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Macrophage Activation Syndrome: A Report of a Case Triggered by Mycoplasma Pneumoniae Infection in Childhood

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Abstract

Macrophage activation syndrome (MAS) is a rare, life-threatening condition, characterized by excessive inflammation due to uncontrolled and dysfunctional immune response – a continuous activation of T-lymphocytes and macrophages, leading to hypersecretion of proinflammatory cytokines. It is most commonly reported to occur in rheumatic diseases. However, development of MAS can be triggered by numerous infectious agents. We present the clinical case of a 12-year old girl with congenital bilateral optic nerve hypoplasia, in whom based on fever, cough, chest X-ray findings of right-sided pneumonia and positive IgM antibodies to Mycoplasma pneumoniae, a diagnosis of mycoplasma pneumoniae was made. In addition, rash, hepatomegaly, lymphadenopathy and laboratory changes – thrombocytopenia (PLT 89x10⁹/l), elevated transaminases (Aspartate aminotransferase 228 U/L), hyperferritinemia (1844 ng/ml), hypofibrinogenemia (3.2 g/l), positive D-dimers, were found. Based on the described findings, a diagnosis of macrophage activation syndrome, triggered by Mycoplasma pneumoniae was made. The initiated treatment with intravenous Methylprednisolone pulse therapy and Cyclosporine in combination with definitive antibiotic therapy resulted in clinical improvement and normalization of lab parameters, except ferritin value and platelet count. Addition of a recombinant IL1R antagonist resulted in continuously stable ferritin levels and cessation of cyclosporine therapy.

Keywords: Macrophage activation syndrome, Mycoplasma pneumoniae, Childhood

Introduction

Macrophage activation syndrome (MAS) is a severe, life-threatening condition caused by excessive activation and expansion of T cells and macrophages, leading to hemophagocytosis, overwhelming inflammation and cytokine overproduction. It is reported as a complication of rheumatic diseases, most commonly in the systemic type of juvenile idiopathic arthritis, systemic lupus erythematosus, juvenile dermatomyositis, Kawasaki disease, autoinflammatory diseases and malignancies. MAS is commonly triggered by infectious agents: viruses, bacteria, fungi, and parasites.

Case Report

We present the clinical case of a 12-year-old girl with congenital bilateral optic nerve hypoplasia.

Natural History of Disease

The girl presented with acute onset of symptoms – fever up to 39°C, progressively worsening cough and dysphonia. Empirical antibiotic treatment with third generation cephalosporin – cefixime was prescribed. Due to lack of resolution of symptoms, a chest X-ray, showing right sided pneumonia, was performed. The girl was admitted to Pediatric Department where intravenous antibiotic treatment with ceftazidime and amikacin, followed by meronem, was performed. Because of persistence of fever and cough and development of a generalized rash, the child was referred to the Pediatric Department of Acibadem City Clinic Tokuda Hospital.

The girl presented in fair overall condition, febrile and with severe cough. Bilateral conjunctivitis and chaotic eye movements were noticed. A generalized papular non-

pruritic rash over her face, trunk and limbs was observed. Enlargement of the cervical lymph nodes was detected. In the right supramamillar region dull percussive sounds, diminished vesicular breathing and bronchial breathing with fine crackles were auscultated. Vesicular breath sounds with fine and coarse crackles were detected in the left lung. The examination of cardiovascular system was in reference range. The liver edge was palpated 2 cm below the right costal margin. No splenomegaly was detected. Nonexudative pharyngitis was observed.

