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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

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

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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, a potentially life-threatening condition. While macrophage activation syndrome and adult-onset Still's disease share similar features, early recognition is very difficult in clinical praxis.
Case outline We report a young woman, whose 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 was followed by cytopenia, elevated liver enzymes, and high serum levels of ferritin. She was diagnosed with macrophage activation syndrome in the early course of adult-onset Still's disease. She was treated with high doses of 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 the successful outcome in this condition.-
Keywords: macrophage activation syndrome; adult-onset Still's disease; hyperferritinemia

INTRODUCTION

Macrophage activation syndrome (MAS) is a severe, hyperinflammatory, life-threatening complication of an inflammatory rheumatic disease, 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 a secondary form of hemophagocytic lymphohistiocytosis (HLH). HLH is classified into the primary (genetic) and the secondary (reactive) form, which can be induced by an infective, autoimmune, or malign-related disease. MAS is caused by widespread activation and proliferation of cytotoxic CD8+ T cells and macrophages, which 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 the "cytokine storm" [1]. Clinical presentation is sustained fever, lymphadenopathy, hepatosplenomegaly, dysregulation of the central nervous system, and hemorrhagic manifestation. Blood analysis showed pancytopenia, elevated liver enzymes, falling erythrocyte sedimentation rate (due to hypofibrinogenemia), disturbances of hemostasis, significantly more elevated serum level of ferritin than in other autoimmune diseases [2].

It has been estimated that the incidence of MAS in patients with AOSD ranges 10–25%. MAS can occur any time during the disease and can be activated by an infection or a flare of the basic disease. The mortality rate of MAS in rheumatic diseases is up to 30% [3]. While MAS and AOSD share similar features (fever, hepatosplenomegaly, elevated liver enzymes, hyperferritinemia), 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 complication in the early MAS course and successfully treated with high doses of 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, the 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-colored rash on arms and legs. She had vesicles in the mouth during one day. She was admitted to a local hospital and initially received antibiotics for 10 days (amoxicillin three days, ceftriaxone seven days), without improvement. Laboratory studies showed erythrocyte sedimentation rate (ESR) 90 mm/h, leukocytes 17.5×10^9/L with neutrophils 91%, serum hemoglobin 111 g/L,

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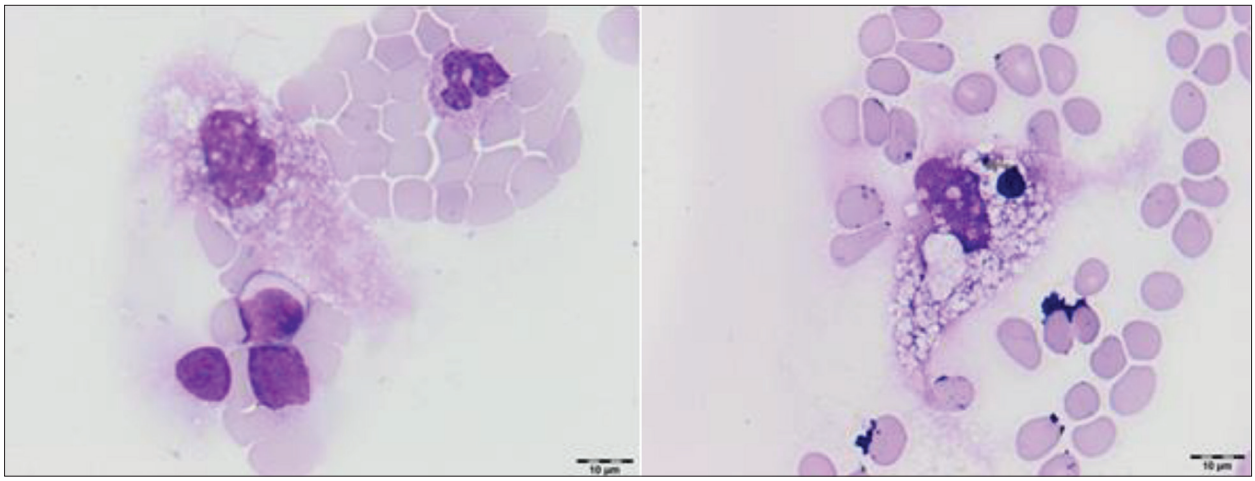

Figure 1. Cytological smear of bone marrow aspiration; in hypocellular bone marrow, a few macrophages were found and only one showed hemophagocytosis, which is not enough for macrophage activation syndrome diagnosis (May–Grunwald–Giemsa, 1000×)

platelets 199 × 10^9/L. In suspicion of sepsis, the patient was 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, laboratory findings showed thrombocytopenia 53 × 10^9/L followed by pancytopenia and elevated liver enzymes. Serum ferritin level was extremely high (24,900 μg/L). The suspicious of AOSD and administration of corticosteroids started with a dose of 60 mg per day. The patient's state was deteriorating despite the treatment, and after 25 days she was transferred to our hospital.

