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Macrophage Activation Syndrome in a Context of Pre-B Type Lymphoblastic Acute Leucemia: A Case Report

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Abstract

Macrophage activation syndrome (MAS) is linked to inappropriate stimulation of macrophage cells in the bone marrow and lymphoid system, resulting in abnormal phagocytosis of figurative blood elements and the release of pro-inflammatory cytokines. It is a rare and serious hyper-inflammatory condition of diagnostic and therapeutic emergency. MAS is characterized by non-specific clinical and laboratory signs associated with images of hemophagocytosis. MAS is either "primary" (familial or pediatric forms), or "secondary/reactive" to infection, neoplasia, or autoimmune disease. Hemopathies dominate MAS secondary to neoplasia. B-type acute lymphoblastic leukemia (ALL) is a hematological malignancy characterized by the proliferation and accumulation of B lymphoid progenitors, blocked at an early stage of differentiation, leading to suppression of polyclonal hematopoiesis and subsequent development of signs associated with bone marrow failure. In this context, we report the observation of a macrophage activation syndrome (MAS) associated with ALL, diagnosed at Hôpital Principal de Dakar/Senegal, in a 69-year-old patient with a well-controlled type 2 diabetes under oral antidiabetic therapy (OAD) and good general condition.

Keywords

Macrophage Activation Syndrome, Acute Lymphoblastic Leukemia, Adult

1. Introduction

Macrophage activation syndrome (MAS) is a serious hyperinflammatory condition with a poor prognosis [1] [2]. Also known as hemophagocytic lymphohistiocytosis (HL), it is characterized by nonspecific clinical and laboratory signs associated with images of hemophagocytosis. Annual incidence has been estimated at 1.2 cases/million, but adult forms, secondary to infectious or neoplastic pathologies, are probably much more frequent [3]. Familial HL is a genetically determined model of hemophagocytic syndrome, occurring early in childhood. Inappropriate macrophage activation due to infection, autoimmune disease, or malignancy usually occurs in adults [4]. In its reactive form, identification of the underlying pathology is vital, as it is only by treating it that MAS can be halted. The hemopathies responsible for reactive MAS are mainly T or NK lymphomas [5]. B-acute lymphoblastic leukemia (B-ALL) accounts for over 40% of adult-onset ALL (Ad-ALL). This hematological malignancy is characterized by the proliferation and accumulation of B lymphoid progenitors, blocked at an early stage of differentiation, leading to suppression of polyclonal hematopoiesis and subsequent development of signs associated with bone marrow failure. They are characterized by leukocytosis of more than 30 G/l and a pro-B CD10-phenotype [6]. Adult B-ALL is marked by the increasing frequency with age of the presence of a Philadelphia chromosome, found in almost 50% of B-ALL over the age of 50, whereas it is diagnosed in less than 5% of childhood B-ALL [7]. The association of MAS with ALL is rare. We report a case of macrophage activation syndrome in an adult subject secondary to or associated with type B-I or pre-B acute lymphoblastic leukemia at the Laboratory Federation of Hôpital Principal de Dakar (HPD).

2. Patient and Observation

A 69-year-old, with well-controlledtype 2 diabetesunder oral antidiabetic therapy (OAD) was referred to the HPD laboratory for a myelogram, based onthe presence of more than 10% blast cells in the peripheral blood. The patient's general condition was quite good, but he suffered from asthenia and slight weight loss. The patient had reported pruritus for 2 months. Physical examination revealed fever, anemia, and Grade I splenomegaly. The blood count showed anemia at 7.9 g/dl, hyperleukocytosis at 39.11 × 10^9/L with 52% blasts on blood smear, and platelets at 304 × 10^9/L. In regard of these peripheral blasts, the medullogram was performed. It consists of puncturing the sternum with a trocar, then spreading the medullary juice onto slides in the same way as a blood smear. The smears are air-dried and stained with May Grunwald and Giemsa (MGG). The smear is first read at low magnification to assess cell richness, then at high magnification to study the different lineages. Cytological examination revealed a rich marrow characterized by a collapse of the granular and erythrocyte lineages, absence of plasmacytosis (1.4%), images of hemophagocytosis (**Figure 1**), significant eosinophilia, and lymphoblasts (51%). These are heterogeneous cells,