The laboratory studies performed at admission revealed: leucopenia (WBC $3.24 \times 10^9/l$), thrombocytopenia (PLT $89.0 \times 10^9/l$), with no signs of anemia (Hb 142 g/l); slightly elevated inflammatory markers – erythrocyte sedimentation rate (ESR) 20 mm/h; CRP 30.34 mg/l and procalcitonin of 0.14 ng/ml; elevated transaminase levels ASAT – 228 U/l, ALAT 125 U/l; elevated values of LDH – 582 U/l and GGT 110 U/l; albumin – 37.6 g/l; total protein – 63.7 g/l; triglycerides – 1.1 mmol/l; low iron level - 3,8 $\mu\text{mol/l}$ and total iron binding capacity - 45,4 $\mu\text{mol/l}$; high ferritin level – 1844 ng/ml; with INR – 1.02, fibrinogen 3,2 g/l, high D-dimer level – 2,37 $\mu\text{g/ml}$. Kidney function tests (urea, creatinine, uric acid, urinalysis) were in reference range. IgA, IgG, IgM and complement levels were normal. Glucose level and electrolytes were also in reference range. The immunological tests showed antinuclear antibodies (ANA) titer of 1:320, with negative ANA profile. pANCA (perinuclear anti-neutrophil cytoplasmic antibodies) and cANCA (cytoplasmic antineutrophil cytoplasmic antibodies) were negative. Positive IgM for *Mycoplasma pneumoniae* was detected. The blood culture was negative, as well the serology for hepatitis C virus (HCV) and Epstein-Barr virus (EBV). Chest X-rays were performed at the time of admission (showing right-sided pneumonia, affecting the right upper lobe) and before discharge (Figure 1&2).

The ENT (ear, nose and throat) consult showed signs of acute rhinotonsillopharyngitis. The patient was consulted by ophthalmologist - rotary nystagmus, bilateral corneal xerosis, pale papillae, absence of macular reflex, narrowed blood vessels. The described findings were due to congenital bilateral optic nerve hypoplasia.

Based on the described lung examination findings, the chest X-ray finding of right sided pneumonia, the positive *Mycoplasma pneumoniae* IgM serology in combination with the observed clinical (fever, rash, lymphadenopathy, hepatomegaly) and laboratory (leucopenia, thrombocytopenia, elevated transaminases, hyperferritinemia) changes, a diagnosis of MAS, triggered by *Mycoplasma pneumoniae*, was made

Figure1: Chest X-ray at the time of diagnosis.

Figure 2: Chest X-ray at the end of antibiotic treatment.

Treatment

A pulse therapy with methylprednisolon (1 g/day in 3 consecutive days), ciprofloxacin 2x400 mg intravenously and symptomatic mucolytic and bronchodilator treatment were initiated. Due to persistence of fever, hyperferritinemia, elevated D-dimer levels, and hypofibrinogenemia, cyclosporine A (2mg/kg) was added on Day 4. Resolution of clinical symptoms was observed during follow up. However, a subclinical activity was registered with low platelets count below $181 \times 10^9/l$ and high ferritin levels. Therefore, a treatment with interleukin-1 receptor antagonist – Anakinra – 100 mg daily subcutaneously was started.

Follow Up

The patient was with normal ferritin levels 3 1/2 months after the beginning of interleukin-1 receptor antagonist treatment. During the following 6 months the therapy was continued with oral Methylprednisolon 4mg/daily and Anakinra 100 mg/daily.

Discussion

MAS is a rare, life-threatening condition, characterized

by excessive inflammation due to uncontrolled and dysfunctional immune response – a continuous activation of T-lymphocytes and macrophages, leading to hypersecretion of proinflammatory cytokines [1-3]. H. Kornreich and colleagues describe in 1971 four children with juvenile idiopathic arthritis and acute liver failure of unknown etiology in whom rapid improvement of the arthritis and normalization of the ESR were observed [4]. Most probably this is the first description of MAS. Later on, Boone [5] in 1976 and Hadchouel et al [6] in 1985 made similar reports in the literature. 1993 is the year when Stephan and colleagues introduce for the first time the term “macrophage activation syndrome” [7].

