

Hemophagocytic Syndrome Associated With Visceral Leishmaniasis

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Abstract: Visceral Leishmaniasis (VL), also called Kala Azar, is a parasitic disease. It is due to the multiplication in the reticulo-histiocytic system of a protozoan of the genus *Leishmania*. It is transmitted by the bite of female sandflies. It affects the young child preferentially. VL is a common cause of Hemophagocytic Syndrome (HS) among children. This association can represent a real life threat without treatment. We report the case of a child with visceral leishmaniasis associated to HS.

Key words: Visceral Leishmaniasis- Hemophagocytic Syndrome-Child.

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I. Introduction:

The hemophagocytic syndrome (HS) is a non-proliferative malignant pathology, that affects the antigen-presenting activated macrophages resulting in an uncontrolled hemophagocytosis[1]. This pathology is uncommon but not exceptional and is very often under-diagnosed in our context. There are two categories: the primary hemophagocytic syndrome and the secondary HS that occurs in lymphoid or malignant pathologies (30%) auto-immune (5 to 10%) or infectious diseases (50%)[2]. The latter can be serious and may even be life threatening.

In this observation we report the case of a child with visceral leishmaniasis associated with a hemophagocytic syndrome.

II. Case Report :

This is a girl aged 14, without particular medical history, who presented for an infectious syndrome with fever (39°C), reflecting bone marrow impairment; associated with intracranial hypertension syndrome and bone pain. Clinical examination revealed pallor, altered general condition, meningeal stiffness and pressure sores on the coccyx with no other associated signs, in particular no hepato-splenomegaly or adenopathies.

Blood tests revealed bicytopenia, normocytic normochromic anemia (Hb at 9.8g/dL, VGM at 86fL, TCMH at 30pg and CCMH at 34.8g/dL), and leucopenia (WBC =2540/mm³ and PNN=630/mm³). Platelets were normal =162G/μl). CRP and SV were elevated. Hemostasis test showed a prothrombin level of 90%. Lumbar puncture was sterile. Abdominal ultrasound showed homogeneous hepatomegaly. Leishmaniasis serology was positive at a rate of 1/640. The myelogram confirmed the diagnosis of VL. It showed the presence of leishmaniasis bodies.

Our patient was put under etiological treatment based on N-Methylglucamine: Glucantime at the rate of a deep intramuscular injection at an average dose of 60mg/Kg/J (20mg SbV+/Kg/d). The symptomatic treatment consisted in red blood cells and fresh frozen plasma transfusion.

The clinical course was marked by persistent fever, non-response to treatment and worsening of the general condition. The biological assessment showed a worsening of the hematological abnormalities (WBC= 1970/mm³, PNN= 137/mm³, Hb=6.9g/dL, VGM= 84fL, TCMH= 28.9pg and reticulocytes= 2 2900/uL), a prothrombin level of 83%. A biochemical assessment was performed, with hyponatremia (133 mmol/L), hepatic cytolysis (aspartate aminotransferase (ASAT) = 233 IU/L; alanine aminotransferase (ALAT) = 19 IU/L), hyperferritinemia (7473 mmol/L), lactate dehydrogenase (LDH) at 1281 IU/L and hypertriglyceridemia (6.02 mmol/L) were found. A second myelogram was performed. It showed the presence of hemophagocytosis images

(Figure 1). Faced with this cascade of arguments, the diagnosis of HS associated with VL was retained. Immunosuppressive therapy was undertaken, combining etoposide 150 mg/m² every 48 h (3 intakes) with corticosteroid therapy 0.6 mg/kg per day for 5 days.

After three days of treatment without significant clinical improvement, a blood culture was positive for *Enterobacter cloacae* strain resistant to C3G, the patient died before the start of antibiotic therapy.

III. Discussion:

Hemophagocytosis syndrome, also known as macrophagic activation syndrome (MAS), is a rare but potentially fatal condition. Its incidence varies between 1 and 2 per million children per year and is most likely underestimated due to the rarity of incidence studies, which are mostly retrospective and limited by the need for cytological documentation to include patients. Mortality can be as high as 22% depending on the context [3][4]. HS is part of a group of conditions called lymphohistiocytose-hemophagocytic disease due to hyper stimulation of the immune system and severe inflammation in the body.

Clinically, the manifestations are not very specific and it is their association that should make one think of the diagnosis. HS is characterized by the generally rapid, even sudden, onset of intense fever, accompanied by a rapid alteration of the general state and splenomegaly [5]. Jaundice, hepatomegaly, and adenopathies are frequently associated with SAM. Morbilliform rash or neurological signs are less common [6].

Currently, Henter's criteria [7] are those accepted as diagnostic criteria for HS, so the diagnosis of SAM is retained when five of the eight criteria are present (Table I). HS can be encountered at all ages, but pediatric series remain the most documented in the literature.

