic guidelines for HLH in the diagnosis of macrophage activation syndrome [10]. The criteria for MAS complicating systemic juvenile idiopathic arthritis (SJIA) were established by Ravelli A et al [16]. Laboratory criteria include decreased platelet and white blood cell counts, elevated levels of aspartate amino-transferase, decreased levels of fibrinogen, and increased levels of ferritin. Clinical criteria include hepatomegaly, hemorrhagic manifestations, and central nervous system dysfunction. The diagnosis of MAS requires the presence of at least 2 laboratory criteria or the presence of at least 1 laboratory and 1 clinical criteria [16]. The demonstration of macrophage hemophagocytosis in the bone marrow aspirate is required only in doubtful cases.

In our patient, a diagnosis of MAS secondary to acute SLE was established based on laboratory and clinical findings. Clinically, she had bleeding, convulsion, and hepatomegaly. Regarding laboratory findings, she had a low ESR, thrombocytopenia, hypofibrinogenemia, and hyperferritinemia.

SLE-associated MAS might be underdiagnosed. Cytopenias are common and may have various origins in SLE. In a review of 38 MAS associated SLE patients, thrombocytopenia was a better indicator of MAS than leucopenia and anemia [17], and we observed the same findings in this patient. However, hyperferritinemia is reported to be the best parameter to differentiate between MAS-associated SLE and active SLE with a sensitivity and specificity of almost 100% [11]. In our patient, the ferritin level was also very high on admission.

There is no well-established therapeutic strategy for MAS complicating SLE. As infections are a common trigger, their exclusion is important to establish an appropriate treatment. In case of infection, it is important to decrease the dose of immunosuppressive agents.

Clinical suspicion for MAS is higher when an infection is ruled out or inflammation persists and does not respond to treatment of an underlying infection. In this case, it could be useful to start an immunomodulatory therapy even in the presence of infection. To date, several therapeutic options are available, including nonbiologic and biologic treatments. Intravenous methylprednisolone pulse therapy (e.g. 30 mg/kg for three consecutive days) followed by oral prednisolone 2-3 mg/kg/day is the most common schedule [18]. Multiple case reports have also discussed the importance of immunosuppressive medications, such as IV cyclosporine A and cyclophosphamide in patients who do not respond to steroids [17]. Newer drugs like biologic agents, such as Anakinra and rituximab, may be effective in resistant cases [19,20].

Due to unavailability of IV cyclosporine, our patient was treated with IV cyclophosphamide along with steroids. After 15 days, she achieved remission and was discharged with follow up advice.

Conclusion

MAS associated with SLE should be considered a severe complication that puts the patient's life at risk. Early diagnosis and aggressive treatment is necessary to save the patient's life.

Conflict of Interest

None declared

Financial Support

None declared

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