Available online at www.scientiaresearchlibrary.com

Scientia Research Library

ISSN 2348-0416
USA CODEN: JASRHB

Journal of Applied Science And Research, 2017, 5 (4):9-16

(*http://www.scientiaresearchlibrary.com/arhcive.php*)

Viral encephalitis revealing macrophage activation syndrome

S.kalouch yaqini* ;A.chlilek

Service de réanimation polyvalente, CHU Ibn Rochd,Casablanca

ABSTRACT

Macrophage activation syndrome (SAM) is a rare but life-threatening disease. It is characterized by a set of non-specific clinical and biological signs, but the combination of which must evoke the diagnosis. These abnormalities result from cytokine dysregulation and benign lympho-histiocytoma. Among several etiologies, viral infection holds an important place. This is the case of our patient who was admitted for viral encephalitis following which he developed the SAM.

Keywords: viral encephalitis; macrophage activation syndrome; prolonged fever; pancytopenia.

INTRODUCTION

Macrophage activation syndrome (SAM) or hemophagocytosis syndrome or lympho-histiocyte activation syndrome (SALH) is a rare but potentially fatal disease. It is observed in a multitude of clinical situations encountered in internal medicine (infectiology, hematology and oncology, systemic diseases), transplantation (organ transplant or marrow transplant) and in resuscitation or this syndrome is both under- and overestimated, sometimes difficult to discern from a severe sepsis where it can contribute to the occurrence of multi-visceral failure [1]. It is characterized by a set of clinical signs and biological non-specific but whose association must evoke the diagnosis and lead to a cytological or histological examination of haemophagocytosis confirming it. Its occurrence imposes a quite exhaustive etiological assessment, because the associated diseases are multiple. This is a severe condition, the prognosis of which is severe and the treatment is still poorly codified [2].

MATERIAL AND METHODS

This is a 9-year-old child with no specific pathological history admitted to the pediatric intensive care unit for febrile fever disorder on viral encephalitis revealed 3 days ago by headache with dietary vomiting in a febrile context at 38 : 6 ° complicated with disorder of consciousness. Clinical examination finds an unconscious child (GCS: 10/15), hemodynamically stable and respiratory; Abdominal examination finds splenomegaly. After resuscitation measurements, the patient received a lumbar puncture which was in favor of a 25-element viral encephalitis, predominantly lymphocytic, with a normal glycorrhizal / glycemic ratio and normal proteinorachia (<1 g / L); the PCR is negative. Cerebral CT scan with and without injection of contrast medium showed temporal fronto cerebral edema and magnetic resonance imaging (MRI) showed bilateral parietal plaques poorly limited in hyper T2 signal. The antiviral treatment was started with acyclovir. The evolution

was marked by the installation of haematological disorder. See Table 1:

Table : 1

date	**J3**	**J5**	**J6**
HB	10,3	8,7	6,9
LEUCOCYTES	1630	460	420
PNN	220	10	10
PQ	73000	4000	22000

The etiological assessment showed a fetritinemia at 5338 µg / l (20-100 µg / l), triglycerides at 2 g / l (<1.6 g / l), fibrinogen at 1.2 g / l and the myelogram showed absence of blast cells, without hemophagocyte images. The diagnosis of macrophage activation syndrome was selected as an etiology based on the following criteria: prolonged fever, splenomegaly, cytopenia (2 lines), high ferritin, hypertriglyceridemia and hypoalbuminaemia. Etoposide (selective cytotoxic agent of the monocytic line): 150mg / m2 (2 times / week) but the patient died in a context of multi-visceral failure at its inpatient hospitalization.

Epidemiology:

Macrophage activation syndrome is probably underestimated. Its overall incidence in Japan has been estimated at 51.7 cases per year, including pediatric and adult SAM. Pediatric forms are often better documented and a Swedish series records an incidence of one annual case per million children. When the prevalence of hemophagocytosis is studied from series of medullary samples, this is estimated to be around 1% [1,3].

