FEBRILE SYNDROME ASSOCIATED WITH MACROPHAGE ACTIVATION

VICTORIA BÎRLUŢIU

Adult Infectious Diseases Hospital, Sibiu

Abstract. *Macrophage activation syndrome (MAS), is a clinicobiological entity, characterized by non-specific activation of monocyte-macrophagic cell-line, tissular infiltration with normal activated macrophages, by uncontrolled proliferation of histiocytes, characterized by hemophagocytosis, immune dysfunction; clinicobiologically characterized by fever, hemophagocytosis, hepatosplenomegaly, pancitopenia, hypertriglyceridemia and coagulopathy. Viral, bacterial or parasitic infections and medication play an important part in producing the disease.*

Diagnosis criteria are the clinicobiological ones, such as: fever more than 7 days, pick >38,5°C, cytopenia affecting minimum 2/3 cell-lines, unassociated to a medullar infection: Hb < 9g/dl, trombocytes < 100 000/mm^3, Neutrophils < 1000/mm^3, a high ferritin level > 3N or over 1000 UI/l and histological criteria of medullar/hepatic, splenic or ganglionar hemophagocytosis. The treatment is based on corticotherapy, vepeside (VP 16) in monotherapy or associated to other chemotherapy, thalidomide, cyclosporine, anti-lymphocyte serum, purinic analogues, alfa-interferon, plasmapheresis, intravenous immunglobulins, antiTNF-alfa agents - etanercept.

We present the case of MI, a 82 years old male patient, diagnosed with macrophage activation syndrome.

Keywords: *macrophage activation- infections*

Rezumat. *Sindromul de activare macrofagică (SAM), este o entitate clinico-biologică caracterizată prin activarea nespecifică a sistemului monocit-macrofag, infiltrare tisulară cu macrofage normale activate, prin proliferarea necontrolată a histiocitelor cu hemofagocitoză, difuncţie imună, clinico-biologic presupunând febră, hemofagocitoză, hepatosplenomegalie, pancitopenie, hipertrigliceridemie şi coagulopatie. În declanşare se atribuie rol important infecţiilor virale, bacteriene, parazitare sau medicaţiei. Criteriile de diagnostic sunt clinico- biologice: febră cu durata peste 7 zile, pick >38,5^0 C, citopenie afectând minim 2/3 linii neasociate unei afecţiuni medulare: Hb< 9g/dl, Trombocite < 100 000/mm^3, Neutrofile < 1000/mm^3, hiperferitinemie > 3N sau peste 1000 UI/l şi criterii histologice de hemofagocitoză medulară şi/sau hepatică, splenică sau ganglionară. Tratamentul în SAM se bazează pe corticoterapie, vepeside (VP16) în monoterapie sau asociat altei chimioterapii, thalidomidă, ciclosporina, ser antilimfocitar, analogi purinici, interferon alfa, plasmafereză, imunoglobuline intravenos, agenţi antiTNF-alfa- etanercept.*

Prezentăm cazul pacientului MI, 82 ani, diagnosticat cu sindrom de activare macrofagică secundară.

Cuvinte cheie: *activare macrofagică-infecţii*

INTRODUCTION

Macrophage activation-syndrome. (MAS) is a clinicobiological entity, characterized by non-specific activation of monocyte-macrophagic cell-line with tissular infiltration with activated normal macrophage.

Two types of MAS are described: **primary MAS** or familial hemophagocytic lymphohistiocytosis and **secondary MAS**, reactive to an infection, malign or autoimmune affection, drugs.

Annual incidence of the secondary MAS is of about 4 cases, in patients above 16 years old (aleatorily chosen limit due to the difficulty of differentiating primary or secondary MAS in child).

Particularly, it is associated to viral infections with Ebtein Barr virus, CMV (cytomegalovirus), parvovirus B19; herpes simplex, herpes 6 virus, myxovirus parainfluenzae, adenoviruses, HIV, hepatic viruses, measles, chickenpox, enteroviruses may rarely occur in the evolution of other viral diseases generated by parvovirus 19.