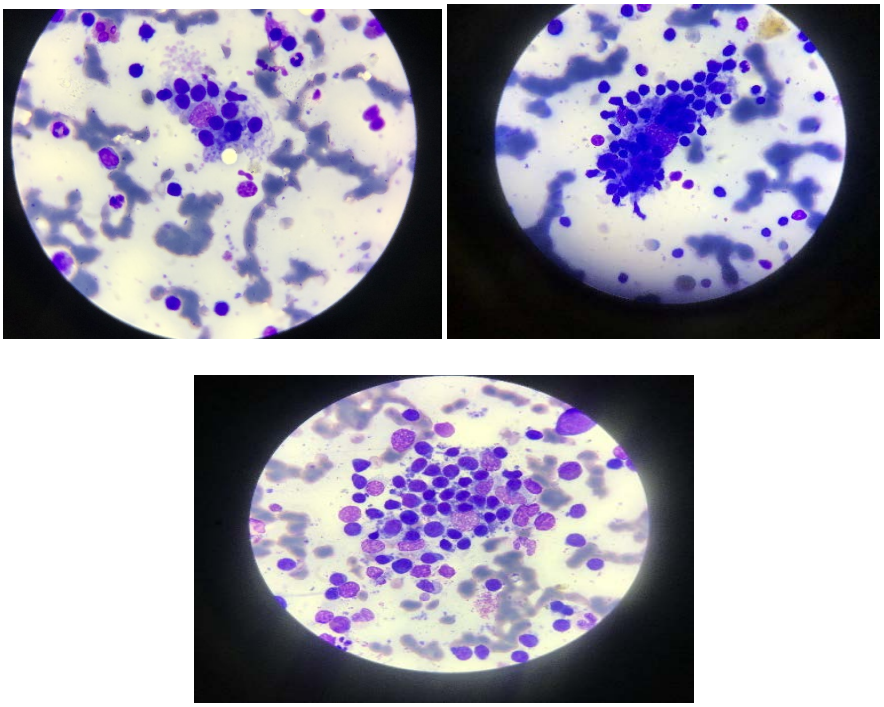

Figure 1. Myelogram with May-Grunwald-Giemsa staining (10× magnification). Image of hemophagocytosis: macrophage phagocytosing blood components (patient images).

with a high nucleocytoplasmic ratio, fine chromatin, sometimes with 1 or 2 nucleolar indent(s), and an often irregular nuclear perimeter. The cytoplasm is basophilic, without granulation (**Figure 2**). The megakaryocytic lineage was unremarkable. Macrophage activation syndrome (MAS) in the context of acute lymphoblastic leukemia (ALL) was considered. Flow cytometric immunophenotyping (FCI) using Sysmex Cube 8TM on peripheral blood showed pre-B acute lymphoblastic leukemia (according to the EGIL score) with absence of CD10. Serum protein electrophoresis (**Figure 3**) revealed hyperprotidemia at 103 g/l with a peak in the gamma zone (43.9 g/l), which could not be characterized by serum protein immunofixation. C-reactive protein (CRP) was positive at 89.60 mg/l and D-Dimer at 616 ng/ml. Hypertriglyceridemia was not observed (0.85 g/l). Ferritinemia and fibrinogen were not available. Glycemia and glycated hemoglobin were elevated at 1.55 g/l and 6.9% respectively. An elevated LDH level of 662 IU/L, hyperuricemia of 89 mg/l, normal serum calcium of 98 mg/l, and normal serum creatinine of 8 mg/l were noted.

3. Discussion

First described by Scott in 1939, hemophagocytosis can associate with, complicate, or even reveal progressive neoplasia [8]. The first diagnostic classification of HS was established in a pediatric population (HLH-2004) [9], and the presence of at least five of the following criteria is required for the diagnosis of HS: fever, splenomegaly, cytopenias, hypertriglyceridemia or hypofibrinogenemia, hyperferritinemia, and histological hemophagocytosis. However, MAS in all

