

HEMOPHAGOCYtic SYNDROME SECONDARY TO VISCERAL LEISHMANIASIS IN A 5-YEAR-OLD BOY

LE SYNDROME D'ACTIVATION MACROPHAGIQUE SECONDAIRE À UNE LEISHMANIOSE VISCERALE CHEZ UN GARÇON 5 ANS

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Abstract

Hemophagocytic syndrome secondary to visceral leishmaniasis is a rare clinicopathological entity. We report a previously healthy five-year-old boy admitted for pallor, fever and splenomegaly. In laboratory analysis, there were pancytopenia, hypertriglyceridemia, hyperferritinemia and raised liver enzymes. Bone marrow examination revealed hemophagocytosis and *Leishmania* amastigotes. A diagnosis of infectious hemophagocytic syndrome secondary to visceral leishmaniasis was established. No other cause of hemophagocytic syndrome was found despite extensive microbiologic and serologic investigation. The boy was treated with intramuscular meglumine antimoniate (Glucantime®) and recovered rapidly with definitive remission.

Visceral leishmaniasis associated hemophagocytic syndrome is a life-threatening disorder. It is important for any physician to suspect the diagnosis in all children with fever and splenomegaly. Complementary investigations should be done to confirm this association urgently for initiate appropriate treatment.

Key words : Hemophagocytic syndrome, visceral leishmaniasis, children

Résumé

Le syndrome d'activation macrophagique secondaire à la leishmaniose viscérale est une entité clinique rare. Nous rapportons le cas d'un garçon de cinq ans sans antécédents pathologiques particuliers admis pour pâleur, fièvre et splénomégalie. Les analyses biologiques ont révélé une pancytopénie, une hypertriglycéridémie, une hyperferritinémie et des enzymes hépatiques élevés. L'examen de la moelle osseuse a révélé la présence d'hémophagocytose et de *Leishmania* amastigotes. Un diagnostic de syndrome d'activation macrophagique secondaire à la leishmaniose viscérale a été établi. Aucune autre cause du syndrome d'activation macrophagique n'a été trouvée malgré une vaste enquête microbiologique et sérologique. L'évolution sous antimoniate de méglumine intramusculaire (Glucantime®) a été marqué par la disparition de la symptomatologie clinique et la normalisation des analyses biologiques.

La leishmaniose viscérale associée à un syndrome d'hémophagocytose est grave et peut mettre le pronostic vital en danger. Il est important pour tout médecin de soupçonner le diagnostic chez tous les enfants atteints de fièvre et splénomégalie. Les examens complémentaires doivent être effectués pour confirmer cette association de toute urgence afin d'initier un traitement approprié.

Mots clés: Syndrome d'activation macrophagique, la leishmaniose viscérale, enfants

ملخص

متلازمة تنشيط البلاعم الثانوية لداء الليشمانيات الحشوي تمثل كيان سريري نادر. نقدم تقريرا عن حالة صبي يبلغ من العمر خمس سنوات دون سوابق صحية تذكر وقع قبوله بالقسم لشحوب وحمى وتضخم الطحال. وكشفت الاختبارات البيولوجية قلة الكريات الدموية، زيادة شحوم الدم و الفريتين وأنزيمات الكبد. وكشف فحص نخاع العظام وجود بلعمة الكريات و ليشمانيا. وأنشئ تشخيص متلازمة البلعمة الثانوية مع داء الليشمانيات الحشوي. لم يتم العثور على سبب آخر متلازمة تنشيط البلاعم رغم تحاليل ميكروبيولوجية واسعة ومسح مصلي. وقد تحسنت الحالة بعد استعمال حقن عضلية الميغلو مين انتيمونيائي من خلال اختفاء الأعراض السريرية وتطبيع التحاليل البيولوجية

داء الليشمانيات الحشوي المرتبطة متلازمة بلعمة الكريات خطير ويمكن أن يمثل خطر مهدد للحياة. من المهم بالنسبة لأي طبيب التفكير في هذا التشخيص عند جميع الأطفال الذين يعانون من الحمى وتضخم الطحال. وينبغي إجراء اختبارات إضافية لتأكيد هذا الارتباط بشكل عاجل لبدء العلاج المناسب

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INTRODUCTION

Haemophagocytic syndrome (HS) is a rare, but potentially fatal disorder. It is characterized by clinical and biological manifestations secondary to uncontrolled proliferation of macrophages and oversecretion of cytokines [1,2]. It may be primary or secondary to many etiologies mainly infections such as visceral leishmaniasis (VL) [3-5]. We, herein, report a case of HS following VL.

CASE-REPORT

A previously healthy five-year-old boy, who lived in a rural region in Tunisia, was admitted to pediatric department with a twenty-day history of fever, pallor and anorexia. On physical examination, he was asthenic, pale and febrile (40°C). Abdominal palpation showed tenderness in the upper right quadrant and a splenomegaly of 3 cm below left costal margin without hepatomegaly. The rest of the somatic exam was within normal limits.

