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Case Report / Приказ болесника

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Macrophage activation syndrome complicating early course of adult-onset Still's disease

Синдром активације макрофага као рана компликације Стилове болести код одраслих

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SUMMARY

Introduction Adult-onset Still's disease is a rare inflammatory disorder of unknown etiology. It can be complicated by macrophage activation syndrome, potentially life-treatening condition. While macrophage activation syndrome and adult-onset Still's disease shared similar features, early recognition is very difficult in clinical praxis.

Case outline We report a young woman, which illness was presented suddenly, with spiking fever, sore throat, myalgia, arthralgia and maculopapular rash. In suspicion of sepsis, she received antibiotics, despite no evidence of infection. After two weeks, her condition worsened, which has been followed by cytopenia, elevated liver enzymes and high serum levels of ferritin. She was diagnosed as macrophage activation syndrome in early course of adult-onset Still's disease. She was treated with high dose corticosteroids and cyclosporine A and recovered completely.

Conclusion Macrophage activation syndrome can occur at the beginning of adult-onset Still's disease. Early recognition and timely administration of immunosuppressive drugs are important for successful outcome in this condition.

Keywords: macrophage activation syndrome'; adult-onset Stills disease; hyperferritinemia

САЖЕТАК

Увод Стилова болест у одраслих је ретко запаљенско обољење непознате етиологије. Може се компликовати синдромом активације макрофага, који је потенцијално животно угрожавајуће стање. Како синдром активације макрофага и Стилова болест у одраслих имају сличне клиничке одлике, њихово разликовање у клиничком раду је тешко.

Приказ болесника Приказали смо младу болесницу, која се разболела из пуног здравља наглим порастом температуре, гушобољом, миалгијама, артралгијама и макулозном оспом. Због сумње на септичко стање, лечена је антибиотицима, иако није било доказа за инфекцију. Након две недеље, њено опште стање се погоршало, што је било праћено панцитопенијом, повишеним вредностима ензима јетре и врло високом концетрацијом феритина у крви. Дијагностикован је синдром активације макрофага у раној фази Стилове болести у одраслих. Примењена терапија високим дозама глукокортикоида и циклоспорином А је довело до потпуног опоравка болеснице.

Закључак Синдром активације макрофага се може испољити у раној фази Стилове болести у одраслих. Рано препознавање и правовремена примена имуносупресивне терапије су неопходни за повољан исход болести.

Кључне речи: синдром активације макрофага; Стилова болест код одраслих; хиперферитинемија

INTRODUCTION

Macrophage activation syndrome (MAS) is severe, hyperinflammatory, life-threatening complication of inflammatory rheumatic disaese, primarily in adult onset Still′s disease (AOSD) and systemic lupus erythematosus. Among children with Juvenile idiopathic arthritis (JIA), MAS is most frequent in systemic onset (sJIA). MAS is secondary form of hemophagocytic lymphohistiocytosis (HLH). HLH is classified in primary (genetic) and secondary (reactive) form which can be induced by infective, autoimmune or malign-related disease. MAS is caused by widespread activation and proliferation of cytotoxic CD8+ T cells and macrophages, which are express hemophagocytic activity. Immune dysregulation leads to

the extensive production of proinflammatory cytokines: interleukin (IL)-2, IL-1, interferon-γ, IL-6, IL-18 and tumor necrosis factor alfa which results in "cytokine storm" [1]. Clinical presentation is sustained fever, lymphadenopathy, hepatosplenomegaly, dysregulation of central nervous system and hemorrhagic manifestation. Blood analysis showed pancytopenia, elevated liver enzymes, falling erythrocyte sedimentation rate (due to hypofibrinogenemia), disturbances of hemostasis, significantly elevated serum level of ferritin than in other autoimmune diseases [2].