Physiopathology:

The etiology of SAM remains obscure. The onset of this condition appears to be related to abnormal activation of T lymphocytes (Th1 profile) favored by infection or congenital deficiency of immunomodulatory mechanisms. These T lymphocytes produce large amounts of pro-inflammatory cytokines that stimulate the macrophage response. The production of other cytokines by activated macrophages seems to exert a positive feedback on the T lymphocytes maintaining a deleterious overactivation of the immune system (FIG. 1), the CD8 + lymphocytes are thus in a state of excessive activation. The activation of macrophages is responsible for both the general inflammatory syndrome and the fever, pancytopenia by the phagocytosis of the figurative elements of the blood. Organomegaly is related to tissue infiltration by activated macrophages. Disruption of liver function is the consequence of intra-hepatic macrophage activation with hepatic cytolysis. Hypertriglyceridemia is linked to the inhibition of lipoprotein lipase by cytokines (TNFα and IL-1). Hperferritinemia is the result of erythrophagocytosis, systemic inflammation and hepatic dysfunction [3,4].

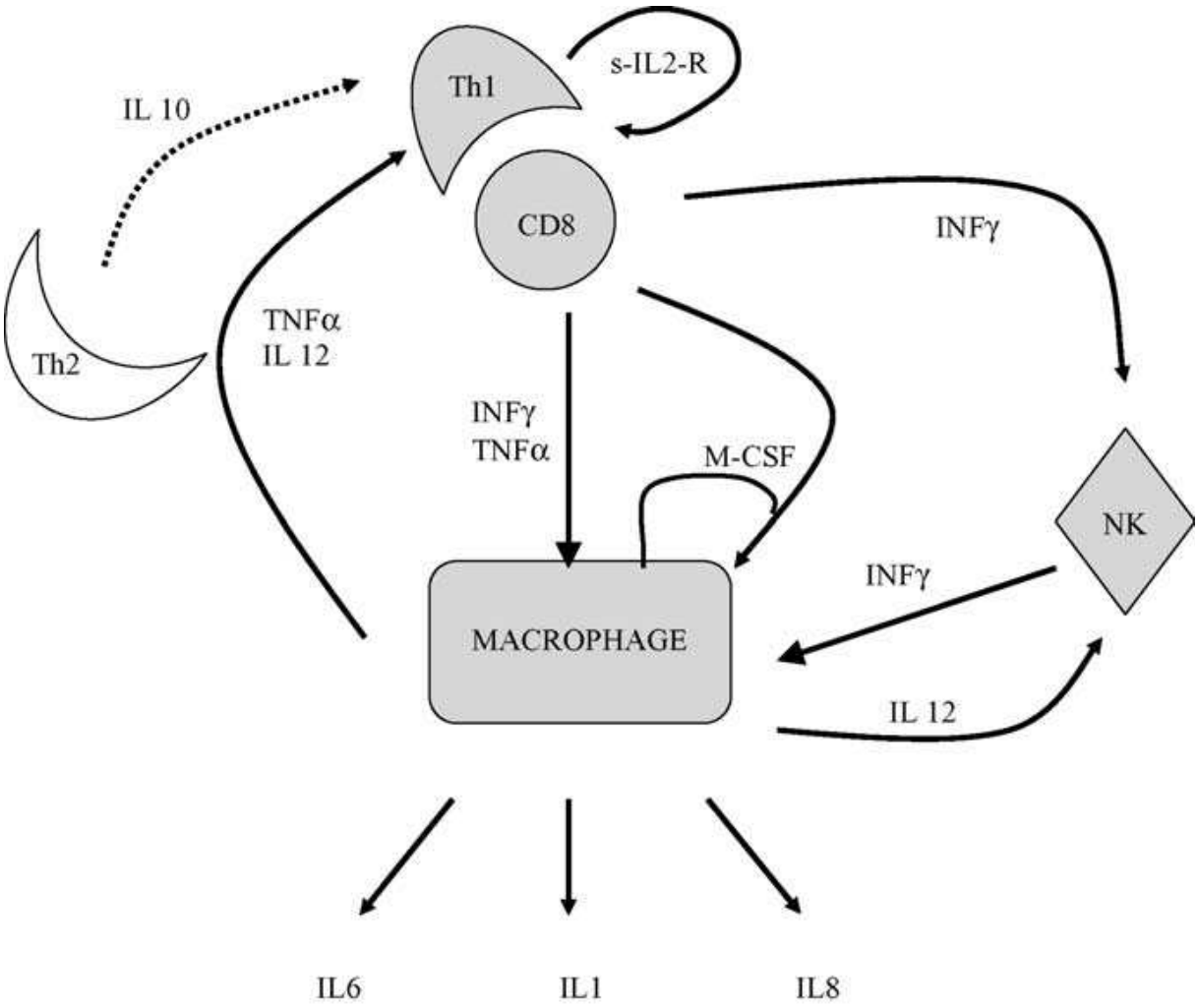

Fig.1. Th1 activation loop [4]

Diagnostic:

The diagnosis of SAM is based on the association of clinical, biological and histological or cytological signs. The diagnostic criteria are presented in Table 4. They were established for the diagnosis of primary forms and are used by extension for secondary forms [5].

Table : 2

Clinical signs of SAM	Frequency
Fever	70—100 %
splenomegaly	70—100 %
hepatomegaly	40—95 %
lymphadenopathy	15—50 %
Skin Rash	5—65 %
Neurological signs	20—50 %

Table : 3

Biological signs of SAM	Frequency
Anemia	90—100 %
thrombocytopenia	80—100 %
neutropenia	60—90 %
hypertriglyceridemia	60—70 %
hypofibrinogenaemia	65—85 %
Elevation of transaminases	35—90 %
hyperbilirubinemia	35—75 %
Increase in LDH	45—55 %
hyperferritinemia	55—70 %

The reference examination for the diagnosis of SAM is the myelogram which confirms the diagnosis and sometimes makes suspect or confirm the etiology of this syndrome.

