Successful resolution of Hemophagocytic lymphohistiocytosis associated to brucellosis in the adult

Résolution favorable du syndrome d'activation macrophagique secondaire à une brucellose de l'adulte

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RÉSUMÉ

hémophagocytose touchant differents organes notamment la rate et la moelle osseuse. Le SAM est de plus en plus diagnostiqué dans un contexte infectieux, tumoral ou encore au cours des connectivites. Malgré le statut endémique de l'infection brucellienne en Tunisie, son association avec le SAM est très rare et devrait être évoquée devant toute splénomégalie associant une ou plusieurs cytopénies. Nous décrivons une rare observation de brucellose révélée par un SAM chez un adulte de 31 ans. Il était hospitalisé dans notre service dans un tableau de fièvre, fatigue et hypersudation. L'examen physique avait révélé une splénomégalie isolée et les bilans biologiques avaient mis en évidence une pancytopénie, cytolyse, hyper triglycéridémie et une hyper ferritinémie. Le myélogramme a retrouvé des images d'hémophagocytose et la sérologie brucellienne était fortement positive. Le diagnostic de SAM compliquant une infection brucellienne était retenu et le patient a complètement récupéré après instauration d'une double antibiothérapie à base de rifampicine et doxycycline.

Mots-clés

brucellose, syndrome d'activation macrophagique, pancytopénie, splénomégalie

SUMMARY

Hemophagocytic lymphohistocytosis (HLH) is a proliferation of histiocytes with important hemophagocytosis occurring in different organs such as the spleen and the bone marrow. HLH is now increasingly diagnosed in the context of infections, malignancies and connective tissue diseases. Although brucellosis is an endemic infection in Tunisia, its association with HLH is a very rare condition which should be considered in patients with splenomegaly and cytopenia. Here, we describe brucellosis associated HLH in a 31 year-old man. The patient was admitted to our hospital with fever, sweating, and fatigue. Physical and laboratory findings revealed splenomegaly, pancytopenia, elevated serum transaminases, triglycerides, lactate dehydrogenase, and ferritin, and bone marrow hemophagocytosis. The Brucella agglutination test was positive. The patient improved after treatment with Rifampin and doxycyclin.

Key-words

brucellosis; hemophagocytic lymphohistiocytosis; pancytopenia; splenomegaly

Hemophagocytic lymphohistocytosis (HLH) is characterized by generalized proliferation of begnin macrophages with hemophagocytosis throughout the reticuloendothelial system which could be life threatening [1]. HLH could be primary or secondary which is associated with a large variety of diseases like malignancies, infections, and autoimmune diseases [2]. The HLH diagnosis can be assessed by different scores; the HLH-2004 score is based on five criteria (fever, hepatosplenomegaly, cytopenia affecting at least two series, ferritin above 500 µg/L, decreased natural killer cell activity, elevated soluble CD25 level above 2,400 U/mL, fasting triglyceride above 265 mg/dL or fibrinogen below 1.5 g/L, and hemophagocytosis in the bone marrow, spleen, or lymph nodes [3]. This score has been purposed, using pediatric population affected by familial lymphohistocytosis and has then frequently been used for adult screening. An other score, the H-Score, has been established since 2014 using clinical and biological datas from reactive adults HLH. It is calculated using 12 criteria and gives a probability of HLH [4]. Early recognition of HLH and evaluation of potential causes is critically important, as survival generally requires urgent treatment with immune suppression and resolution of the activating antigen [5]. Infectious diseases related to HLH represent 33% of secondary HLH etiologies [6]. Although Brucellosis is a major worldwide zoonosis (500,000 infections per year worldwide) [7], Brucella-associated HLH has been rarely reported in the literature [8, 9]. The present study demonstrates an uncommon case of HLH associated to Brucella in a patient, who recovered totally by medical treatment.

