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HAEMOPHAGOCYTIC SYNDROME: AN ENTITY NOT TO BE INGESTED IN ACUTE HEPATIC FAILURE

Loubna Dehou*, Hakima Abid, Nada Lahmidani Mounia Elyousfi, Mohammed El Abkari, Adil Ibrahimi and Dafr Allah. Benajah

Hepato-Gastroenterology Department, CHU Hassan II of Fez Faculty of Medicine and Pharmacy, Sidi Mohamed Ben Abdallah University of Fez-Morocco.

***Corresponding Author: Loubna Dehou**
Hepato-Gastroenterology Department, CHU Hassan II of Fez Faculty of Medicine and Pharmacy, Sidi Mohamed Ben Abdallah University of Fez-Morocco.

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SUMMARY

Haemophagocytic Syndrome (SAM), whether genetic or acquired, is a clinico-pathological entity characterized by an excessive and uncontrolled inflammatory response, which can be life-threatening. The liver is an important target organ: hepatomegaly is found in half of patients, hepatic biological damage is present in 75% of cases. The appearance and/or worsening of cholestasis is an element of poor prognosis in this situation. The liver biopsy is informative in making the diagnosis of SAM and finding the etiology when it is an acquired SAM. The clinical spectrum ranges from mild SAM which resolves with treatment for the triggering etiology, to rapidly fatal SAM in the absence of specific treatment. The frequency of this syndrome is probably underestimated in the gastroenterology department. Haemophagocytic syndrome should be suspected in patients with fever and jaundice without infection.

KEYWORDS: Haemophagocytic syndrome; Liver failure; Pancytopenia.

INTRODUCTION

Macrophage activation syndrome (MAS) has been individualized since the description of post-viral haemophagocytosis by Risdall in 1979.[1] The incidence of SAM is rare but probably underestimated.[2] MAS, whose clinical and biological signs are not very specific, is observed in many clinical situations in internal medicine, in transplantation (organ transplant or bone marrow transplant) as well as in intensive care. We report the case of MAS in a patient who initially presented with acute liver disease.

OBSERVATION

This is a 67-year-old patient, followed for psoriasis since childhood under no treatment. Complained for a week by the onset of a flu-like syndrome complicated two days later by the appearance of cholestatic-like febrile jaundice made up of dark urine and normal-colored stools with hepatic colic and vomiting of food late post-prandial, evolving in a context of unquantified fever and asthenia, hence his admission to the emergency room and then to the gastroenterology department for treatment. Clinical examination found an icteric patient who was respiratory stable, tachycardia at 100 beats/min, febrile 39-40°C, mucocutaneous pallor was noted, abdominal examination found slight tenderness of the right hypochondrium, no hepato-splenomegaly, the rectal examination had objectified normo-colored stools. The dermatological examination objectified a diffuse xerosis with ichtiform scales on the limbs and on the trunk. The pleuro-pulmonary and cardiovascular examination were unremarkable. Biologically, there was pancytopenia (Hb at 11.6VGM 78.8 MCHC 35.5 leukocytes at 1630 platelets at 39000), liver balance was disturbed with significant cytolysis (GOT at 153, GPT at 152) and cholestasis (GGT at 564, PAL 414) the hemostasis assessment was disturbed with a prothrombin level at 48%, CRP at 183, From the outset, abdominal ultrasound had eliminated the diagnosis of cholangitis by compensating the bile ducts which were not dilated, this observation was confirmed by the data of a Bili-MRI showing a parietal thickening of the gallbladder with absence of dilatation of the VBIH.

The patient had benefited from a complete etiological assessment, the search for a viral infection (hepatitis A, B and C virus, HIV, Epstein Barr, Ketomegalovirus) was negative, no immunological cause was highlighted: the dosage of antinuclear antibodies (AC) ANN, anti ALS, anti smooth muscle, anti LC1, anti anti LKM1) were negative. The complement of the biological assessment had objectified a level of triglycerides at 11mmol/l, a ferritinemia at 4000 ng/ml and an LDH level which was at 499U/L. Given these data, the diagnosis of SAM was strongly suspected. Corticosteroid therapy was then

started. The evolution was marked by a good clinico-biological improvement then the patient was transferred to Internal Medicine for etiological research and additional care. A liver biopsy puncture was performed late after improvement, the histological analysis had not shown hematophagocytosis.