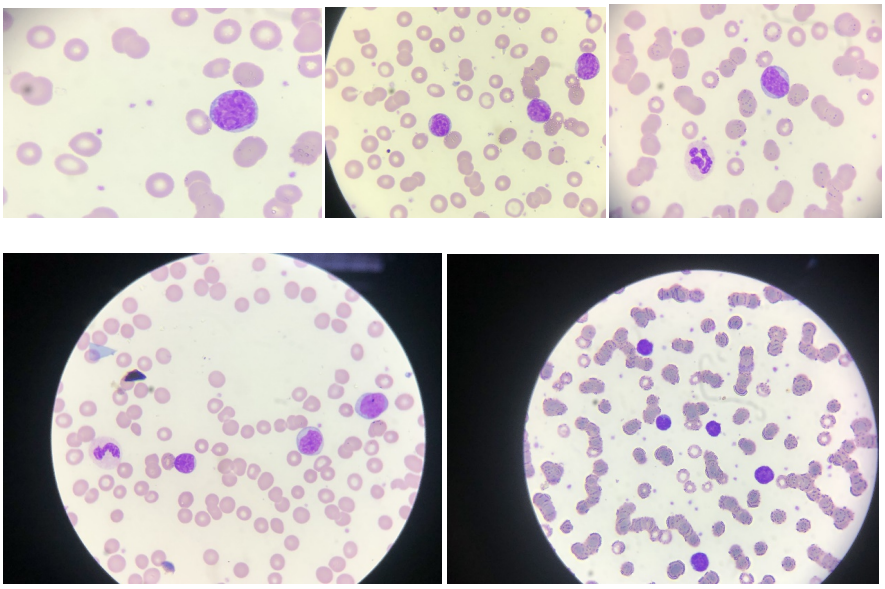

Figure 2. Blood smear with May-Grunwald-Giemsa staining (magnification 100×). Image of lymphoblasts (patient images).

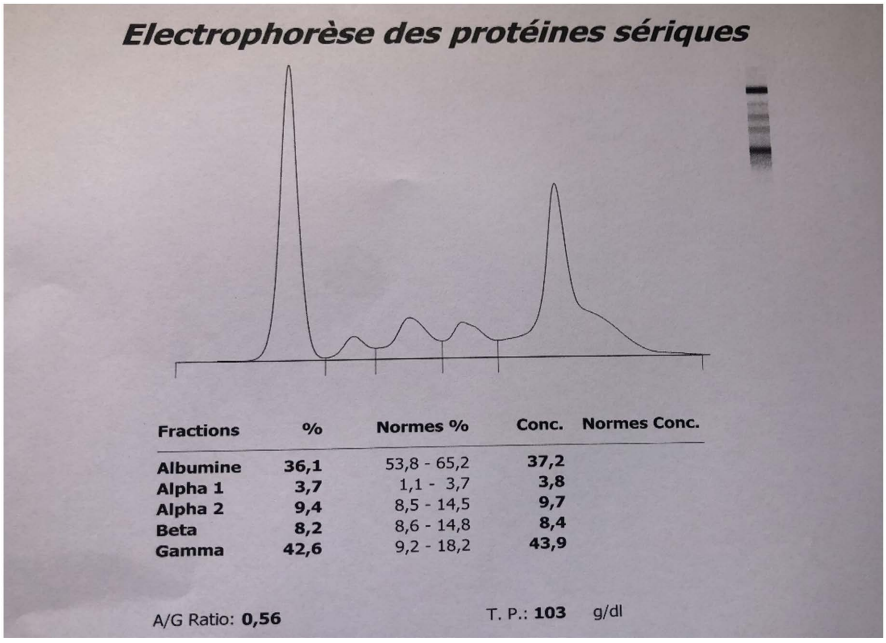

Figure 3. Serum protein electrophoresis using Hydrasis 2 Scan SEBIA (patient image).

these conditions is probably still underestimated, as it is a complication encountered in many clinical situations. In intensive care, for example, MAS associated with an infectious context is a frequent cause of thrombocytopenia in patients with severe sepsis (60% of cases) [8]. The percentage of hemophagocytic syndromes attributable to neoplastic disease is difficult to determine and varies from series to series [10]. The most frequent etiology in this group of MAS is high-grade lymphoma [11]. The incidence of MAS in adults treated for hematological malignancies at a Swedish hematology center (Karolinska Institute) is es-