It has been estimated that the incidence of MAS in patients with AOSD range between 10-25%. MAS can occur any time during disease and can be activated by infection or flare of basic disease. The mortality rate of MAS in rheumatic diseases is up to 30% [3]. While MAS and AOSD shared similar features (fever, hepatosplenomegaly, elevated liver enzymes, hyperferritinemia) and in absence of diagnostic criteria for MAS in AOSD, early recognition of this state or condition is very difficult in clinical praxis. If inadequately treated, MAS can result in multiorgan failure and death.

We present a patient with AOSD complicating in early course MAS and successfully treated with high dose steroids and cyclosporine A.

CASE REPORT

A 33-year-old Caucasian women, was admitted to our hospital with suspicion of AOSD. A month before admission, illness was presented suddenly, with sore throat, spiking fever of 39,4°C, myalgia of arms and legs and painful knees. Also, she had a salmon rash on arms and legs. She had a vesicles in the mouth during one day. She was admitted to a local hospital and initially received antibiotics for 10 days (amoxicillin 3 days, ceftriaxone 7 days), without improvement. Laboratory studies showed erythrocyte sedimentation rate (ESR) 90mm/h, leukocytes 17.5 $x10^9$/L with neutrophils 91%, serum hemoglobin 111 g/L, platelets 199 $x10^9$/L. In suspicion of sepsis, the patient treated with empiric widespread spectrum of antibiotics and antimycotics, despite no evidence of infection. After two weeks of treatment, she became febrile continuously > 40°C. At that time a laboratory findings were thrombocytopenia 53 $x10^9$/L and afterwards pancytopenia and elevated liver enzymes. Serum ferritin level was extremely high 24 900 ug/L. The suspicious of AOSD and administration of

corticosteroids started with dose of 60 mg per day. Patient′s state was deteriorating despite the treatment and after 25 days she was transferred to our hospital.

On admission in our department the patient had a fever 38.3˚C, the blood pressure was low (80/60 mmHg), auscultatory was heart murmur of mitral valve 2/6, skin and conjunctivae were icteric. Abdomen was diffusely tender and hepatosplenomegaly were detected. Her knees were tenderness, with overall impression of severely ill patient. Blood test showed ESR 13 mm/h, c-reactive protein (CRP) 20,68 mg/l (<5 mg/L), leukocytes $1.37x10^9$/L (4-$10x10^9$/L), neutrophils of 0.4 $x10^9$, erythrocytes $2.74x10^9$ (3.8-5.8$x10^9$/L), hemoglobin 74 g/L (130-180 g/L), platelets $25x10^9$ (160-370$x10^9$). Chemistries showed: albumin 23 g/l (32-50 g/L), total bilirubin 74 umol/L (< 18 umol/l), aspartate aminotransferase 144 U/L (< 37 U/L), alanine aminotransferase of 384 (14-59U/L), alkaline phosphatase 1161 (70-290 U/L), lactate dehydrogenase 703 (120-246 U/L), gama GT 968 (< 38 U/L), triglyceride was 3,52 mmol/l (< 1.7 mmol/l). Coagulation studies showed fibrinogen 1.5 g/l (2.1-4.0 g/l), D-dimer 6.98 mg/l (< 0.5 mg/l), INR at 1.26, aPTT 34 seconds. Ferritin was elevated 14 600 ug/l (20-280 ug/l). Two sets of blood and urine cultures were negative. Aspiration of bone marrow showed hypocellular pattern with macrophages in normal bloodline and only one macrophage who showed hemophagocytosis (Figure 1). Subsequently serology tests showed negative findings for rheumatoid factor (RF), antinuclear antibodies (ANA), anticardiolipin antibodies (aCL), lupus anticoagulant (LA), anti-beta2 glycoprotein I antibodies (anti β2GP-I), antineutrophil cytoplasmic antibody and antimitochondrial antibodies. Extensive findings for infectious disease included: Epstein-Barr virus (EBV), cytomegalovirus (CMV), parvovirus, herpes simplex virus, hepatitis B, hepatitis C and human immunodeficiency (HIV) were negative. Transthoracic and transoesophageal ultrasound of heart detected mitral regurgitation 2+, without evidence of vegetations. Computed tomography (body scan) showed only hepato-splenomegaly without any pathologic morphological findings.

