Annales Africaines de Médecine
Cas clinique

Macrophage activation syndrome revealing Hodgkin lymphoma

Un syndrome d'activation macrophagique révélant un lymphome hodgkinien

Hajar Maataoui-Belabbes[1], Hanaa Bencharef[2], Bouchra Oukkache[2], Abdellah Madani[1], Mouna Lamchahab[1]

Correspondence
Hajar Maataoui-Belabbes
Email: maataoui.hajar@gmail.com
Tel: +212611616967
Department of Hematology and Pediatric Oncology August 20th - Ibn Rochd University Hospital -Casablanca – Morocco

Résumé
Le syndrome d'activation macrophagique est une entité anatomo-clinique due à une stimulation inappropriée des macrophages. Elle peut être d'origine primaire ou secondaire. Les hémopathies responsables du syndrome d'activation macrophagique sont principalement les lymphomes T ou NK. L'association avec le lymphome hodgkinien est exceptionnelle. Nous rapportons un cas d'un jeune adulte chez qui le syndrome d'activation macrophagique a révélé un lymphome hodgkinien. Le diagnostic du syndrome d'activation macrophagique a été posé devant des arguments cliniques, biologiques et cytologiques compatibles. Le diagnostic étiologique a été guidé par la biopsie ostéo-médullaire et confirmé par l'étude anatomopathologique d'une biopsie ganglionnaire. Le pronostic reste plus péjoratif par rapport aux syndromes d'activation macrophagique secondaires aux infections ou aux maladies auto-immunes.

Mots-clés : syndrome d'activation macrophagique, hémopathies, lymphome hodgkinien

Reçu le 10 janvier 2024
Accepté le 23 avril 2024
https://dx.doi.org/10.4314/aamed.v17i3.15

1. Department of Hematology and Pediatric Oncology August 20th - Ibn Rochd University Hospital - Casablanca - Morocco
2. Hematology Laboratory, Ibn Rochd University Hospital - Casablanca – Morocco.

Summary
Macrophage activation syndrome is an anatomo-clinical entity due to inappropriate stimulation of macrophages. It can be of primary or secondary origin. Blood diseases responsible for reactive macrophage activation syndrome are mainly T or NK lymphomas. The association with Hodgkin lymphoma is exceptional. We report a case of a young adult whose macrophage activation syndrome revealed Hodgkin lymphoma. The diagnosis of macrophage activation syndrome was assured in the light of compatible clinical, biological, and cytological signs. The etiological diagnosis was guided by the bone marrow biopsy and confirmed by the anatomopathological study of a lymph node biopsy. The prognosis remains more pejorative compared to macrophage activation syndromes related to infections or autoimmune diseases.

Keywords: Macrophage activation syndrome, Blood diseases, Hodgkin lymphoma

Received January 10th, 2024
Accepted April 23th, 2024
https://dx.doi.org/10.4314/aamed.v17i3.15

Introduction

Macrophage activation syndrome (MAS) or hemophagocytic lymphohistiocytosis is an excessive, inadequate, and uncontrolled immune response, characterized by proliferation and non-specific activation of macrophages, with phagocytosis of blood cells. It is a rare pathology combining non-specific clinical and biological signs and images of hemophagocytosis. It can be primary or secondary to an infection, autoimmune or neoplasic disease. The blood disease associated to Macrophage activation syndrome are mainly T-cell or NK lymphomas (1). Hodgkin lymphoma (HL) is exceptional. Macrophage activation syndrome is a diagnostic and therapeutic emergency given the risk of progression to systemic failure (2).

In this clinical case, Macrophage activation syndrome reveals Hodgkin lymphoma in a 43-year-old patient.

Case presentation

43 years old male, without a particular pathological history, were hospitalized for subacute installation of an anemic syndrome and infectious syndrome in a context of deterioration of the general condition. On clinical examination, the general condition was very impaired, Performance Status at 4, febrile at 40 °, blood pressure at 80/50 mmHg generalized cutaneous pallor, skin rash in the chest and neck (Figure 1), hepatosplenomegaly, sub centimeter bilateral inguinal lymph nodes.