DISCUSSION

For most authors, the onset of this pathology seems to be linked to an abnormal activation of T lymphocytes which is favored by an infection or a dysregulation of immuno-modulatory mechanisms. Th1 cells produce large amounts of pro-inflammatory cytokines that stimulate macrophages.[3] Their activation leads to a state of "hypercytokinemia" with cytokines of macrophage and lymphocyte origin (IL1, IL6, TNF, IL2, interferon c, GMCSF). The clinical manifestations of MAS are not specific: long-term fever often associated with hepatosplenomegaly, rash, oedemato-ascitic syndrome, superficial lymphadenopathy, more rarely neurological and pulmonary signs (cough, dyspnoea or respiratory distress).[1,4,5] Biologically, cytopenias concerning two to three lineages (most often anemia and thrombocytopenia) and hyperferritinemia (often greater than 1000 ng/mL, with a glycosylated fraction less than 20%) are almost constant. Liver function abnormalities such as cholestasis and/or cytolysis are noted in 3/4 of cases. Serum alanine aminotransferase (ALT) is on average 5 times normal (range: 0.3-125 N), alkaline phosphatase is on average 2.73 times normal (range: 0.23- 47 N), the average total bilirubin is 136 µmol/L (extremes: 4-681) with a marked increase in conjugated bilirubin compared to free bilirubin, respectively 93 µmol/L (extremes: 0-610) and 39 µmol/L (extremes: 0-157), in the study by De Kerguennec et al.[6] Severe acute liver failure may be at the forefront of SAM[7,8], or may be part of multiple organ failure syndrome.[9,10] Exceptionally, the severity of the liver damage required emergency liver transplantation.[11,12] and the diagnosis of SAM post-transplantation on liver histology was made in two cases.[8,13]

An elevation of LDH and triglycerides with a rate that exceeds 4mmol/l and those similar to the results of our case, linked to an inhibition of lipoprotein lipase by TNF-α, is found in 2/3 of cases while the decrease isolated from fibrinogen or in the context of disseminated intravascular coagulation is less frequent. None of the clinical symptoms or biological abnormalities are specific to SAM, as these may be confused with the manifestations of the underlying pathologies (particularly sepsis or lymphoma). It is their association that makes it possible to evoke the diagnosis of SAM. Bi- or pancytopenia is constant with normochromic normocytic and nonregenerative anemia (90% of cases), early, central or peripheral thrombocytopenia (87% of cases), more inconstant and late leukopenia. In addition, hemostasis disorders are present in 50 to 70% of cases with hypofibrinogenemia[14] isolated or associated with a lowered prothrombin level and/or a prolonged activated partial thromboplastin time. Diagnostic criteria for SAM have been proposed by several teams[15]: table-1.

Table 1: Diagnostic criteria for SAM have been proposed by several teams.[15]

Critères cliniques	Fièvre > 7 jours, avec pics > 38,5 °C
Critères biologiques	Cytopénie sur 2 ou 3 lignées (Hb < 9 g/dl, polynucléaires neutrophi- les < 0,1 G/l, plaquettes < 100 G/l), non expliquée par une moelle pauvre ou dysplasique Augmentation de la ferritine plasmatique (> 3 DS ou > 1000 ng/ml) Augmentation de la LDH (> 3 DS ou > 1000 UI/l)
Critères histologiques	Hémophagocytose (médullaire, splénique ou ganglionnaire)

The diagnosis of SAM is made when there are five out of eight criteria. These criteria do not distinguish between genetic and acquired SAM. In our case, the diagnosis of SAM with hepatic involvement was retained on a set of clinical (fever), biological (pancytopenia, hyperferritinemia and hypertriglyceridemia) arguments.

Hepatic manifestations of MAS (cytolysis, hepatocellular insufficiency, cholestasis) are found in 40 to 60% of cases.[2,6] In a retrospective study reporting 30 cases of MAS with hepatic involvement, hepatic manifestations were the reason for hospitalization for 19 of these patients.[6] The association of fever, jaundice, hepatomegaly or splenomegaly was found in 50% of patients. The elevation of transaminases was constant.

The liver biopsy puncture (PBH) is interesting both to make the histological diagnosis of SAM and to find its etiology. The exact place of the PBH remains to be defined. It can be offered as first-line treatment in adult MAS in the event of rapidly progressive liver damage without an obvious diagnosis, or when coagulation abnormalities contraindicate bone marrow biopsy. Histologically, the hepatic architecture was preserved in all cases; the main abnormalities observed were dilation of the sinusoids with images of hemophagocytosis, Kupffer cell hyperplasia and signs of inflammation at the portal level.

SAM mortality remains high (30 to 45% of deaths).[14,16] The prognosis of this syndrome is multifactorial. It is related to the early initiation of treatment and therefore to the positive diagnosis of SAM, to the associated disease, to the severity of the syndrome and to the previous immune status. Treatment of the underlying disease is paramount. In case of infection, early and appropriate

antibiotic therapy is recommended. In addition to corticosteroid therapy, the use of immunoglobulins is classic[17] ciclosporin A allowed the cure of a patient with MAS with severe liver damage.[7]

4. CONCLUSION

The liver is a major target organ during MAS, and the clinical expression of which is hepatomegaly and a modification of the hepatic biological balance sheet. The appearance and/or worsening of cholestasis and hepatocellular insufficiency are probably elements of poor prognosis. The early start of a specific treatment can sometimes avoid a fatal outcome, hence the interest of knowing this entity and of evoking it in the face of unexplained liver damage.

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