CASE REPORT

A 32-year-old man was admitted to our hospital with fever lasting for two weeks and fatigue. He had a history of consumption of fresh milk products. Physical examination was as following: temperature 38.2°C, arterial blood pressure 145/90 mmHg, heart rate 105 beats per minute,

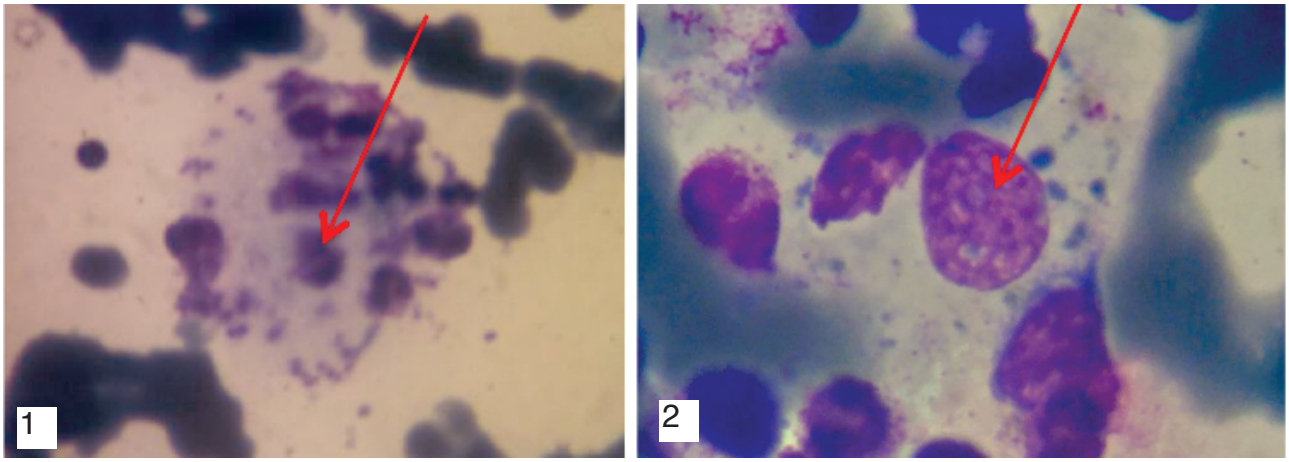

Figure 1 and 2: May-Grünwald Giemsa coloration stained bone marrow aspiration smear with hemophagocytosis