On admission to our department, the patient had a fever of 38.3°C, the blood pressure was low (80/60 mmHg), auscultatory method showed heart murmur of the mitral valve 2/6, skin and conjunctivae were icteric. The abdomen was diffusely tender and hepatosplenomegaly was detected. Her knees were tender, with the overall impression of a severely ill patient. Blood test showed ESR of 13 mm/h, C-reactive protein of 20.68 mg/L (< 5 mg/L), leukocytes of 1.37 × 10^9/L (4–10 × 10^9/L), neutrophils of 0.4 × 10^9, erythrocytes of 2.74 × 10^9 (3.8–5.8 × 10^9/L), hemoglobin of 74 g/L (130–180 g/L), platelets of 25 × 10^9 (160–370 × 10^9). Chemistries showed: albumin 23 g/L (32–50 g/L), total bilirubin 74 μmol/L (< 18 μmol/L), aspartate aminotransferase 144 U/L (< 37 U/L), alanine aminotransferase 384 (14–59 U/L), alkaline phosphatase 1161 (70–290 U/L), lactate dehydrogenase 703 (120–246 U/L), γ-glutamyl transferase 968 (< 38 U/L), triglyceride 3.52 mmol/l (< 1.7 mmol/L). Coagulation studies showed fibrinogen 1.5 g/L (2.1–4 g/L), D-dimer 6.98 mg/L (< 0.5 mg/L), international normalized ratio at 1.26, activated partial thromboplastin time 34 seconds. Ferritin was elevated to 14,600 μg/l (20–280 μg/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, which showed hemophagocytosis (Figure 1). Subsequent serology tests showed negative findings for rheumatoid factor (RF), antinuclear antibodies (ANA), anticardiolipin antibodies, lupus anticoagulant, anti-beta2-glycoprotein I antibodies, antineutrophil cytoplasmic antibody, and antimitochondrial antibodies. Extensive testing for infectious diseases showed that Epstein–Barr virus, cytomegalovirus, parvovirus, herpes simplex virus, hepatitis B, hepatitis C, and human immunodeficiency were negative. Transthoracic and transoesophageal ultrasound of the heart detected mitral regurgitation 2+, without any evidence of vegetation. Computed tomography (body scan) showed only hepato-splenomegaly without any pathologic morphological findings.

Due to the aforementioned findings, the suspicion for MAS was raised. Pulse dosing of methylprednisolone 500 mg daily was started for three days, continued with antibiotics (4.5 g of tazobactam intravenously every eight hours, 1 g of vancomycin every 12 hours, 1 gram of amikacin per day, and 200 mg of fluconazole per day). The patient became afebrile, but moderate bleeding appeared. Analyses showed that hematologic parameters dropped (leukocytes 0.51 × 10^9/L, hemoglobin 74 g/L, platelets 22 × 10^9). She was transferred to 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 three days. Due to the absence of improvement of the hematological parameters, cyclosporine A was introduced in a dose of 5 mg/kg/day (with continuing until 200), continuing with high doses of dexamethasone. Following this kind of regimen, hematological parameters were improved on the seventh day, with fibrinogen normalized as well.

After three weeks, the patient was without complaints and blood tests resolved, except easily elevated γ-glutamyl transferase and ferritin (634 μg/L). The patient was discharged, with prescribed therapy of 0.5 mg of dexamethasone and 5 mg/kg/day of cyclosporine A, with planned gradual reduction. During the follow-up at the outpatient clinic over the next 12 months, the patient was without medical problems. Currently, her therapy is 0.5 mg/kg/day of cyclosporine.

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 a rare, systemic, inflammatory disease of unknown etiology. Its estimated incidence rate is 0.16–0.4 cases in 100,000 people, and the prevalence is 1–34 cases in one million people [4]. The characteristic triad is a 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, elevated liver function tests (enzymes in the blood) can be found. If suspicion for AOSD exists, 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 an infectious disease did not find any cause for concern, and sepsis was excluded. Hence, the initial clinical presentation was the early course of AOSD. Our patient had all four major criteria (fever of 39°C or higher for more than week, arthralgia, skin rash, leukocytosis > 10,000 mm^3 with > 80% granulocytes) and most of the minor criteria (sore throat, splenomegaly, elevated liver enzymes, negative RF and ANA) for AOSD [5]. Two weeks later, the fever became persistent, followed by pancytopenia, hypofibrinogenemia, with an extreme elevation of ferritin level in the blood. This is indicated in the expression of MAS in the initial course of AOSD. At that moment, there are no valid diagnostic criteria for MAS in rheumatologic diseases in adults, and according to the literature data, we apply recommended HLH-2004 diagnostic guidelines [6]. In our patient, based on five of the 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 the liver, the spleen, and the lymph nodes, which we did not examine in our patient.

Hyperferritinemia is a significant laboratory feature in MAS – it is not only an indicator of the acute inflammatory response, but it also has an immunomodulatory role. Extremely high serum values of ferritin play a role in the high release of cytokines. According to the contemporary findings, four conditions are classified as "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 eliminating a potential cause of abnormal immune responses and using immunosuppressive drugs for the suppression of a 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, has a 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 refractory patients with MAS and AOSD, which is unfortunately not available in all countries [11]. In recent years, several genetic and immunological studies are trying to elucidate the 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 treating AOSD-associated MAS patients.

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

Conflict of interest: None declared.

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Синдром активације макрофага као ране компликације Стилове болести код одраслих

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САЖЕТАК

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

Приказ болесника Приказали смо младу, претходно здраву болесницу чија је болест започела наглим порастом температуре, гушобољом, миалгијама, артралгијама и макулозном оспом. Због сумње на септичко стање лечена је антибиотицима, иако није било доказа за инфекцију. После две недеље њено опште стање се погоршало, што је било праћено панцитопенијом, повишеним вредностима ензима јетре и врло високом концентрацијом феритина у крви. Дијагностикован је синдром активације макрофага у раној фази Стилове болести код одраслих. Терапија високим дозама глукокортикоида и циклоспорина А довела је до потпуног опоравка болеснице.

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

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