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(CASE REPORT)

# Macrophagic activation syndrome complicating miliary tuberculosis: A case report

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## Abstract

Macrophage activation syndrome (MAS), also known as hemophagocytic syndrome or lymphohistiocytic activation syndrome, is a rare but potentially fatal disease. It results from inappropriate stimulation of macrophages in the bone marrow and lymphoid organs. The diagnosis of MAS is based on a combination of clinical, biological, and histological or cytological signs. MAS is categorized into primary forms, which mainly affect newborns and infants with a family history, and secondary forms, which occur in the context of neoplastic, autoimmune, or infectious diseases. Treatment involves addressing the specific causative agent of MAS and, in certain cases, early administration of corticosteroids and immunoglobulins. MAS is rarely associated with tuberculosis. We report the case of an immunocompetent patient presenting with miliary tuberculosis complicated by macrophage activation syndrome.

**Keywords:** Macrophage activation syndrome; Tuberculosis; Immunosuppressants; Miliary tuberculosis; Myelogram

## 1. Introduction

Macrophagic activation syndrome (MAS) is a disease first described in the 1950s, but its more recent individualization is mainly due to Risdall's description of post-viral hemophagocytosis in 1979 [1]. MAS is characterized by a severe inflammatory syndrome resulting from deregulation of the cytotoxic cellular response. Primary (or genetic) forms are mainly seen in children, while secondary (or reactive) forms can occur at any age. Given the often severe prognosis, aggressive diagnostic and therapeutic management is warrantedTwo main nosological frameworks are distinguished:

- Primary" ASMs are hereditary diseases of the immune system with T lymphocyte and macrophage activation. They mainly affect newborns and infants with a family history.
- Secondary MAS, for which there is no family history, affecting older children or adults. They occur in the course of neoplastic, autoimmune or infectious diseases, whether viral (primarily EBV), fungal, parasitic or bacterial (more rarely tuberculosis) [2]. We report a case of tuberculosis miliaria complicated by SAM.

## 2. Patient and Observation

A 47-year-old female patient from Thailand, residing in Marrakech, with occasional alcohol use, presented with the onset of dyspnea classified as Sadoul stage II for the past 2 months, associated with a dry cough without hemoptysis, and asthenia. The condition worsened, with dyspnea advancing to Sadoul stage V, accompanied by fever recorded at 39.8°C, night sweats, and a general deterioration with a weight loss of 7 kg over 6 days. The pleuropulmonary examination was normal, with a tubercular miliary appearance on the frontal chest X-ray (Figure 1). The chest CT scan showed dense, well-limited intraparenchymal and subpleural nodules and micronodules of diffuse centrilobular

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distribution in both pulmonary hemichannels (Figure 2). Xpert gene and sputum BK tests were positive. Biological workup showed pancytopenia: anemia 7. 3 g/dl normochromic normocytic regenerative anemia, leukopenia at 1950/uL with lymphopenia at 170/uL and thrombocytopenia at 72000/uL, cytolytic hepatitis: AST: 2 times normal; ALAT: 3 times normal, and cholestasis: PAL 3 times normal, GGT 4 times normal, hyperferretinemia 3760 ng/ml, hypertriglyceridemia 3.95 g/L, LDH 744U/L, HIV, liver and syphilitic serologies negative. Abdominal ultrasound showed no abnormalities, notably no hepatomegaly or splenomegaly. The myelogram showed numerous activated macrophages with rare images of hemophagocytosis (Figure 3 and 4).

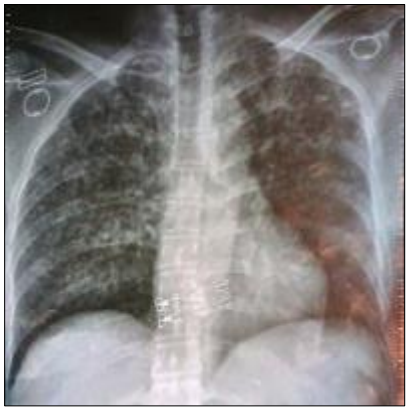

**Figure 1** well-limited micronodular opacities scattered over the 2 lung fields

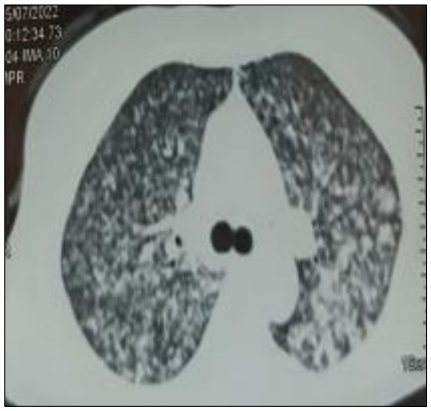

**Figure 2** Dense, well-limited intraparenchymal and subpleural nodules and micronodules of diffuse centrilobular distribution in both pulmonary hemichannels