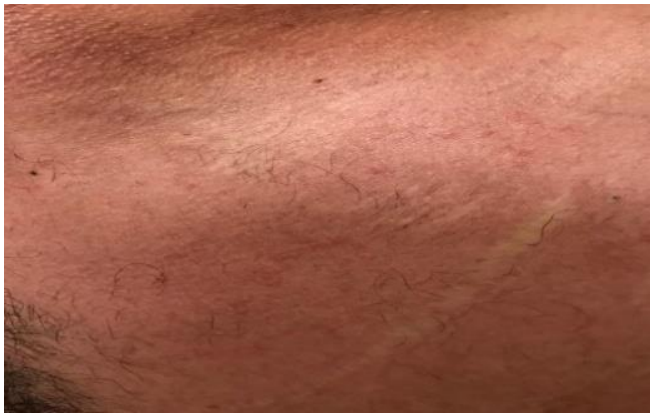

Figure 1: Morbilliform rash in our patient

The biological assessment had objectified cytopenia with normochromic normocytic aregenerative anemia (Hb: 4.3 g / dl; MCV: 91fL; CCMH: 33.6 g/dl; reticulocytes: 8600/mm³), leukopenia at 1190/mm³ (neutrophils: 762/mm3; lymphocytes: 309/mm³; monocytes: 107/mm³; PNE: 0) and thrombocytopenia at 21000/mm³; without vitamin deficiency (vitB12: 1653pg/ml [N: 243–894]; vitB9: 5.3mg/ml [N: 7.2–15.4]), associated with inflammatory syndrome (C Reative protein: 279.12 mg/l, fibrinogen: 5.64g/l) and hepatic cytolysis (ASAT: 223 IU/L; ALAT: 286 IU/L). Lactate dehydrogenase was 759 U/L, triglycerides were 4.85 mmol/L (N: 0.35–1.7), ferritinemia >2000 µg/L (N: 30–400) and Coombs test positive for IgG. The bone marrow aspiration revealed macrophages actively phagocytosing hematopoietic cells (Figure 2).

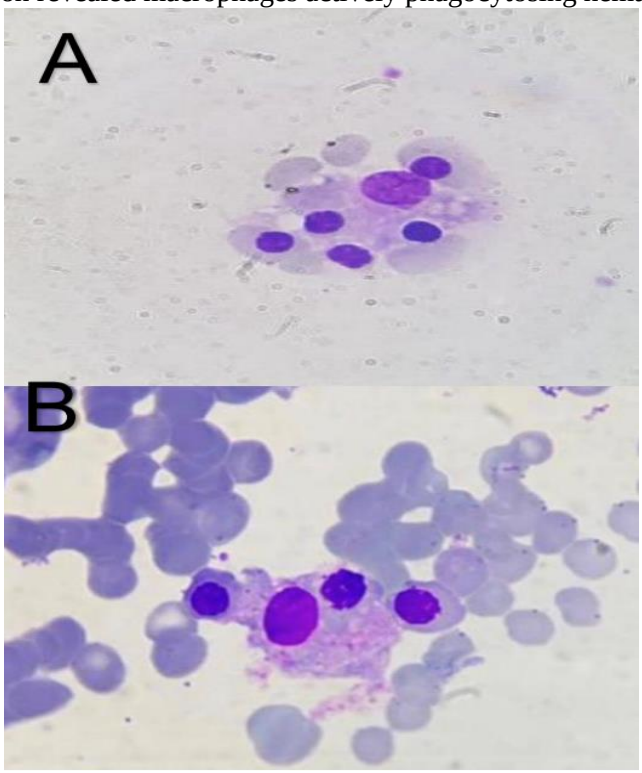

Figure 2 (A et B): bone morrow aspiration objectifying images of hemophagocytosis in our patient

A CT-SCAN showed homogeneous hepatosplenomegaly, iliac and inguinal sub centimeter lymph nodes. Six items out of the eight HLH-2004 criteria were present and the HScore was 274 (probability of having MAS greater than 99%), confirming the diagnosis. Viral serologies came back negative or affirmed

previous infections (EBV serology (VCA-IgG>750U/ml; EBNA-IgG: 267 U/ml; VCA IgM: <20U/ml), CMV serology (IgG: 399.20 U/ml; IgM: 0.15) and HIV1+2, HBV, HCV negative). The bone marrow biopsy performed as part of the etiological assessment, found a largely involvement with atypical cells CD30+ (CD15 having taken on some). This aspect making discuss a bone morrow involvement of a Classical Hodgkin lymphoma.