MAS most commonly develops as a complication of rheumatologic diseases - systemic subtype of juvenile idiopathic arthritis [8,9], systemic lupus erythematosus [10], Kawasaki disease [11], autoinflammatory diseases [12-14] and malignancies. It is now evident that development of MAS most commonly is triggered by infection [15]. Epstein-Barr virus (EBV) is the most commonly reported triggering agent [16]. Other viruses are also associated with MAS. The development of MAS can be precipitated by bacterial agents, as well: Enterobacteriaceae, Salmonella, Haemophilus, Pneumococcus, Mycobacteria, Mycoplasma, Brucella, Staphylococcus. To our knowledge, there are few reports of MAS, triggered by Mycoplasma pneumoniae infection in childhood. Yoshiyama and colleagues describe four children (age range 1-11 years; 2 boys and 2 girls) who develop Mycoplasma-associated MAS [17]. Yasushi Ishida report two children (10 and 11 years of age) with triggered by Mycoplasma MAS [18]. Blanca Szolga and colleagues describe an 18-year old boy with similar signs [19]. Motoko Yasutomi and colleagues investigate the clinical and laboratory changes and the cytokine profile in a 3-year old child with Mycoplasma-associated MAS [20]. Asaad Alkoht et al report the development of MAS in two girls (9 and 4 years of age) - in one of the patients MAS is triggered by SLE [21]. We present the clinical case of a 12-year old girl in whom based on the following clinical and laboratory changes the diagnosis of MAS was made (Table 1& 2).

In addition, leucopenia, normal ESR values, high LDH values, increasing levels of serum D-dimer and hypoalbuminemia were found. The negative blood microbiology ruled out the possibility for underlying sepsis.

Intravenous methylprednisolone pulse therapy (1g/d) for three consecutive days in combination with definitive antibiotic treatment of Mycoplasma pneumoniae infection with ciprofloxacin was started. The corticosteroid regimen was continued intravenously in a dose 1.8 mg/kg followed

by slowly tapering of the dose. Due to persistence of fever and hyperferritinemia, on the 4th day Cyclosporine A (2mg/kg/d) was added to the treatment regimen. Administration of cyclosporine A lead to rapid improvement of symptoms - resolution of fever and improvement of overall condition. The described treatment plan is in accordance with the reported initiating therapy for patients with MAS [22-24].

The described laboratory changes were reported in reference range as follows:

1. Leucocytes – the second day of treatment
2. Platelets– eight day of treatment
3. ASAT– fifth day of treatment
4. D-dimer – first month of treatment

Despite the treatment with Methylprednisolon and Cyclosporine A, the persistently elevated ferritin and platelets values of 181x109/l were suggestive of subclinical MAS. Therefore, treatment with Anakinra, a recombinant IL1R antagonist, 100 mg s.c. daily was started. Three and a half months later, a continuous normalization of the ferritin and platelets level was observed. Based on this, the treatment with Cyclosporine A was stopped.

In the 6-month follow up the child is in good overall condition, without clinical or laboratory signs of MAS. The treatment plan continued with Methylprednisolon 4 mg/kg/d and Anakinra 100 mg/d subcutaneously. We present a clinical case of a severe, life-threatening condition – MAS, triggered by uncommon agent – Mycoplasma pneumoniae. The initiated treatment with intravenous Methylprednisolone pulse therapy and Cyclosporine in combination with definitive antibiotic therapy resulted in clinical improvement and normalization of lab parameters, except ferritin values and platelet count. Addition of a recombinant IL1R antagonist lead to continuously stable ferritin levels. Therefore, the treatment with Cyclosporine A, well known for its nephrotoxic side effects, could be stopped. The observed therapeutic effect of IL1R antagonist is in accordance with reports by other authors [25-27].

Disclosure of Interest

The authors report no conflict of interest

Informed consent to publish has been obtained from the parent.

Table 1: Comparison of described clinical findings in MAS and clinical findings in our patient.

Clinical findings in MAS	Presented patient
Fever	+
Rash	+
Hepatomegaly	+
Splenomegaly	-
Lymphadenopathy	+
Lung involvement	-
Kidney involvement	-
Central nervous system involvement	-

Table 2: EULAR/ACR/PRINTO classification criteria for MAS in systemic JIA and the fulfilled criteria in our patient [23].

EULAR/ACR/PRINTO classification criteria for MAS in sJIA	Presented patient
Fever and serum ferritin > 684 ng/ml and any 2 of the following: Platelet count $\leq 181 \times 10^9$ /L Aspartate aminotransferase >48 U/L Triglycerides > 156 mg/dl Fibrinogen $\leq 3,60$ g/l	Fever and serum ferritin 1844 ng/ml Platelet count 89×10^9 /L Aspartate aminotransferase 228 U/L Triglycerides 97,35 mg/dl Fibrinogen 3,2 g/l

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