timated at 1% [12]. In Senegal, Sall *et al*. reported a case of MAS secondary to type 6b erythro-leukemia in an adult patient, while Sow *et al*. in pediatrics revealed a case secondary to type 2 acute myeloblastic leukemia (AML2) in a 4-year-old child [13] [14]. In Tunisia, M. Becheur *et al*. reported a case of MAS associated with erythro-leukemia in a 5-year-old child [15]. Fever, which is almost always present, is the most characteristic symptom and is often the first sign of the disease. Organomegaly bears witness to tissue infiltration by the histiocytic contingent. It is variable, sometimes taking on a pseudotumoral appearance in infantile forms [1]. In the case of MAS, the myelogram remains the most sensitive examination. Histiocytes often account for more than 5% of marrow-nucleated cells in this syndrome; however, they may be very few or difficult to quantify. In the initial stage, hematopoietic activity may be preserved, with normal or even increased marrow cellularity, particularly as regards megakaryocytes. The red blood cell line may appear dysplastic. Plasmacytosis and the presence of activated lymphocytes are frequently found in cases of MAS associated with an infectious context. During the disease, there is a decrease in the number of precursors of the erythroid and granulocytic lineages, with a maximum appearance of myeloid aplasia [16]. A generalized rash of the transient non-pruritic type may be observed (26% of cases) [17]. The non-negligible eosinophilia present in our patient could explain the pruritic cutaneous involvement. The high monoclonal peak observed in the gamma globulinemia zone, in contrast to plasmacytosis, could be linked to non-geode marrow puncture or plasma cell hyperactivity. From the point of view of lymphoid pathology diagnosis, the greatest advance has been the availability of immunophenotyping. However, cytogenetics and molecular biology were not available, due to a lack of technical settings, to be able to explain the clinical stability observed in our patient and apply a therapeutic regimen adapted to the variants of ALL. In the 2016 WHO classification, 2 entities have been individualized, ABL1-like LAL BCR which responds to anti tyrosine kinases, and LALB with intrachromosomal amplification of chromosome 21 LAL B iAMP21 whose prognosis is unfavorable [18]. The association of MAS and ALL may be due to inappropriate stimulation of macrophage cells in the bone marrow and lymphoid system [10]. Neoplasia can trigger a pro-inflammatory state resulting in the release of pro-inflammatory cytokines such as IFN-γ, TNF-α, and IL-2, which in turn activate monocytes and macrophages. This activation leads to the production of a broad spectrum of pro-inflammatory molecules such as IL-1, IL-6, IFN-γ, IL-18, and MCP1, which once again enter the inflammatory cascade, leading to multivisceral failure, hemophagocytosis, and cytopenia [19] [20].

4. Conclusion

Macrophage activation syndrome secondary to or associated with ALL is a rare pathology with a high mortality. It is characterized by inappropriate activation of the immune system, cytogenetic abnormalities, and bone marrow suppres-

sion. However, cytogenetic and molecular diagnostic tools are needed for early and appropriate management.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Berrady, R. and Bono, W. (2014) Lymphohistiocytic Activation Syndrome (SALH). *French Annals of Anesthesia and Intensive Care*, **33**, 26-32. https://doi.org/10.1016/j.annfar.2013.11.026

[2] George, M.R. (2014) Hemophagocytic Lymphohistiocytosis: Review of Etiologies and Management. *Journal of Blood Medicine*, **5**, 62-86. https://doi.org/10.2147/JBM.S46255

[3] Ishii, E., Ohga, S., Imashuku, S., Yasukawa, M., Tsuda, H., Miura, I., Yamamoto, K., *et al*. (2007) Nationwide Survey of Hemophagocytic Lymphohistiocytosis in Japan. *International Journal of Hematology*, **86**, 58-65. https://doi.org/10.1532/IJH97.07012

[4] Ghita, E., Ilham, K., Raja, N., Hicham, Y., Mohammed, C. and Sanae, S. (2021) SAM Revealing Hodgking Lymphoma: About a Case. *Annales de Biologie Clinique*, **79**, 345-348. https://doi.org/10.1684/abc.2021.1655

[5] Martinaud, C., Cournac, J.M., Pons, S., Gallard, T., Darles, C., de Jaureguiberry, J.P. and Brisou, P. (2011) Macrophage Activation Syndrome as the Presenting Feature of a Hodgkin's Lymphoma in an Elderly Patient. *Revue de Medecine Interne*, **32**, e15-e17. https://doi.org/10.1016/j.revmed.2010.03.460

[6] Huguet, F. and Tavitian, S. (2016) Acute Lymphoblastic Leukemia in Adults. *Correspondence in Onco-Hematology*, **11**.