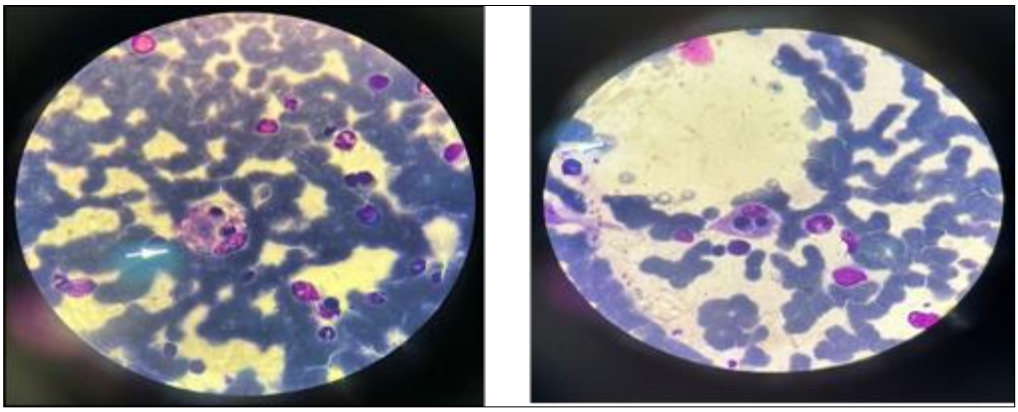

**Figure 3 and 4** 2 images of hemophagocytosis : activated macrophages phagocytosing erythroblasts with a clear vacuole encompassing the phagocytosed cells

The diagnosis of miliary tuberculosis complicated by macrophagic activation syndrome in an immunocompetent patient was accepted. Antibacillary treatment with 2RHZE/7RH was instituted, combined with corticosteroid therapy (1mg/kg/dr), with marked clinical and biological improvement

## 3. Discussion

Macrophage Activation Syndrome (MAS) is a rare but potentially life-threatening condition resulting from excessive and uncontrolled activation of macrophages and T lymphocytes. This excess activation induces massive overproduction of pro-inflammatory cytokines, resulting in a systemic inflammatory response syndrome. Although MAS is generally associated with viral infections, autoimmune diseases and neoplasia, its association with tuberculosis, particularly miliary tuberculosis, is rare and poorly documented.

Post-tuberculosis MAS is the consequence of an excessive and dysregulated immune response to infection by Mycobacterium tuberculosis, resulting in disproportionate activation of macrophages and cytotoxic T lymphocytes. Under normal conditions, these cells play a crucial role in the defense against pathogens by eliminating infected cells and regulating the inflammatory response. However, in the case of MAS, this response becomes uncontrolled. Tuberculosis infection, particularly in its miliary form, spreads widely throughout the body, strongly stimulating the immune system. This massive stimulation leads to hyperactivation of macrophages, which begin to phagocytose not only infected cells but also normal blood cells such as erythrocytes, leukocytes and platelets, resulting in pancytopenia. At the same time, T lymphocytes, unable to adequately regulate this activation due to genetic or acquired dysfunction, fail to control inflammation. This dysregulation leads to excessive production of pro-inflammatory cytokines such as TNF-α, IL-6 and IL-1β, which in turn causes systemic inflammation, leading to severe clinical symptoms such as persistent fever, hepatosplenomegaly and multivisceral failure [3] [4] [5]. Diagnosis of MAS is based on a combination of clinical, biological and histological or cytological signs. Diagnostic criteria have recently been redefined by a group of experts and are presented in Box 1 [6]. The major clinical signs are an almost constant fever, at 39-40 ◦ C, associated with altered general condition and splenomegaly. Adenopathy, hepatomegaly and jaundice are common. A morbilliform skin rash or neurological signs (convulsions, localization signs) are less frequent [4,7]. Biological abnormalities, although numerous, are not specific. It is their association with clinical signs that leads to the diagnosis of MAS. These abnormalities are generally manifested by constant hematological impairment in the form of bicytopenia. Thrombocytopenia, often below 100,000 per cubic millimeter, is the earliest abnormality, as is a profound normocytic normochromic anemia. Hypertriglyceridemia is also present, often early on, and can reach levels up to ten times higher than normal, and hyperferretinemia in excess of 1000 ng/L. These abnormalities are highly suggestive of MAS when associated with cytopenias. Hypofibrinogenemia is observed in 35% to 85% of cases, depending on the author [4,8]. Cytolysis and cholestasis are evidence of liver damage. The almost constant increase in lactate dehydrogenase (LDH) indicates cellular lysis. The myelogram shows a marrow that is usually normal in cell richness. Hemophagocytic histiocytes generally account for 2-75% of nucleated elements, are of normal morphology and show only phagocytic activity. Osteomedullary biopsy can often underestimate active hemophagocytosis, and appears to be less effective than myelogram [4, 9]. The untreated course of MAS is often fatal within a few months [10], justifying a rapid and aggressive therapeutic approach. The management of MAS must include three components: symptomatic treatment, elimination of the causative agent and suppression of T-cell activation and the inflammatory response. Prompt treatment of the causative agent is imperative if an infectious or oncological etiology is found [11].