Laboratory data showed pancytopenia : total leukocyte count at 1560/mm³, neutrophil count at 440/mm³, hemoglobin level at 7 g/dl and platelets count at 93000/mm³.

Liver tests were abnormal with Aspartate amino transferase at 420 IU/L, Alanine amino transferase at 150 IU/L, Alkaline phosphatase at 990 IU/L, gammaglutamyl transferase at 104 UI/l and serum bilirubin at 7 mmol/L, Prothrombin time was normal at 92%.

Increased ferritinemia level (1000µg/l) and hypertriglyceridemia (3,7 mmol/l) were objectived. No obvious source of infection was found on any of the biological investigations: blood culture and serological tests for Brucella, Salmonella typhi, HIV, hepatitis B, C, cytomegalovirus, Epstein-Barr virus were negative. The tuberculin test was negative. Abdominal ultrasound disclosed a normal liver; however, splenomegaly and scarce hypoechoic fluid. Serological study for *Leishmania* was positive (1/1280). The bone marrow examination was paramount in the patient's diagnosis, revealing hemophagocytis and amastigote forms of Leishmaniasis. A diagnosis of infectious hemophagocytic syndrome secondary to visceral leishmaniasis was established.

Treatment with intramuscular meglumine antimoniate (Glucantime®) was instituted for 21 days. By day 7, the child condition gradually improved, the fever disappeared. There was a good response to treatment and the infant was discharged home. During follow-up, his blood values improved markedly (Table 1).

Table 1: patient characteristics at onset and outcome

Biological parameters	Before	After treatment	
	treatment	Day 7	Day 15
White blood cells (/mm ³)	1560	3360	4250
Neutrophiles (/mm ³)	440	1280	1510
Hemoglobin (g/dl)	7	8.4	10.7
Platelets (/mm ³)	93000	378000	267000
SGT/SPT (UI/L)	420/150	71/24	40/24
PAL (UI/L)	990	400	380
GGT (UI/L)	104	40	39
PT (%)	92	95	94
Triglyceridemia (mmol/l)	3,7	-	1,2
Ferritinemia (µg/l)	1000	-	240

DISCUSSION

Visceral leishmaniasis remains an important public health problem in Tunisia [6]. It is among the most commonly identified causes of HS in children in endemic areas including North Africa [3,6].

HS is a life-threatening clinicopathological entity, which results from defective apoptotic pathways activity. The overstimulation of the immune system leads to numerous organ infiltration, mainly the reticuloendothelial system and the central nerve system [1-2].

The typical clinical presentation of HS includes acute onset of fever unresponsive to antibiotics, hepatosplenomegaly, rapid deterioration of general condition [1]. Our patient experienced almost all of these signs.

HLH is diagnosed on the basis of Henter et al's guidelines [2]. five criteria were required from the following: (a) fever, (b) splenomegaly, (c) bicytopenia (hemoglobin < 9 g/dl, platelets <100x10⁹/l, neutrophils <1 x10⁹/l), (d) hypertriglyceridaemia (>3 mmol/l) and/or hypofibrinogenaemia (<1.5 g/l) (e) hyperferritinaemia (>500 µg/l), (f) increased plasma concentration of the interleukin-2 receptor (s CD25) (>2400 UI/ml), (g) impaired natural killer cells activity and (h) hemophagocytosis in bone marrow, liver, spleen or lymph nodes [2]. The pathological hallmark of HLH is the presence of benign histiocytes phagocytosing the hematopoietic cells [1,2]. Our patient had 6 criteria for HS diagnosis. He presented with 3 common signs to HS and VL (fever, splenomegaly and pancytopenia). Similitude features between HS and VL may delay the diagnosis [5,7-9]. Moreover, serologic testing for *Leishmania* may be negative at the onset of the disease [5].

Liposomal Amphotericin B represents the treatment of choice for HS associated with VL [3-5, 10]. It supplanted antimonials, previously considered as the treatment of reference of VL, as it proved to be effective, provides favorable efficacy/tolerance ratio and seems to control the disease [5]. Intravenous immunoglobulin seems to have a positive effect on refractory cases [10]. Our patient has received meglumine antimoniate, the only drug available in Tunisia. No further aggressive therapy was added and the evolution was quiet favorable.

The majority of cases associated with *Leishmania* reported in the literature had a successful outcome

[9]. Patients may require intensive care unit admission because of multiple organ dysfunction [10]. The non specificity of symptoms is responsible for delayed diagnosis and treatment initiation, resulting in low curability of the disease and fatal outcome [5, 10].

In conclusion, diagnosis of VL associated with HS may be difficult, fatal if untreated and continues to elude physicians. It should be considered in all children with fever, splenomegaly and cytopenia. Early and well-conducted medical treatment achieves a good outcome.

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