It will objectify hemophagocytosis essential for diagnosis. It usually shows a rich marrow, infiltrated by "benign" histiocytes-macrophages. These macrophages are of normal morphology and show a phagocytic activity of the elements of the three haematopoietic lines, observed within numerous intracytoplasmic vacuoles. Reactive erythroblastosis is common.

Medullary biopsy but also lymph node or hepatic can often reveal hemophagocytosis in the hematopoietic organs, with proliferation of macrophages. In spite of a less important contribution to the confirmation of the diagnosis of SAM, the medullary or lymph node biopsy must be almost systematic in the etiological balance of hemophagocytosis to affirm or rule out malignant haemopathy. The existence of an aspect of haemophagocytosis on the cytological or histological samples is not sufficient to make the diagnosis, hence the interest of the diagnostic criteria [2.5].

Table 4: Diagnostic Criteria for Macrophage Activation Syndrome [5]

At least five of the following criteria:
Fever
splenomegaly
Cytopenias affecting at least two lines
Hemoglobin <9 g / dL
Plates <100000 / mm3
Neurotrophic neutrophils <1000 / mm3
Hypertriglyceridemia and / or hypofibrinogenemia
Triglycerides> 3 mmol / LFibrinogène < 1,5 g/L

Hemophagocytosis in the bone marrow, spleen or lymph nodes
No neoplasia
Natural Killer cell activity low or zero (according to local laboratory references)
Ferritinémie≥500g / L
IL-2-soluble receptor ≥2400 IU / ml

In summary:

fever + bi cytopenia + hperferritinemia = suspicion of SAM

fever + bi cytopenia + hemophagocytosis image = suspicion of SAM

Etiologies:

5-1. Primary SAMs:

Several hereditary pathologies of the immune system are characterized by macrophage T lymphocyte activation, often triggered by intercurrent infection, these diseases are often described in children and young adults. Four syndromes are well-defined and the genetic abnormalities at their origin are beginning to be known:

Familial lymphohistiocytosis: the most frequent among primary SAMs, is an autosomal recessive disease, it is revealed in early childhood (2 months), the clinical presentation is that of a SAM with a clear predominance of the reach of the system central nervous system (50%).

CHediak-Higashi syndrome: characterized by SAM, partial cutaneous and ocular albinism and the presence of large intracytoplasmic granulations.

Griscelli syndrome: identical to that of CHediak-Higashi without intracytoplasmic granulation.

