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Case Report **Open Access**

A case report of macrophage activation syndrome of infectious origin in the clinical haematology department of the Ignace Deen University Hospital, Conakry, Guinea

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Abstract:

Background: Macrophage activation syndrome (MAS) is a rare but often fatal condition. It is linked to inappropriate stimulation of macrophages leading to abnormal phagocytosis of the formed elements of the blood and the release of pro-inflammatory cytokines. The aim of this study is to report a case of MAS of infective origin, and call the attention of medical practitioners to this potential life-threatening condition.
Case presentation: This was a 45-year-old male patient, admitted on account of febrile pancytopenia (anaemia, leukopaenia and thrombocytopaenia) of chronic course. No particularly significant past medical history of the patient. Clinical and paraclinical examinations showed that the MAS was due to tuberculosis
Conclusion: MAS is a life-threatening condition often associated with infections such as tuberculosis as described in this case.

Keywords: Macrophage activation syndrome; pancytopenia; infection; tuberculosis

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Rapport de cas de syndrome d'activation des macrophages d'origine infectieuse au service d'hématologie clinique de l'hôpital universitaire Ignace Deen, Conakry, Guinée

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Résumé:

Contexte: Le syndrome d'activation des macrophages (SAM) est une pathologie rare mais souvent mortelle. Il est lié à une stimulation inappropriée des macrophages entraînant une phagocytose anormale des éléments figurés du sang et la libération de cytokines pro-inflammatoires. L'objectif de cette étude est de rapporter un cas de SAM d'origine infectieuse et d'attirer l'attention des médecins sur cette pathologie potentiellement mortelle.
Présentation du cas: Il s'agit d'un homme de 45 ans, hospitalisé pour pancytopénie fébrile (anémie, leucopénie et thrombopénie) d'évolution chronique. Pas d'antécédents médicaux particulièrement significatifs du patient. Les examens cliniques et paracliniques ont montré que le SAM était dû à la tuberculose.
Conclusion: Le SAM est une pathologie potentiellement mortelle souvent associée à des infections telles que la tuberculose comme décrite dans ce cas.

Mots clés: Syndrome d'activation des macrophages ; pancytopénie ; infection ; tuberculose

Introduction:

Macrophage activation syndrome (MAS) is a rare but often fatal condition. It is linked to inappropriate stimulation of macrophages leading to abnormal phagocytosis of the formed elements of the blood and the release of pro-inflammatory cytokines (1) from activated

T-lymphocytes. It is a disproportionate reaction of the immune system linked to a cytokine storm. These cytokines (interferon-γ, tumor necrosis factor-α and interleukin-6) produced by $CD8^+$ T-cells and Natural Killer (NK) lympho cytes that have lost their cytotoxic but not their secretory power, exaggeratedly activate macrophages, which in turn lose their self-tolerance, and phagocytose the medullary precursors and the formed elements of the blood (2).

MAS can be primary or secondary to various disease conditions including haematological, infectious and autoimmune disorders. Diagnosis is based on clinical, biological, and cytological criteria as revised by Henter et al., (1) and Jennane (3). The detection of haemophagocytosis images on the medullogram is a major diagnostic criterium but may not be found in some cases (4). The prognosis of MAS is poor, with mortality rate of nearly 50% from all causes. The treatment of secondary MAS is essentially etiological and depends on the causative pathology.

Among the many etiologies of MAS, infectious causes are the most common. However, in the case of infectious MAS (MAS I), it is often difficult to attribute the occurrence of haemophagocytosis to the underlying infectious agent in a direct cause-and-effect relationship. On the one hand, the infectious agent can trigger MAS in an immunocompromised environment, and on the other hand, the immunosuppression that results from MAS can promote secondary superinfections.

In the event of infection, the causative agent, whether bacterial, viral, fungal or parasitic, must be identified and treated urgently, in order to improve the prognosis of MAS (5). In Guinea, few cases of MAS have been reported. The aim of this report is to highlight the case of MAS of infectious origin and to call the attention of medical practitioners to this potential life-threatening condition.