Bacterial infections associated to MAS include both the germs usually encountered in pathology - piogenii, salmonella, ehrlichia, and the atypical germs - mycoplasmas, rickettsia, legionella, micobacteria, brucella. Cases of MAS are described in the evolution of the parasitary diseases, such as Leishmaniasis, Plasmodium falciparum, anguillosis, babesiosis, toxoplasmosis.

MAS may be associated with certain immune deficiencies such as Purtilo syndrome, Chediak Higashi, immunosuppresor or cytotoxic treatment, splenectomy, HIV infection, alcoholic intoxication, drugs administration such as fenitoine, carbamazepine, minocycline, phenobarbital, prolonged parenteral nutrition with soluble lipids.

There were other cases associated to different neoplasias: Non-Hodgink lymphoma, especially, NHL-T peripheral type AILD, nonlimphoid LA, myelom, myelodysplasia, solid tumours, tricholeucocytes leukaemia, or to collagen/inflammatory diseases: LES, Still disease, rheumatoid poliarthritis, sclerodermy,

sardoidosis, inflammatory intestinal diseases, cytophagic histiocytic panniculitis, Kikuchi disease.

MAS physiopathology is centred on the activation of the macrophage and T lymphocyte; it is uncontrolled, brings about hypercytokinemia and is responsible for the clinical biological picture.

The activation of T lymphocyte brings about the uncontrolled release of the interleukine 2 (IL-2) and of gamma interferon (IFNγ) with the activation of the macrophages that will phagocytate the blood figurate elements; the release of the necrotic tumoral factor (TNFα) stimulates the activation of the T lymphocyte, which is reflected in the increase of the blood and urinary levels of β_2 macroglobulins, the increase of the serous titre of the soluble receptors of IL-2 (sIL-2R), the increase of the titre of the soluble CD8. The large titre of sIL-2R and IFNγ is correlated with severe forms of MAS and severe prognostic. In parallel, in the patients with MAS, the NK lymphocytes function is diminished or even null.

The excessive activation of macrophages represents the appanage of the cytokines secreted by the activated T lymphocytes: IFNγ, TNFα, M-CSF (Macrophage colony stimulating factor), especially of the CD8+ macrophages; at their turn, the macrophages secret cytokines that will maintain the vicious circle of MAS.

CLINICOBIOLOGIC ASPECT

MAS starts brutally, with fever, sometimes preceded by shivers, alternation of the general mood; frequently, a tumoral syndrome may be found, splenomegaly and/or hepatomegaly, that may become voluminous rapidly, rarely peripheral adenopathies.

At tegument level, rash, morbiliform eruptions, panniculites, pulmonary infiltrate, CNS affection with meningeal irritation signs, cutaneous-mucous hemorrhagic syndrome, a consequence of coagulation activation in MAS severe forms.

Biologically, the following may be observed:

- Bicytopenia/pancytopenia: normochromic, normocytary, aregenerative anemia, thrombocytopenia, leukoneutropenia, mononucleosic syndrome;
- Hypertriglyceridemia, by the inhibition of the lipoprotein-lipase through TNFα
- Hyperferritinemia- indicator of the macrophage activation (accumulation of ferritin in macrophages through the fagocitation of granulocytes and overproduction of ferritin by the macrophages stimulated by IL-1);
- Anomalies of hemostasis: fibrinopenia, CID (50-68%);
- Cytolysis and/or cholestasis with the increase of bilirubin (60-90%);
- Autoimmune anomalies: antinuclear antibodies, Coombs direct positive test, antiplatelet IgG polyclonal hypogammaglobulinemia;
- LDH constant increase;
- Hyponatremia by inadequate selection of ADH;
- β_2 serous and urinary microglobulines increase.

From histologic point of view, MAS is a proliferation of the mature macrophages, of normal aspect, which fagocitate erythrocytes, nuclear detritus, other figurate elements in the ganglionar corticale sinus, spleen, hepatocytary sinusoids. The characteristic aspects may be emphasized by myelogramme, ganglionar cytopuncture, ascitis liquid, osteomedullar biopsy, ganglionar biopsy, hepatic biopsy puncture.

