# MACROPHAGE ACTIVATION SYNDROME IN A PATIENT WITH SEPSIS DUE TO STREPTOCOCCUS PNEUMONIAE

**BOGDAN VINTILĂ[1], ALINA BEREANU[2], MIHAI SAVA[3]**

[1] *"Lucian Blaga" University of Sibiu,* [2]*County Clinical Emergency Hospital of Sibiu*

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***Abstract:*** *Macrophage activation syndrome (MAS) is characterized by an acute systemic inflammation, caused by a "cytokine storm". Most frequently, it is a deadly complication of a rheumatic disease and the pathogenity consists of an expansion and activation of CD8+T lymphocytes and macrophages with hemophagocytic activity. This massive hyperinflammatory status is associated with three cardinal signs: cytopenia, liver dysfunction and coagulopathy. The diagnostic approach in early stages is often difficult and is only based on a molecular diagnosis or when 5 of 8 HLH-2004 criteria are met. From the two types of macrophage activation syndrome (familial/reactive), we report the case of a splenectomized patient with a secondary type of MAS, reactive to sepsis due to S. pneumonia. Further on, we assert our diagnostic approach based on clinical and laboratory criteria, presented in dynamics. Last but not least, we relate our "modus operandi" in the Intensive Care Unit management of the patient.*

## INTRODUCTION

Macrophage activation syndrome (MAS) is a clinical, biological entity characterized by nonspecific activation of the monocyte-macrophage system, with tissue infiltration and activated normal macrophages.

The pathophysiology of the macrophage activation syndrome is centered on the activation of the macrophage and the T lymphocyte, uncontrolled, at the origin of hypercitokinemia, responsible for the clinical-biological picture.

Uncontrolled proliferation of macrophages was explained by decreased function of NK lymphocytes and cytotoxic T lymphocytes (CD8 +), most often caused by mutations in the gene encoding perforin synthesis (PRF1).

Patients with MAS have a diminished ability to control some infections, by diminishing the cytotoxic function of NK lymphocytes and cytotoxic T lymphocytes and, as a result, cytolysis of infected cells does not take place, so the source of antigenic stimulation is not removed. The persistence of antigenic stimulation leads to the persistence of the antigen clearance reaction and, more specifically, the proliferation of T lymphocytes, with a persistent and excessive production of cytokines which, in turn, excessively stimulates the proliferation of macrophages.

## CASE REPORT

A 37-year-old male patient with a diagnosis of spherocytosis, splenectomized at the age of 4 years, for which prophylaxis for pneumococcal infection was not performed, was brought to the Emergency Room of Sibiu County Clinical Emergency Hospital with the following symptoms: diarrhea, vomiting, rash, myalgia, anuria, altered general condition, fever. From the Emergency Room, the patient was transferred directly to the Intensive Care Unit, his condition being very serious.

At the clinical examination, there have been noted: purpura in the lower limbs, facial erythema, cyanosis of the extremities, jaundice, dyspnea with tachypnea, basal crackles in the left basal pulmonary field, tachycardia, hepatomegaly and anuria.

**Paraclinical and laboratory investigations**

Laboratory tests showed marked hepatic cytolysis, nitrogen retention, coagulopathy, increased creatine phosphokinase (CPK), myoglobinuria.

The values of the tests were summarized in the tables below (table no.1.1, figure no. 1.2, table 2.1, figure no. 2.2, figure no. 2.3, figure no. 2.4, table 3.1, figure no. 3.2, figure no. 3.3).

Hemocultures, urocultures, pharyngeal exudate and nasal exudate were collected. Hemocultures, urocultures were positive for S. pneumoniae, resistant to benzylpenicillins, chloarmephicol, erythromycin, trimethoprim \ sulfamethoxazole, tetracycline, cefotaxim and with intermediate resistance to ceftriaxone, imipenem, sensitive to ofloxacin, vancomycin, moxifloxacin, quinupristin/dalfopristin, levancomycin, rifampicin, sparfloxacin, pristinamycin, amoxacillin and telithromycin.

The established diagnosis was sepsis with multidrug-resistant S. pneumoniae associated with multiple organ failure (MOF), with coagulopathy, hepatic impairment, renal failure with myoglobinuria, acute respiratory distress syndrome (ARDS). Following the hematological consultations and carrying out the specialized investigations, the diagnosis of macrophage activation syndrome was confirmed. The etiology of MAS was pneumococcal infection, which was isolated from the cultures harvested from the patient.