[7] Benzineb, B., Bouayed, B., Mesli, N., Taoussi, S., Lamraoui, F., Abad, M.T., *et al*. (2016) Results of Treatment of Acute Lymphoblastic Leukemia (ALL) in Adults Using the GRAALL 2005 Protocol. *Revue Algérien d'Hématologie*, No. 12.

[8] Stéphan, J.L., Koné-Paut, I., Galambrun, C., Mouy, R., Bader-Meunier, B. and Prieur, A.M. (2001) Reactive Haemophagocytic Syndrome in Children with Inflammatory Disorders. A Retrospective Study of 24 Patients. *Rheumatology* (*Oxford*), **40**, 1285-1292. https://doi.org/10.1093/rheumatology/40.11.1285

[9] Henter, J.I., Horne, A., Aricó, M., Egeler, R.M., Filipovich, A.H., Imashuku, S., *et al*. (2007) HLH-2004: Diagnostic and Therapeutic Guidelines for Hemophagocytic Lymphohistiocytosis. *Pediatric Blood & Cancer*, **48**, 124-131. https://doi.org/10.1002/pbc.21039

[10] Karras, A. and Hermine, O. (2002) Hemophagocytic Syndrome. *La Revue de Médecine Interne*, **23**, 768-778. https://doi.org/10.1016/S0248-8663(02)00673-2

[11] Shimazaki, C., Inaba, T. and Nakagawa, M. (2000) B-Cell Lymphoma-Associated Hemophagocytic Syndrome. *Leukemia & Lymphoma*, **38**, 121-130. https://doi.org/10.3109/10428190009060325

[12] Machaczka, M., Vaktnäs, J., Klimkowska, M. and Hägglund, H. (2011) Malignancy-Associated Hemophagocytic Lymphohistiocytosis in Adults: A Retrospective Population-Based Analysis from a Single Center. *Leukemia & Lymphoma*, **52**, 613-619. https://doi.org/10.3109/10428194.2010.551153

[13] Sow, A., Keita, Y., Touré, S.A., Sall, A., Sarr, M.L., Ouattara, A., Akondé, F.B., *et al*.

(2017) Secondary Macrophage Activation Syndrome in Children: Report of 5 Senegalese Cases. *Médecine d'Afrique Noire*, **64**.

[14] Sall, A., Akonde, F.B., Sall, F.B., *et al*. (2015) Hemophagocytic Syndrome and Acute Myeloid Leukemia. *Pediatric Hematology and Oncology*, **3**, 221-223.

[15] Becheur, M., Jarraya, S., Saada, V., Brini, I., Mrad, K., Boussetta, K., *et al*. (2015) Pure Erythroblastic Leukemia Associated with Macrophage Activation Syndrome about a Case. *Journal Africain du Cancer*, **7**, 263-268. https://doi.org/10.1007/s12558-015-0401-x

[16] Papo, T. (2011) Hemophagocytic Syndrome, Macrophage Activation Syndrome. *EMC—Traité de Médecine AKOS*, **14**, 1-8. https://doi.org/10.1016/S1634-6939(11)56293-3

[17] Fardet, L., Galicier, L., Vignon-Pennamen, M.D., Regnier, S., Noguera, M.E., de Labarthe, A., *et al*. (2010) Frequency, Clinical Features and Prognosis of Cutaneous Manifestations in Adult Patients with Reactive Haemophagocytic Syndrome. *British Journal of Dermatology*, **162**, 547-553. https://doi.org/10.1111/j.1365-2133.2009.09549.x

[18] Baranger, L., Cuccuini, W., Lefebvre, C., Luquet, I., Perot, C., Radford, I. and Lafage-Pochitaloff, M. (2016) Cytogenetics in the Management of Children and Adult Acute Lymphoblastic Leukemia (ALL): An Update by the Groupe Francophone de Cytogénétique Hématologique (GFCH). *Annales de Biologie Clinique*, **74**, 547-560. https://doi.org/10.1684/abc.2016.1176

[19] Crayne, C.B., Albeituni, S., Nichols, K.E. and Cron, R.Q. (2019) The Immunology of Macrophage Activation Syndrome. *Frontiers in Immunology*, **10**, Article No. 119. https://doi.org/10.3389/fimmu.2019.00119

[20] Fajgenbaum, D.C. and June, C.H. (2020) Cytokine Storm. *The New England Journal of Medicine*, **383**, 2255-2273. https://doi.org/10.1056/NEJMra2026131