Because all of above-mentioned findings, the suspicion for MAS was raised. Pulses doses of methylprednisolone 500 mg daily was started for 3 days, continued with antibiotics (tazobactam of 4.5 grams intravenously every 8 hours, vancomycin of 1 gram every 12 hours, amikacin of 1 gram per day and fluconazole of 200 mg per day). She became afebrile, but appeared the moderate bleeding in the mount. Analyses showed that hematologic parameters were dropped (leukocytes 0.51 $x10^9$/L, hemoglobin 74 g/L, platelets $22x10^9$). She was transferred in an isolation unit. Bone marrow biopsy showed hypoplastic pattern and did not

reveal evidence of hemophagocytosis or hematological malignancy. Then we started treatment with dexamethasone of 32 mg in two doses, intravenous immunoglobulin (IVIG) 400 mg/kg per day for 3 days. Due to absence of improvement for hematological parameters, cyclosporine A was introduced in dose 5 mg/kg/day (with continuing level till 200), continuing with a high dosed dexamethasone. Following this kind of regimen on the 7th day hematological parameters were improved and fibrinogen was normalized as well.

After three weeks, patient was without complaints and blood tests resolved, except easily elevated gama GT and ferritin 634 ug/L. The patient was discharged, with prescribed therapy 0.5 mg dexamethasone and cyclosporine A 5 mg/kg/day, with planned gradual reduction. During follow-up at the outpatient clinic for next 12 months, patient was without any medical problem. Currently, her therapy was cyclosporine at dose 0,5 mg/kg/day.

This case report was approved by the institutional ethics committee, and written consent was obtained from the patient for the publication of this case report and any accompanying images.

DISCUSSION

AOSD is rare, systemic, inflammatory disease of unknown etiology. It estimates the incidence rate 0.16-0.40 cases in 100000 people and prevalence 1-34 cases in million people [4]. Characteristic triad is spiking fever, arthralgia and salmon colored maculopapular rash. Typical blood analyses show leukocytosis (mostly neutrophils), elevated acute phase reactants, high serum levels of ferritin and negative RF and ANA. Also, it can be find elevated liver function tests (enzymes in blood). If suspicion exists for AOSD, diagnosis is made by excluding many other diseases with similar presentation including other autoimmune disorders.

In our patient, sepsis was a leading concern at the beginning, and she had received empirical antibiotics. Sepsis and MAS have similar clinical presentations, extensive findings for infectious disease did not find any of results for concern, and sepsis was excluded. So, initially clinical presentation was early course of AOSD. Our patient had all 4 major (fever of 39°C at higher >1 week, arthralgia, skin rash, leukocytosis >10 000 mm^3 with >80% granulocytes) and most of minor criteria (sore throat, splenomegaly, elevated liver enzymes,

negative RF and ANA) for AOSD [5]. Two weeks later, fever became persistent, followed by pancytopenia, hypofibrinogenemia, with an extreme elevation of ferritin level in blood. This is indicated in the expression MAS initially course of AOSD. At that moment, there are no valid diagnostic criteria for MAS in rheumatologic diseases in adults, and according to literature data we apply recommended HLH-2004 diagnostic guidelines [6]. In our patient, based on five of eight HLH criteria: persistent fever, splenomegaly, 3-line cytopenia, hypertriglyceridemia, hypofibrinogenemia, hyperferritinemia, the diagnosis of MAS could be done.

Although the finding of hemophagocytosis in bone marrow applies to the gold standard of diagnosis of HLH, it is not determined in 30% of patients [7]. This can be explained with hemophagocytosis in other organs such as liver, spleen, and the lymph nodes, which we didn't examine in our patient.