From the diagnostic criteria of MAS, the patient presented: coagulopathy, fibrin degradation products, positive D-dimers, prolonged activated partial thromboplastin time (APTT), thrombocytopenia, hypofibrinemia, hyperferritinemia: and hypertriglyceridemia.

Normocytic normochromic erythrocytes, microspherocytosis with spherocytes and frequent polymorphonuclear macrocites, red blood cells with Howell-

[1]Corresponding author: Alina-Simona Bereanu, Bd Corneliu Coposu, Nr. 2-4, Sibiu, România, E-mail: alinabereanu@gmail.com, Phone: +4074 1662969

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Jolly bodies (splenectomy), rare dacryocytes and schizocytes were noted on the peripheral smear. Polymorphonuclear cells were revealed with vacuolated cytoplasm (gram positive cocci, in diplo, encapsulated intra and extracellularly).

Bone marrow biopsy was collected in hematoxylin-eosin staining, a large number of activated macrophages were detected with prominent hemophagocytosis and hematopoietic elements.

Other possible etiologies of MAS (viral/parasitic, rheumatic diseases, malignancies) were excluded.

Cardiac ultrasound was performed, which did not reveal images suggestive of infectious endocarditis or other degenerative valvular pathology.

Radiologically, initially no pulmonary changes were noticed, but bilateral pulmonary condensation and left pleurisy appeared in evolution. Subsequently, the patient developed ARDS which required oro-tracheal intubation and mechanical ventilation.