The diagnostic criteria, after FHL group of the Histiocyte Society are:

- **clinical criteria**: fever more than 7 days, pick >38,5^0 C, splenomegaly >3 cm under the costal rebord
- **biological criteria**: cytopenia affecting minimum 2/3 lines un associated to a medullar affection: Hb< 9g/dl, Trombocytes < 100 000/mm^3, Neutrophils < 1000/mm^3
- hypertriglyceridemia and/or hypofibrinogenemia
- **histologic criteria**: Hemophagocytosis. at the level of MO, spleen or ganglions, in the absence of other affections.

Recent criteria for SAM diagnosis:

- fever for more than one week
- inexplicable progressive cytopenia, affecting at least 2 cell lines
- MO: mature histiocytes > 3% or 2 500/ml, with aspect of medullar and/or hepatic, splenic or ganglionar hemofagocitosis

Other authors consider the following as sufficient data for establishing the diagnosis: fever more than 7 days, pick >38,5^0 C, cytopenia affecting minimum 2/3 cell lines unassociated to any medullar affection: Hb< 9g/dl, Trombocytes < 100 000/mm^3, Neutrophils < 1000/mm^3, hyperferritinemia > 3N or more than 1 000UI/l associated to the histologic criteria: aspect of medullar and/or hepatic, splenic or ganglionar hemophagocytosis.

The treatment associated to MAS is based on corticotherapy, vepeside (VP 16) in monotherapy or associated to other chemotherapy, thalidomide, cyclosporine, anti-lymphocyte serum, purinic analogues, alfa-interferon, plasmapheresis, intravenous immunglobulins, antiTNF-alfa agents- etanercept. MAS evolution is very serious, with mortality according to the launching factor of up to 100% (associated to EBV infection, malignity etc.).

CASE PRESENTATION

The patient M.I., aged 82, coming from the rural environment, without significant pathological personal antecedents is hospitalized in the Adult Infectious Disease Hospital of Sibiu in 25 October 2007, two weeks after first symptoms occurred: shivers, fever, cough with muco-purulent expectoration, inappetence, followed by pains in the upper abdominal floor, vomiting, hyperchromic urine, sytmptomatology for which the patient is examined by the family doctor, treated with amoxicillin, biseptol, symptomatic medication (the patient cannot mention which). In evolution, the general health state of the patient alters progressively, with physical

asthenia marked by the impossibility of maintaining orthostatism, lack of air. Because of these subsequent symptoms, the patient's family require hospitalization. Upon hospitalization: severe general health condition: afebrile, sclero-tegumental icterus with rapid intensification during hospitalization, stethacoustically - bilateral basal crepitant pulmonary-rales, rhythmic cardiac noises, easily heard, AV= 64/min, TA= 90/60 mmHg, fried tongue, mobile abdomen on respiratory movements, painful cystic point, hepatomegaly 4-5 cm under the costal rebord (upper edge in the right intercostals V area), spleen palpable when inspiring (splenomegaly level), oliguric, temporal-spatial oriented, without signs of meningeal irritation.

Praclinical examinations: Leucocytes= 1100- 580- 700- 350-230-180-120-100/mm^3, severe neutropenia in leukocytary formula NS =4,9% (490-320-40/mm3)
Hb = 13,4 -11,9- 10,9 -9,9-7,2 g/dl, trombocytes Tr = 44 x 10^3/l – 33-29x 10^3/l- 17-14x10^3/l- 8 000/l; PCR: 48 mg/l, VSH = 6 mm/h, fibrinogen = 296 mg%; leukocytary phosphatasis FAL = 320 (VN= 10-100); Absent fibrin monomers; D-dimeri=positive (400-800 mg/ml). APTT= 32,7 sec (1,13)-37,7; INR: 1,41, IP= 58,0%.

Hepatic tests prove: TGO = 436 U/L-595- 617- 429-164 U/L, TGP = 446 U/L-584-756-398-200 U/L, alkaline phosphatasis = 343 -398U/L, GGT= 257-610 mg/dl, BT = 4,04 -9,17-12,36 -14,24-12,94 mg/dl, BD = 3,65-6,71-8,88-9,72-4,12 mg/dl, LDH = 992 U/L (VN= 131-225 U/L). Glycaemia = 122 -143-132 mg/dl, urea = 123-113 - 84-110 mg/dl, creatinine = 1,74-1,38-1,22-1,24-1,01-0,46 mg/dl, uric acid = 4,2 mg/dl, sterile bacteriological culture of urine – Sputum examination: epithelial cells, mucous, frequently years, poor polymorph flora, cultures – candidiasis .