The Pet-scan was compatible with lymphoma, lymphadenopahy above (bilateral cervical, mediastinal, and bilateral axillary) and subdiaphragmatic, splenic and bone morrow location. Left axillary ADP (SUV max 15.7) was the most accessible for biopsy. The anatomo-pathological (morphological and immunohistochemical) study of lymph node biopsy affirmed classical Hodgkin lymphoma with mixed cellularity. The diagnosis of mixed cellularity HL, stage IVB according to the Lugano classification (IVB Ann Arbor) was saved. The patient received conditioning chemotherapy combined with dexamethasone (Table 3).

Table 3. Chemotherapy protocol established in our patient

Molecule	Dose	Period
Cyclophosphamide	150 mg/m^2	J1 et J2
Vincristine	0.7 mg/ m^2 (max 1mg/j)	J1 et J2
Dexamethasone	10 mg/m^2	J1 – J14
	5 mg/m^2	J15 - J28
	2.5 mg/m^2	J29- J42
	1.25 mg/m^2	J43-56

J26= J1 ABVD

The spinal cord MRI performed after installation of burn pain in the two inferior members, showing vertebral lesions associated with cervical epiduritis without spinal cord compression. After a good clinical and biological evolution, the patient was included in the ABVD protocol. After two cycles ABVD, the patient had developed a fever with hemodynamic instability controlled by antibiotics and vasoactive drugs and the disease was stable. The decision was to switch to the BeGEV protocol. The Pet-scan after two cycles BeGEV classified the patient in fifth Deauville score. The DHAOx protocol was introduced in response to the progressive disease. Complete metabolic remission (Deauville score at 1) was achieved. The patient received an autologous transplant.

Discussion

The diagnosis of MAS is based on a combination of clinical, biological, cytological, or histological signs. The criteria have been established for the diagnosis of primary forms and are used by extension for secondary forms (3-4). In our patient the HScore was at 274 so the probability of having a MAS was greater than 99%.

We distinguish, in order of frequency, infectious etiologies 49%, hemato-oncology 27% (hematologic disease first, solid cancers being less frequent), autoimmune disease. Approximately 1% of hematological malignancies are associated with MAS (5). Aggressive non-Hodgkin lymphomas, especially T-cell or NK lymphomas are frequently found and should be actively researched for MAS without clear etiology (after 60 years = NHL in 2/3 of cases) (6). The etiological investigations may include a chest and abdominal computed tomography, a bone marrow aspiration or even a bone morrow biopsy (lymphoma, tuberculosis) (2). The association MAS and Hodgkin lymphoma is exceptional. In 34 patients followed for MAS secondary to HL stage IVB Ann Arbor, the median age of diagnosis was 43 years and 46 years in HIV-negative patients, with a male predominance (sex ratio 3.3:1). The lymphocyte depleted classic form exists in 45% of cases, a mixed cellularity in 40% of cases and an association with EBV in 94% of cases (7). A reported case of chronic MAS, which etiology is poorly elucidated due to the concomitant existence, at the time of death, of active EBV infection, active CMV infection and Hodgkin lymphoma. HL remains the most likely diagnosis unless occult lymphoma has existed for years. However, acute EBV and CMV infections are associated with fever, pharyngitis, lymphadenopathy, and fatigue. EBV antigen is commonly expressed by Reed-Sternberg cells in patients followed for MAS associated HL (7). In this patient EBV-LMP is negative to RS cells, indicating that her HL and EBV reactivation are two independent processes. Treatment with azathioprine and steroids would have facilitated the reactivation of EBV and CMV later in the course of his disease while partially treating his MAS and LH (8).

In our patient, the various assessments show old infections, which is in favor of a MAS secondary to Hodgkin lymphoma. In patients with MAS secondary to malignancy, it is recommended to start immunochemotherapy to control inflammation first, and then consider specific treatment of the disease once inflammatory markers normalize (2). According to other authors, Treatment of secondary MAS depends on the etiology and its phase of occurrence versus treatment. In case of early occurrence, etiological treatment is necessary. If MAS occurs during chemotherapy, discontinuation of chemotherapy should be considered if the malignancy is controlled. The combination of steroids with etoposide (HLH-94 protocol) maybe appropriate. Subsequently, chemotherapy associated with allogeneic stem cell transplant is recommended (9).