**Figure no. 1. Liver enzymes trend**

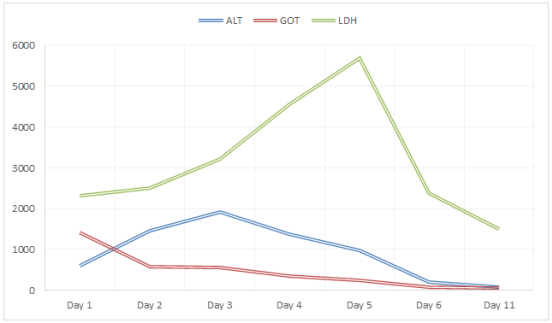



**Figure no. 2. Coagulation profile trend – Platelets**

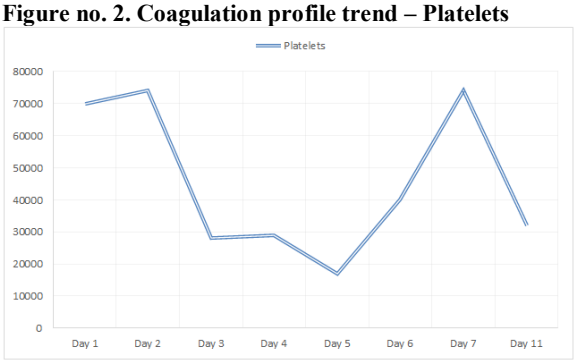



**Figure no. 3. Coagulation profile trend - APTT, INR**

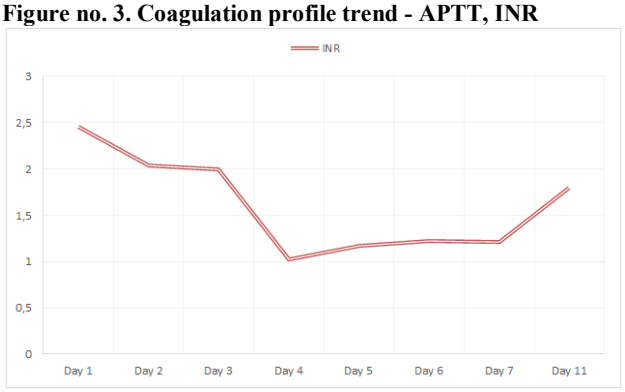



**Figure no. 4. Coagulation profile trend - APTT**

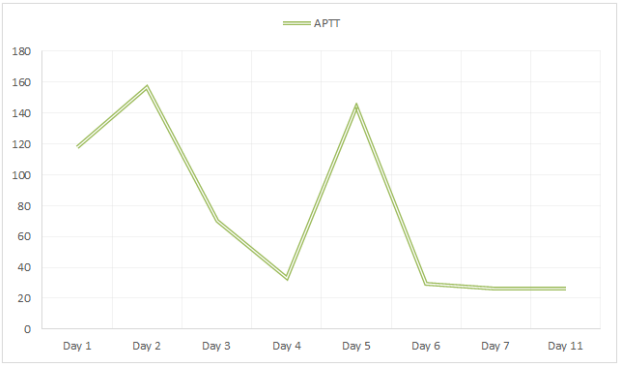



**Figure no. 5. Other relevant blood tests - CPK**

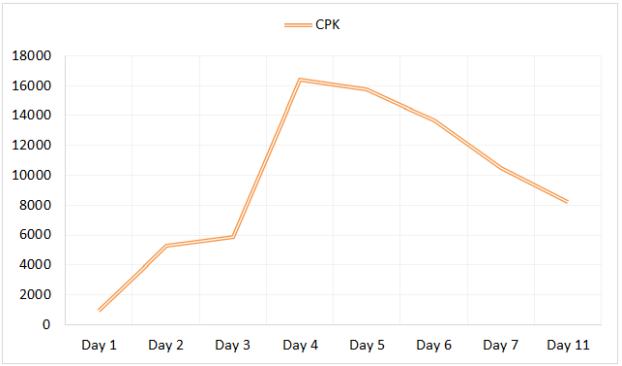



**Table no. 1. Liver enzymes**

| | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 11 |
|---|---|---|---|---|---|---|---|
| **ALT** | 605U/L | 1455U/L | 1922U/L | 1373U/L | 982U/L | 201U/L | 72U/L |
| **AST** | 1419U/L | 578U/L | 552U/L | 351U/L | 253U/L | 82U/L | 69U/L |
| **LDH** | 2312U/L | 2500U/L | 3210U/L | 4564U/L | 5684U/L | 2372U/L | 1500U/L |
| **Direct bilirubin** | | 4,45mg/dl | | | | 2mg/dl | |
| **Total bilirubin** | | 7,39mg/dl | | | | 2,25mg/dl | |

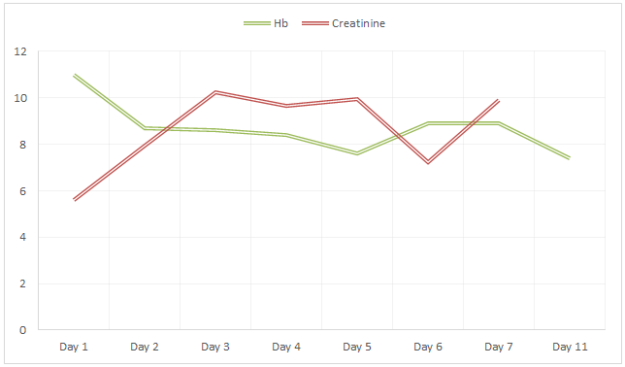
**Table no. 2. Coagulation profile**

| | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 | Day 11 |
|---|---|---|---|---|---|---|---|---|
| **Platelets** | 70000/mcL | 74000/mcL | 28000/mcL | 29000/mcL | 17000/mcL | 40000/mcL | 74000/mcL | 32000/mcL |
| **APTT** | 118 | 157 | 69.9 | 33 | 144 | 29.5 | 26 | 26.3 |
| **INR** | 2.45 | 2.04 | 2 | 1.02 | 1.17 | 1.22 | 1.21 | 1.8 |

**Table no. 3. Other relevant blood tests**

| | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 | Day 11 |
|---|---|---|---|---|---|---|---|---|
| **CK** | 961 | 5314 | 5848 | 16417 | 15731 | 13661 | 10506 | 8237 |
| **Hb** | 11 | 8.7 | 8.6 | 8.4 | 7.6 | 8.9 | 8.9 | 7.4 |
| **Creatinine** | 5.58 | 7.95 | 10.25 | 9.65 | 9.96 | 7.21 | 9.9 | 8.68 |
| **Fibrinogen** | 107,8 mg/dl | 71mg/dl | | | | | 86,9mg/dl | |
| **Fibrinogen monomers** | neg | ++ | | | | | + | |
| **Ferritin** | | >1500ng/ml | | | | | | >1500 |
| **Triglycerides** | | 267mg/dl | | | | | 289mg/dl | |

**Figure no. 6. Other relevant blood tests - Hb, Creatinine**




**Treatment**

The patient was continuously monitored invasively (blood pressure, central venous pressure) and non-invasively (AV, SpO2, diuresis, temperature) with the administration of hydroelectrolytic resuscitation, broad-spectrum antibiotics, antifungals, transfusion and correction of the coagulation deficiency by plasma and apheresis administration, stimulation of diuresis, gastric and liver protection, vitamins. The evolution was still unfavorable, with the onset of MOF, ARDS, the patient becoming comatose and requiring mechanical ventilation.