Pulmonary radiography: bilateral basal minimum congestive process; in evolution – imprecisely delimitated hemidiaphragmas, right paratracheal ovalar opacity; pulmonary interstice, infrahilar edematous charge, confluent in laterotoracal alveolar focus. Left posterobasal lamelar atelectasis.

Myelogramme: MO with hypocelllular areas, much diluted with medullar juice, together with areas with increased cellularity. There are also certain elements belonging to the red series, plasmocytes, relatively frequent magacariocytes. The granulocytary series: about 4-5% blasts may be found, some of them having myeloblast aspect, others are undifferentiated, myelocytes, metamyelocytes and many segmentary neutrophils.

MOB – medullar osseous biopsy: MO with low cellularity. G/E inverse relation. The erythroid series is made up of normoblasts and rarely sideropenic. The granulocytary series is much reduced and is made up of mature elements and rare precursors. Present magacariocytes, relatively frequent, small and medium groups of thrombocytes.

Hyperplasiated monocyto-macrophagic series with a percentage that varies between 10-35%. Frequent macrophages that present the phenomenon of hemophagocytosis – phagocytary of red cells, thrombocytes, erythroblasts, ganulocytes. The macrophages are disposed in groups (small-large), Rare mastocytes, small lymphocytes and palsmocytes.

Conclusion: MO with low cellularity, hypoplasia predominant on the granulocytary series. Hyperplasia of the monocyto-macrophagic series with frequent hemophagocytosis series. Compatible aspect with a syndrome of macrophagic (hematophagocitosis) secondary to the infectious process. Medullar hemosiderin: MOS in macrophages – much increased, sideroblasts – 40%, ferritin: 32 000 u

Abdominal echography: liver with global hypertrophy LHD= 17,5 cm, LHS= 8 cm, caudate lobe 4 cm, homogenous echostructure, preserved echogenity. VP with the diameter at the upper limit 12,5 cm. Free CBP. Cholecyst presents a hyperechogen nucleus of 12 mm, with posterior shadow cone, double walls. Screened pancreas, moderately enlarged spleen 12,7/6,5 cm, homogenous, without the dilatation of the vessels of the splenic hilus. Kidneys without echographic changes, transonic VU, Enlarged prostate, with the diameter of 4/5 cm homogenous.

Echographic re-evaluation: enlarged liver, hyperechogenous, sonic inhomogeneous, CBP 6mm, VP 13 mm. Relatively relaxed cholecyst with walls slightly thickened, with infundibulocystic hyperechogenous nucleus with posterior shadow cone. Spleen 13,2 cm, sonic homogenous. RD and RS – normal without dilatations of excretion ducts, without calculi. Interhepatorenal perihepatic peritoneal liquid in the VB lodge too.

In evolution, the general health state of the patient alters progressively, sclerotegumentar icterus strengthens at the same time with the increase of hepatosplenomegaly, due to severe thormobocytopenia, cutaneous – mucous bleedings occur, HDS exteriorised through hematemesis and melena (14-20 vomiting, 2 stools in a quantity of 400 ml each).

Superior digestive endoscopy reveals: esophagus with hiatal hernia and ulcerations at the level of the herniary package, without active bleeding, small blood quantity suppressed from stomach.

Higieno-dietetic treatment was administered, as well as hydroelectrolitic reequilibration, large spectrum antibiotics, Neupogen, thrombocytary, leukocytary concentrate, fresh plasma, immunoglobulin iv, antispastics, gastric antisecretories, hemostatics, erythrocytary mass at HDS occurrence, for which the patient is taken over and supervised in the intensive care section, where he dies 9 days after hospitalization through irrescuscitable caridiorespiratory arrest.

The factors that were correlated with a unfavourable prognostic were the level of ferritin, LDH, Hb< 10g/dl, Trombocytes < 100 000/mm3, fibrin deregulation products > 10 μg/ml, feritinemia> 500 μg/l, accentuation of total hyperbilirubinemia, age > 30 years old, absence of palpable adenopathies in the absence of a subjacent malign pathology.

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