Treatment is not yet clearly defined. For primary forms, treatment with immunosuppressants and bone marrow allografts is currently recommended. For infectious secondary forms, there are currently no studies evaluating a specific treatment regimen. All treatment proposals to date have been based on case series, mainly pediatric, which are highly heterogeneous in terms of patient characteristics, infectious etiologies and treatments administered. However, it is possible to structure the management of infectious MAS around three axes: etiological treatment of the causative infectious agent, specific immunomodulatory treatment of hemophagocytosis and symptomatic treatment, and organ failure replacement. In cases associated with tuberculosis, the use of corticosteroids or immunosuppressants raises concerns about the potential risk of initial, potentially fatal, worsening of the mycobacterial infection. In their retrospective study, Brastianos et al. set up two groups: a treatment group, subdivided into a subgroup receiving anti-tuberculosis treatment alone and a subgroup combining anti-tuberculosis treatment and immunosuppressants (as in the patient's case), and a no-treatment group. Survival was 60% in the group combining anti-tuberculosis treatment and immunosuppressants, 77% in the group with anti-tuberculosis quadritherapy alone, and 0% in the no-treatment group (diagnosis of hemophagocytosis made post-mortem at autopsy of nine patients) [12]. Corticosteroid therapy is often used as a first-line treatment for its rapid anti-inflammatory effects. Dexamethasone (10 mg/$m^2$/day for 2 weeks, followed by tapering over 6-8 weeks) and methylprednisolone are commonly administered in high doses, followed by tapering based on clinical and biological response [13]. The effect of corticosteroid therapy is rapid, but close monitoring of side effects is necessary. Currently, most authors recommend a combination of corticosteroids (at least 1 mg/kg per

day) and etoposide (VP-16) (100 to 150 mg/m$^2$) [8, 14, 15]. Early administration of etoposide, a cytotoxic agent selective for the monocytic lineage, appears to be crucial for treatment success. Intravenous immunoglobulins can be administered for their immunomodulatory effect, although their exact role in the treatment of MAS remains controversial. They are generally reserved for refractory cases or when other treatments are contraindicated [16].

The vital prognosis in MAS is essentially linked to the associated disease. The prognosis is poorer in cases of thrombocytopenia below 100,000/mm3, hyperferritinemia above 500 ng/ml, fibrin degradation products (> 10 µg/ml) and, above all, hepatic cholestasis (bilirubin > 22 µmol/l, alkaline phosphatases > 740 IU/l). The severity of cholestasis is also correlated with a fatal prognosis according to Kerguenec et al [17]. A series of 34 cases, 20 of which had no underlying disease [18]. Risk factors for mortality were: age over 30 years, presence of disseminated intravascular coagulation, anemia with hemoglobin below 10g/dl and/or thrombocytopenia with platelet count below 100,000/mm3, ferritinemia above 500 g/L, jaundice, hyperbilirubinemia, and increased plasma alkaline phosphatase.

**Table 1** Diagnostic criteria for macrophagic activation syndrome, according to [6]

| ***At least five of the following criteria:*** |
|---|
| -Fever |
| -Splenomegaly |
| -Cytopenias affecting at least two lineages: Hemoglobin < 9 g/dl, Platelets < 100000/mm3 Neutrophils < 1000/mm3 |
| -Hypertriglyceridemia and/or hypofibrinogenemia (Triglycerides > 3mmol/L, Fibrinogen <1.5 g/l). |
| -Hemophagocytosis in bone marrow, spleen or lymph nodes. |
| -No neoplasia. |
| -Low or no Natural Killer cell activity (depending on local laboratory references). |
| -Ferritinemia≥500 g/L. |
| -Soluble IL-2 receptor ≥ 2400 IU/ml. |

## 4. Conclusion

Macrophagic activation syndrome is a serious pathology, often unrecognized. The severity of the prognosis calls for an aggressive diagnostic approach and multidisciplinary therapeutic management. The management of haemophagocytic syndrome associated with tuberculosis is complex and not codified. Assessing the benefit-risk ratio is difficult, due to the risk of immunosuppression linked to the use of corticosteroids or immunosuppressants, with possible aggravation of tuberculosis. Further studies are needed to establish optimized treatment protocols for this complex condition.