X-linked lymphoproliferative syndrome or Purtilo syndrome: this is a rare immune deficiency characterized by abnormal susceptibility to infection with Epstein Barr virus (EBV) [1].

Secondary (reactional) SAMs:

Post-infectious SAMs:

Several infectious agents can be identified in the same patient at the same time, especially since many patients are chronically immunocompromised (transplant, HIV infection, chemotherapy, immunosuppressive therapy for systemic disease). Nevertheless, imputing the occurrence of SAM to a given infection is not always easy, as infections can complicate a disease itself responsible for SAM, such as lymphoma, lupus, etc. on the other hand, immunosuppression linked to SAM (neutropenia) favors the occurrence of infections.

Virus:

The incriminated viruses belong mainly to the group of Herpes viruses, primarily Epstein Barr virus (EBV), especially in pediatrics, and cytomegalovirus (CMV), particularly in immunocompromised patients. In the literature, EBV and CMV represent respectively 30 and 40% of the viruses involved.

Bacteria:

In addition to viruses, severe bacterial infections can be complicated by SAM, often in the context of multi-visceral failure. All pyogens have been implicated in the occurrence of SAM, interestingly, tuberculosis is considered a classic cause of SAM.

Mushrooms and parasites:

Fungal infections (histoplasmosis) and parasitic infections (malaria, leishmaniasis) may also be associated with SAM;

The case of HIV:

It should first be noted that HIV itself can induce a SAM. Nevertheless, SAM is essentially at an advanced immunosuppression stage (CD <200 / mm3) and is linked to opportunistic infections and lymphomas. The presence of several infectious agents in patients is common in this situation. CMV infections and mycobacteria predominate with lymphomas.

Neoplasms:

SAM may also complicate neoplasia, particularly malignant haemopathy, which should be systematically investigated. The associated hemopathies are mainly non-Hodgkin's lymphomas (5LNH), including aggressive T or NK lymphomas. The frequency of lymphomas and the severity of the SAM justify an aggressive diagnostic procedure in front of an SZAM without a clear etiology with the rapid realization of an osteo-medullary biopsy and / or a lymph node biopsy.

System Diseases:

SAM can occur in autoimmune diseases. It has been described mainly in systemic lupus erythematosus, juvenile chronic arthritis and adult Still's disease. An inaugural SAM may be the mode of disseminated lupus erythematosus.

Other etiologies:

Some cases of SAM complicating a severe hypersensitivity reaction have been described, especially after taking antiepileptics or antibiotics. Parenteral nutrients with lipid solutes have also been implicated in pediatrics.

Etiologic diagnosis is sometimes difficult and is due to the fact that several pathologies potentially responsible for SAM can be associated. Hemopathy and infections should be systematically investigated. Biopsies should be performed immediately (lymph node, bone) before coagulation disorders occur, and blood research of EBV and CMV viruses will be systematic. Tuberculosis will be sought in the slightest doubt. HIV serology must be systematic and antinuclear antibodies complete the balance of an unexplained SAM. Moreover, the survey will be oriented according to the clinical context: importance of adenoviruses in marrow transplantation, malaria, leishmaniasis and rickettsiosis in case of tropical re-entry. Finally, there are a number of cases (15% to 20%) in which no etiology is found [6].

Treatment :

Treatment is poorly codified. the management of severe forms requires multidisciplinary cooperation in order to determine the best therapeutic strategy and etiological diagnosis.

symptomatic treatment:

Support for SAM often requires an important and rapid care load. These patients must be presented early to the resuscitation team, or the hydro electrolyte balance must be optimized, organ failure is supplemented specifically (artificial ventilation, catecholamines, etc.) and coagulation disorders may require transfusions important.

specific treatment of hemophagocytosis:

The goal of this treatment is to alleviate the inflammatory response and control cell proliferation, using immune modulating or immunosuppressive and cytotoxic products. The specific treatment is only for the most severe patients, with multiple visceral failure, whose causal pathology is treated.

Currently, most authors agree that etoposide (VP-16) (100 to 150 mg / m 2) should be used to combine corticosteroids (prednisone 1 mg / kg / day) or even bolus of methylprednisolone. The use of etoposide, a selective cytotoxic compound of the monocyte cell line for the control of proliferation and overactivation of histiocytes / macrophages, appears to be the key to successful treatment and should be administered early. VP 16, whose repeated use may lead to myelodysplasia and secondary leukemia, is reserved for lymphomas with SAM or in case of failure of other treatments.