The pathological situations associated with the occurrence of hemophagocytic syndrome are diverse, most often marked by an underlying "dysimmune" condition. The Study Group of the Histiocyte Society distinguishes between the primitive and hereditary forms of hemophagocytic syndrome, represented by familial or sporadic lymphohistiocytose-hemophagocytic syndrome, Chediak-Higashi and Griscelli syndrome, X-linked Lymph proliferative (XLP) syndrome or Purtilo syndrome or Duncan's disease. The majority of these syndromes occur in childhood [8]. Lymphohistiocyte activation may be secondary to neoplastic, autoimmune, or infectious conditions. Post infectious AMS are more common. A large number of bacterial, viral, fungal or parasitic infections can cause HS [9]. Infectious agents play a key role in HS. These agents may be responsible for immune dysregulation [10].

Viral etiology is the leader of the most reported infections, with herpes viruses, followed by mycobacteria, intracellular bacteria, pyogens and then parasites with VL as a frequent cause [10]. SAM associated with visceral leishmaniasis (HS-VL) presents some specificities. The similarity of clinical and biological signs between visceral leishmaniasis and HS makes diagnosis more difficult. Thus, the diagnosis of VL can be made without recognizing HS, leading to a specific treatment delay with dramatic consequences. Diagnosis of visceral leishmaniasis is often difficult in the initial phase of the disease and the clinician has to work hard to establish it, especially in endemic areas, repeating if necessary the tests (myelogram, serology). The reference treatment is then amphotericin B, a specific treatment that is often sufficient on its own to regress SAM. In refractory forms, the addition of intravenous immunoglobulin (IVIG) would seem to be beneficial [9]. Even when diagnosed and treated in time, SAM has a very poor prognosis with a mortality rate exceeding 20% [3] [4]. This rate is more alarming when SAM is associated with other underlying infections, as was the case with our patient [3][4].

Bacterial etiologies during HS (18%) are dominated by mycobacteria, but rickettsiosis, leptospirosis, brucellosis and more frequent bacteria (such as enterobacteria or *Staphylococcus* sp) can also be found more rarely [9]. Enterobacteriaceae infections have been documented in the course of HS, without always being able to perfectly establish the cause and effect relationship [10].

The management of HS associated with infections is first and foremost that of the infection itself. In patients with severe forms of HS with organ failure, it may be necessary to urgently start probabilistic treatments targeting the main suspected etiologies [9]. In the most severe forms, in cases of diagnostic uncertainty or when the effectiveness of the etiological treatment is not optimal; it may be necessary to review the diagnosis, look for other etiologies and carry out further investigations in order to ensure complete and adequate management [9].

IV. Conclusion:

Macrophagic Activation Syndrome is a severe condition with a poor prognosis. Its occurrence in visceral leishmaniasis in children is always possible. Hence the need for further biological investigations and a repeated myelogram, especially in case of unfavorable clinical course. **Learning points:**

- ✓ Macrophage Activation Syndrome (MAS) is rare but serious.
- ✓ The association of SAM and visceral leishmaniasis is always possible.
- ✓ There is a need for further biological investigations in the absence of clinical improvement.

- ✓ An initial myelogram without a hemophagocytosis image does not rule out the diagnosis of SAM.
- ✓ Adequate and early management improves the prognosis.

Contributions of the authors:

S.E: conception of the subject, bibliographical research and writing of the article. S.R: clinical data collection. S.S: Proposal of the topic for writing and correction of the article. All authors have read and approved the final version of the manuscript.

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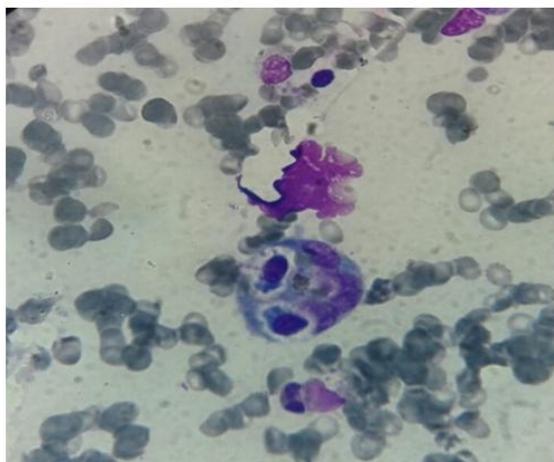
Table :

Table 1: Hemophagocytosis syndrome diagnosis criteria, according to Henter[7]:

At least five of the eight following criteria:	
✓	Fever
✓	Splenomegalia
✓	Cytopenias affecting at least two lineages
➤	Hemoglobin < 9 g/dL
➤	Platelets < 100000/mm ³
➤	Polynuclear neutrophils < 1000/mm ³
✓	Hypertriglyceridemia and/or hypofibrinogenemia
➤	Triglycerides > 3 mmol/L
➤	Fibrinogen < 1,5 g/L
✓	Hemophagocytosis in the bone marrow, spleen or lymph nodes.
✓	Low or no Natural Killer cell activity (depending on local laboratory references)
✓	Ferritinemia ≥ 500g/L
✓	IL-2 Soluble Receiver ≥ 2400U/ml

Figure:

Figure 1 : Myelogram (MGG coloration) : Hemophagocytosis image (HS) ©



MGG: May-Grünwald Giemsa