## Compliance with ethical standards

### *Disclosure of conflict of interest*

No conflict of interest to be disclosed.

### *Statement of informed consent*

Informed consent was obtained from all individual participants included in the study.

## References

[1] Risdall RJ, McKenna RW, Nesbit ME, Krivit W, Balfour HH Jr, Simmons RL, et al. Virus-associated hemophagocytic syndrome: a benign histiocytic proliferation distinct from malignant histiocytosis. Cancer 1979;44:993–1002.

[2] Le Ho H, Barbarot N, Desrues B. Pancytopénie et tuberculose disséminée: penser à un syndrome d'activation macrophagique. Revue des Maladies Respiratoires. 2010; 27(3): 257 260. Google Scholar.

[3] Varghese, B., et al. (2013). "Hemophagocytic Lymphohistiocytosis Secondary to Tuberculosis: Case Series from India and Literature Review." Journal of Global Infectious Diseases, 5(3), 124-126.

[4] Karras, A., et al. (2015). "Hemophagocytic Syndrome: A Review of Literature." Leukemia Research, 39(3), 316-322.

[5] George, M. R. (2014). "Hemophagocytic lymphohistiocytosis: review of etiologies and management." Journal of Blood Medicine, 5, 69-86.

[6] Henter JI, Horne A, Aricó M, Egeler RM, Filipovich AH, Ima shuku S, et al. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer 2007;48:124—31.

[7] Fisman DN. Hemophagocytic syndromes and infection. Emerg Infect Dis 2000;6:601—8.

[8] Rouphael NG, Talati NJ, Vaughan C, Cunningham K, Moreira R, Gould C. Infections associated with haemophagocytic syn drome. Lancet Infect Dis 2007;7:814—22.

[9] Sandrini J,Beucher A B, Rousselet MC, Gardembas M, Lavigne C.Tuberculose compliquée d'un syndrome hémophagocytaire;ou syndrome d'activation macrophagique. Médecine et maladies infectieuses. 2010; 40(8): 476-479.

[10] Li J, Wang Q, Zheng W, et al. Hemophagocytic lymphohistiocytosis: clinical analysis of 103 adult patients. Medicine 2014;93:100–5.

[11] Schram AM, Berliner N. How I treat hemophagocytic lymphohistiocytosis in the adult patient. Blood. 2015;125(19):2908–14.

[12] Brastianos PK, Swanson JW, Torbenson M, Sperati J, Karakousis PC.Tuberculosis-associated hemophagocytic syndrome. Lancet Infectious Diseases. 2006;6(7):447-54.

[13] Henter, J. I., Samuelsson-Horne, A., Aricò, M., Egeler, R. M., Elinder, G., Filipovich, A. H., & Janka, G. (2002). Treatment of hemophagocytic lymphohistiocytosis with HLH-94 immunochemotherapy and bone marrow transplantation. Blood, 100(7), 2367-2373.

[14] Reiner AP, Spivac JL. Hemophagocytic histiocytosis: a report of 23 new patients and review of the literature. Medecine. 1988; 67(6):369-88.

[15] Créput C, Galicier L, Buyse S, Azoulay E. Understanding organ dysfunction in hemophagocytic lymphohistiocytosis. Intensive Care Medicine. 2008; 34(7):1177-87.

[16] Larroche C, Bruneel F, André MH, et al (2000). [Intravenously administered gamma-globulins in reactive hemaphagocytic syndrome. Multicenter study to assess their importance, by the immunoglobulins group of experts of CEDIT of the AP-HP]. Ann MedInterne (Paris) 151:533–9.

[17] De Kerguenec C, Hillaire S, Molinié V, Gardin C, Degott C, Erlinger S, Valla D. Hepatic manifestations of hemophagocytic syndrome: a study of 30 cases. Am J Gastroenterol 2001;96:852–7.

[18] Kaito K, Kobayashi M, Katayama T, Otsubo H, Ogasawara Y, Sekita T, et al. Prognostic factors of hemophagocytic syndrome in adults: analysis of 34 cases. Eur J Haematol 1997;59:247—53.