Hyperferritinemia is a significant laboratory feature in MAS, it is not only indicator of the acute inflammatory response, but also has an immunomodulatory role. Extremely high serum values of ferritin, plays a role in the high release of cytokines. According to the contemporary findings, 4 conditions are classified like "hyperferritinemic syndrome": septic shock, catastrophic antiphospholipid syndrome, MAS and AOSD [8]. There was no evidence of antiphospholipid syndrome or sepsis in our patient.

Treatment of patients with MAS was aimed at elimination a potential cause of abnormal immune responses and using of immunosuppressive drugs for suppression of harmful inflammatory response. Traditional therapy in patients with MAS and AOSD includes high-dose corticosteroids and immunosuppressive drug administration, preferably cyclosporine, IVIG and less methotrexate, cyclophosphamide [9]. In patients refractory to traditional therapy, IL-1 receptor antagonist, anakinra, have significant effect in interrupting cytokine network, which leads to clinical recovery. This was demonstrated in patients with MAS in sJIA [10]. Another, human anti-IL-1β monoclonal antibody, canakinumab, could be used in the refractory patients with MAS and AOSD, which unfortunately were not available in all countries [11]. In recent years, several genetic and immunological studies are trying to elucidate pathogenic mechanism in adult MAS patients and lead to advances in the possible new therapeutic targets in the management of MAS [12]. It is quite clear that IL-1 receptor antagonists in the future may be the main drugs in treatment AOSD associated MAS patients.

In patient with fever of unknown origin, AOSD should be considered as a possible cause. Postponing the administration of immunosuppressive therapy can be complicated by MAS. Leading findings that support the development of MAS in the AOSD are pancytopenia and hypofibrinogenemia. The timely application high doses of corticosteroids and early introduction of cyclosporine A lead to an approving outcome of disease.

Conflict of interest: None declared.

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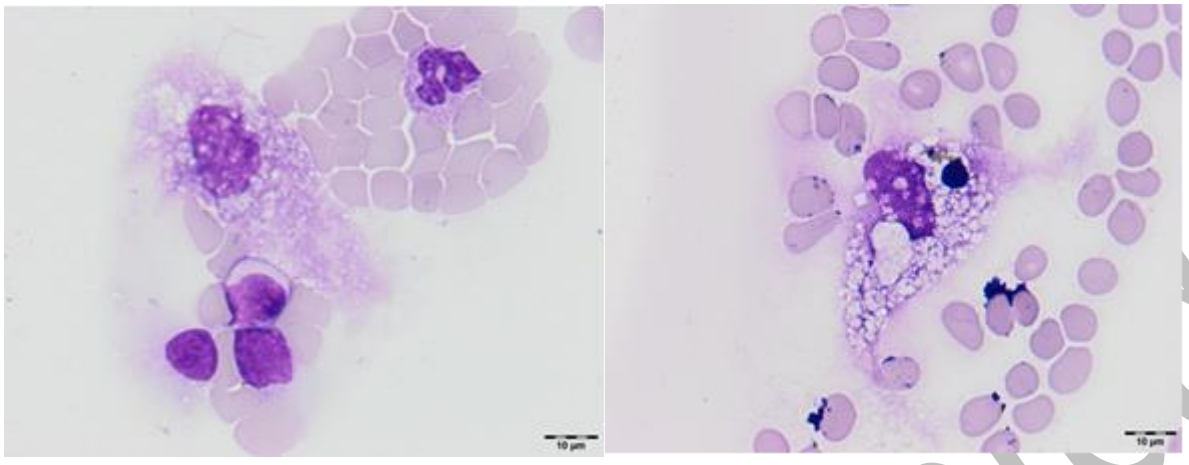

Figure 1. Cytological smear of bone marrow aspiration; in hypocellular bone marrow, a few macrophages were found and only one showed hemophagocytosis, which is not enough for macrophage activation syndrome diagnosis. (May Grunwald-Giemsa, 1000 ×)