Takahashi and al.'s study clearly demonstrate the difference in prognosis between lymphoma with MAS versus other MAS etiologies. In these MASs, median survival is short (83 days), as is overall survival (8%), which differs from other MASs related for mostly (2/3) to viral infections with 83% of overall survival (10).

Conclusion

Macrophage activation syndrome is a rare pathology, with high mortality, related to inappropriate activation of the immune system. It results in tissue infiltration by activated macrophages. Its diagnosis is based on the association of clinical and biological signs, nonspecific, requiring cytological or histological research of hemophagocytosis and an exhaustive etiological investigation. Secondary etiologies are largely dominated by infections and hematological malignancies.

Conflict of Interest

None

Authors contribution

Hajar maataoui-belabbes: data collection, writing the manuscript.

Others: data analysis and interpretation, critical review, supervision, validation and verification.

Références

1. Janka GE. Hemophagocytic syndromes. *Blood Rev.* **2007** Sep;**21**(5):245-253. DOI: 10.1016/j.blre.2007.05.001.
2. Jordan MB, Allen CE, Weitzman S, Filipovich AH, McClain KL. How I treat hemophagocytic lymphohistiocytosis. *Blood.* 2011 Oct 13;**118** (15):4041-4052. doi: 10.1182/blood-2011-03-278127.
3. Henter JI, Horne A, Aricó M, Egeler RM, Filipovich AH, Imashuku S, *et al.* HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer.* 2007 Feb;**48** (2):124-131. DOI: 10.1002/pbc.21039.
4. Fardet L, Galicier L, Lambotte O, Marzac C, Aumont C, Chahwan D, *et al.* Development and validation of the HScore, a score for the diagnosis of reactive hemophagocytic syndrome. *Arthritis Rheumatol.* 2014 Sep;**66** (9):2613-2620. doi: 10.1002/art.38690.
5. George MR. Hemophagocytic lymphohistiocytosis: review of etiologies and management. *J Blood Med.* 2014 Jun 12;**5**:69-86. doi: 10.2147/JBM.S46255.
6. Lu H, Simonetta F, Samii K, Juillet C. Mise au point sur la physiopathologie, le diagnostic et le traitement « Syndrome d'activation macrophagique ». *Forum Med Suisse* 2017;**17** (2829):604-610. DOI:10.4414/fms.2017.02981.
7. Ménard F, Besson C, Rincé P, Lambotte O, Lazure T, Canioni D, *et al*. Hodgkin lymphoma-associated hemophagocytic syndrome: a disorder strongly correlated with Epstein-Barr virus. *Clin Infect Dis.* 2008 Aug 15;**47** (4):531-534. doi: 10.1086/590152.
8. Chan K, Behling E, Strayer DS, Kocher WS, Dessain SK. Prolonged hemophagocytic lymphohistiocytosis syndrome as an initial presentation of Hodgkin lymphoma: a case report. *J Med Case Rep.* 2008 Dec 4;**2**:367. doi: 10.1186/1752-1947-2-367.
9. Janka G, Imashuku S, Elinder G, Schneider M, Henter JI. Infection- and malignancy-associated hemophagocytic syndromes. Secondary hemophagocytic lymphohistiocytosis. *Hematol Oncol Clin North Am.* 1998 Apr;**12** (2):435-444. DOI: 10.1016/s0889-8588(05)70521-9.
10. Takahashi N, Chubachi A, Kume M, Hatano Y, Komatsuda A, Kawabata Y, et al. A clinical analysis of 52 adult patients with hemophagocytic syndrome: the prognostic significance of the underlying diseases. *Int J Hematol.* 2001 Aug;**74** (2):209-213. DOI: 10.1007/BF02982007.

Cite this article as: Maataoui-Belabbes H, Bencharef H, Oukkache B, Madani A, Lamchahab M. Macrophage activation syndrome revealing Hodgkin lymphoma. *Ann Afr Med* 2024; **17** (3): e5728-e5733. https://dx.doi.org/10.4314/aamed.v17i3.15