Intravenous immunoglobulin administration is currently not recommended in the SAM due to lack of evidence, but some successes have been reported.

Despite the frequent efficacy of these treatments, frequent relapses led the pediatric teams to propose an allogeneic marrow transplant as soon as the remission was obtained, the only treatment that could permanently eradicate lymphohistiocytosis.

etiological treatment:

In primary SAMs, bone marrow transplantation remains the only curative treatment of these forms.In the reaction SAMs: the treatment of the cause is obviously essential in this case, with rapid initiation of an anti-infectious treatment in case of post-infectious SAM or chemotherapy in malignant hemopathies or an immunosuppressive treatment if the SAM occurs during an outbreak of a systemic disease [7,8].

Evolution and prognosis:

The prognosis of SAM remains severe with about 50% mortality. It mainly depends on:

- the length of time
- the nature of the underlying pathology: SAMs complicating an infection, except EBV, are often better prognostic than those occurring in malignant hemopathy, or the mortality rate can reach 80%.
- The existence of underlying immunosuppression is a factor of poor prognosis.
- The administration time of etoposide
- Biology:

• Deep cytopenia, particularly severe thrombocytopenia, and DIC are associated with higher mortality.

• The other prognostic factors found in the literature are ferritin levels above 500 µg / l, cholestasis,

high levels of TNFα and IFN γ. The hepatocellular and renal insufficiencies, which are evidence of multi-visceral failure, are undoubtedly a pejorative factor.

The evolution is very variable, the clinical and biological signs are increased in a few days to several weeks, sometimes in the absence of any therapeutics. Remote hemophagocytosis images may persist while the patient is asymptomatic. Recurrences are classical in primary SAM, but are rare in reactive SAM [8].

CONCLUSION

SAM is a severe, often unrecognized, life-threatening condition that complicates various infectious, neoplastic or autoimmune diseases. One must know to detect it and treat it without delay, sometimes even before having the etiologic di agnostic.

The severity of SAM prognosis requires an aggressive diagnostic approach and multidisciplinary therapeutic management combining resuscitators, haematologists and infectiologists to determine the best options according to the etiology and gravity of the array.

REFERENCES

[1] Boussadni YE ;Najib B ;Bousfiha AA ;Ailal F , Macrophage activation complicating family lymphohistiocytosis ,Pan Afr Me J, **2017** Feb 24, 26-93

[2] Crépu C; Galicier I; Oksenhendler E ;Azoulay E , Syndrome d'activation macrophagique lymphohistiocytaire : revue de la littérature, implications en reanimation ,Réanimation 14 (20**0**5) 604-613

[3] Gonzalez F ; Vincent F ; Cohen Y , Syndrome d'activation macrophagique d'origine infectieuse : étiologies et prise en charge Reanimation (**2009**) .284-290

[4] Karras A ; Hermine O , Syndrome d'activation macrophagique La revue de médecine interne 23 (**2002**) ;768-778

[5] Lambotte O ;Mechai F , Syndrome d'activation macrophagique Lettre de l'nfectiologie tome XXII,N° 3 mai ,juin **2007**

[6] Palmanj, May j; Pilkington C , Macrophage activation syndrome triggered by celiac disease/ a unique cas report Pediatr Rheumatolon Line j **2016** dec.9; 9, 14 (1), 66

[7] Ravelli A;Minoie F; Davis S; Horne A , 2016 classification criteria for macrophage activation syndrome complocating systemic juvenile idiopathic arthritis: a europen league again.Rheumatism / American college of Rheumatology /paediatric rheumatology international trials organization collaborative initiative , Ann Rheum dis **2016** mar ; 75(3) : 481-9

[8] Ruscutti P;Cipriani P; Ciccia F , Pronostic factors of macrophage activated at the time of diagnosis, in adult patient affected by autoimmune disease: analysis of 41 cases collected in 2 rheumatologic centers , Autoimmune rev /**2017** Jan; 16(1): 16-21