Initial antibiotic therapy involved the administration of Meropenem 2g\day associated with Linezolid 2x600mg\day. Following the antibiogram, Moxifloxacin 400mg/day was associated. Taking into account the suspicion of MAS, Dexamethasone, Etoposides 150mg\m$^2$\day intravenous immunoglobulin were added to the therapy. There were 13 hemodialysis sessions during the hospitalization period.

During the hospitalization period, a slight but constant balancing of the coagulation with the daily administration of PPC, apheresis, platelet mass was obtained. Coagulation factors - novoseven fl VII and MER were also administered.

The patient was hemodynamically supported and mechanically ventilated and hemodialysis sessions were performed daily.

**Evolution**

The evolution was unfavorable with the progression to MOF, ARDS, deep coma GCS 3p. The prognosis has been reserved since admission. The support of the vital functions has been performed since admission, the patient being admitted to the Intensive Care Unit from the very beginning.

Although the diagnosis of MAS was early, the administration of dexamethasone, intravenous immunoglobulins and etoposides did not influence the prognosis, the death occurring 15 days after admission.

The liver biopsy performed during the anatomopathological examination revealed the following changes: massive infiltration of the portal duct and sinusoids by mononuclear cells. The aspect described, with macrophages with increased phagocytic activity on lymphocytes, erythrocytes and polynuclear cells, supported the diagnosis of macrophage activation syndrome.

The autopsy revealed bilateral renal papillary necrosis secondary to myoglobinuria and the presence of hemophagocytes in the bone marrow and lymph nodes.

## DISCUSSIONS

This case demonstrates the risk of splenectomized patients (1,2,3) who may develop sepsis and septic shock with encapsulated bacteria if no prophylactic vaccine for S. Pneumoniae (3), H. Influenzae and Meningococcus is performed. Lack of vaccination may favour the development of severe S. pneumoniae infections and secondary macrophage activation syndrome, leading to patient death.

Two distinct types of macrophage activation syndrome (1) are described:

- **primary** or familial hemophagocytic lymphohistiocytosis, which causes a genetic defect, is frequently associated with parental consanguinity;
- **secondary** reactive to an infection, malignant or autoimmune disease and drug.

Diseases associated with macrophage activation syndrome are: viral infections (Ebstein Barr virus - EBV, Cytomegalovirus - CMV, influenza viruses, etc.) (4,5,6), bacterial (gram negative, Bacil Koch - BK, Staphyloccoc aureus, etc.) (7,8), parasitic ( 9), fungal (10,11); immune disorders: SLE, rheumatoid arthritis, Still disease, nodular polyarthritis, mixed connective tissue disease, pulmonary sarcoidosis, systemic sclerosis, Sjgören's syndrome; immunodeficiencies (acquired, combined), Kawasaki disease, Griscelli syndrome, Hermansky-Pudlak type 2 syndrome etc.; lymphomas, leukemias etc.

In order to establish the positive diagnosis of MAS, the 20004 criteria, according to the Histiocyte Society are: fever, splenomegaly, bicytopenia, hypofibrinemia, hyperferritinemia, hypertriglyceridemia, presence of hemophagocytosis, reduction/absence of NK cell activity and increased IL-2 receptor concentration, CD25.(12) For diagnosis, five of these criteria must be met. The patient presented the following diagnostic criteria: fever, coagulopathy, hypofibrinemia and thrombocytopenia, hyperferritinemia and hypertriglyceridemia.

The peculiarity of the case consists in the appearance of the macrophage activation syndrome in a patient following the development of a pneumococcal infection, the infection occurring 33 years after the splenectomy, during which the patient was not vaccinated.

Although the etiologic diagnosis and the diagnosis of macrophage activation syndrome were set up shortly after admission, and the therapy was targeted, the evolution of the disease was unfavorable, with the patient's death 15 days after admission.

## CONCLUSIONS

Sepsis with S pneumoniae associated with macrophage activation syndrome in a splenectomized patient for spherocytosis should be considered for cases similar to ours.

In the literature there are very rare cases with the diagnosis of secondary macrophage activation syndrome, a consequence of pneumococcal infection in a splenectomized patient for spherocytosis.

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