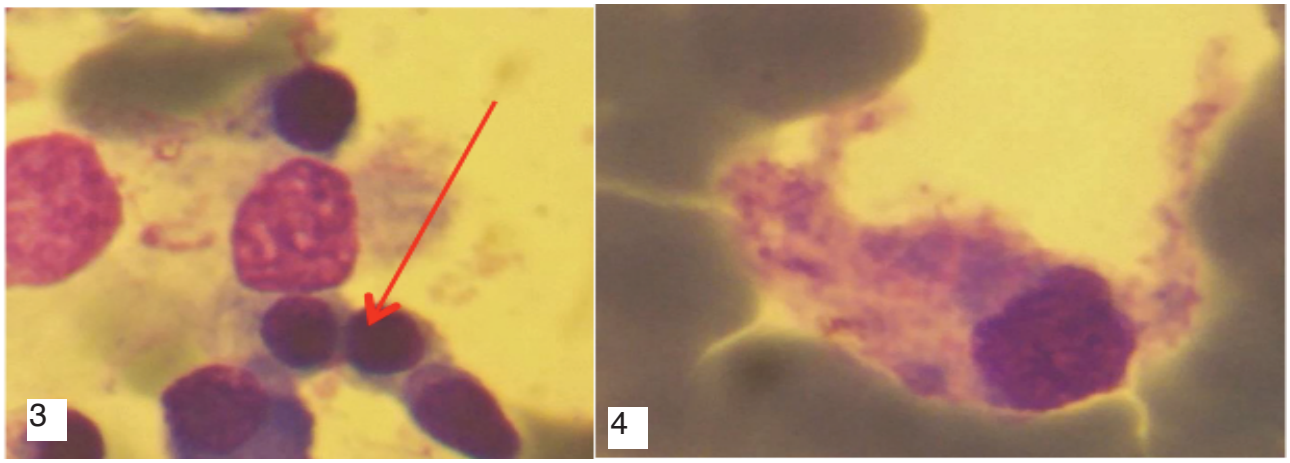

Figure 3 and 4: Bone marrow aspiration showed increased number of histiocytes

respiration rate 14 breaths per minute, labstix proteinuria++ and hematuria++. Abdominal examination showed splenomegaly. Biological tests revealed hemoglobin 10,8 g/dl; white blood cell (WBC) count 9510 /mm3with lymphocytes 960/mm^3, and platelet count 79000/mm^3. The ESR and CRP were 98 mm at the first hour and 138,5 mg/L, respectively. Biochemical analysis revealed alanine amino transferase (ALT) of 69 U/L, aspartate aminotransferase (AST) of 43 U/L, serum triglyceride of 3.15 mmol/L, lactate dehydrogenase (LDH) of 414 IU/L, ferritin of 2763 ng/mL, fibrinogen of 123 mg/dL, $\beta_2$microglobulines of 9,74 and proteinuria of 24 hours=3,22g/day. All blood cultures were sterile and discreet monoclonal gammopathy 14,4 g/l) type IgM kappa was detected on seric electrophoresis. Abdominal echography showed splenomegaly of 165 mm (Figure 1) and a small dedifferenciated left kidney of 73 mm. Trans-thoracic echocardiography was normal. Bone marrow aspiration showed an increased number of histiocytes (Figure 1-2) and rare images of hemophagocytosis (Figure 3-4) and renal biopsy found nonspecific inflammation with presence of healthy areas and fibrosis, absence of glomerular proliferation, mesangial thickening, IgM and C3. Serological tests performed for Epstein-Barr virus, cytomegalovirus, herpes simplex virus, parvovirus, human immunodeficiency virus, hepatitis B, C toxoplasmosis and Widal tests were all negative. Immunological tests (antinuclear antibodies and anti MBG) were negative except cryoglobulinemia which was positive to IgG, A and M. Coombs anti-Brucella test titer was 1/320. Rifampicine (10 mg/kg/day) and doxycyclin (5 mg/kg/day) treatment for brucellosis was initiated. Fever subsided on the third day, with clinical improvement in the following days. Blood analysis demonstrated complete remission of pancytopenia, and liver function tests, CRP, fibrinogen, and serum ferritin levels returned to normal after six weeks of therapy.

DISCUSSION

This observation illustrated a very rare case of benign HLH associated to brucellosis reported typically in children [7, 9, 10]. Common features presented in this case were fever, splenomegaly and bicytopenia shared by both HLH and brucellosis [11].Our patient fulfilled at least 5 criteria of HLH reported by Hunter et al [3].The H Score was 186, which is associated with 75.80% of chance to be a HLH. Thus, the 2 scores confirm the disease. HLH occurs in half cases of brucellosis [12].The pathogeny of HLH associated to brucellosis is still unclear but we know that sequestration of Brucella on the reticuloendothelial system after its ingestion or inhalation [13]. Besides, the nephropathy presented by our patient was a hazardous discovery and didn't seem to be consequent to HLH nor brucellosis. The only similar case reported in the literature of cryoglobulinemia with HLH was described in the autopsy [14]. In contrast to the malignant HLH characterized by a rapidly deteriorating course [15], the Brucella-associated HLH is potentially reversible after introduction of specific antibiotics without need of immunochemotherapy typically introduced for HLH [16, 17] like the case described. We emphasise that treatment of underlying disease is necessary to improve and heal secondary HLH [18].

CONCLUSION

HLH associated to brucellosisis an inflammatory condition that affects typically children but is increasingly diagnosed in adults. Presenting signs like fever, splenomegaly, cytopenia, phagocytosis, elevated ferritin, are common in both entities and HLH must be quickly evocated because of its high lethality. The favorable course of this entity must be considered to introduce the specific antibiotics.

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