Case presentation:

This was a 45-year-old male patient, admitted on account of febrile pancytopenia of chronic course. There was no particularly significant past medical history for the patient. Clinical examination revealed an alteration in the general condition, skin lesions with a type of painless and firm nodules, and ulcerations, located all over the body (Fig 1) and Hackett's hepato-splenomegaly type 2.

At the paraclinical level, blood count showed hypochromic microcytic anaemia (Hb 3.2 g/dL), neutropenia [polymorphonuclear neutrophil (PNN) of 0.6/L or 600/µL], and thrombocytopenia (platelet count of 30/L or 30,000/µL) but myelogram showed absence of haemophagocytosis image. Other laboratory parameters included high serum low density lipoprotein (LDH) level (700 IU/L), high serum triglyceride, and high serum ferritin (900µg/L). Thoraco-abdomino-pelvic computerized tomographic (CT) scan showed polyseritis of the pleural, pericardial, abdominal and peritoneal cavities associated with homogeneous hepatosplenomegaly. Histology of biopsy of the skin lesion showed infiltrating tuberculoid granuloma suggestive of cutaneous tuberculosis.

The patient was treated with antituberculosis drugs (rifampicin, isoniazid, and ethambutol) and given cyclophosphamide at a dose of 400mg/m^2. The course was marked by clinical improvement, with disappearance of fever, hepato-splenomegaly and skin lesions, and also biologically by correction of the pancytopenias.

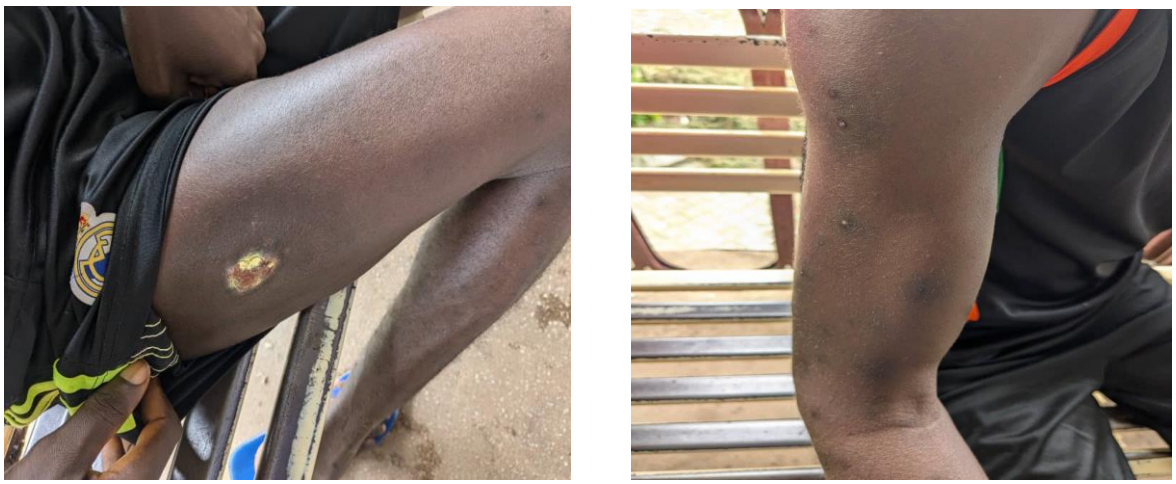

Fig 1: Cutaneous lesions on the arm and leg of the patient

Discussion:

Macrophage activation syndrome is a severe condition related to immune dysfunction. The perforin deficiency found in the NK lymphocytes and the hyperproduction of interleukins (IL-1, 6, 8, 10 and 12) and TNF-α lead to cytokine storm with a disproportionate response of macrophages to the haemophagocytosis type directed against medullary precursors and blood cells (6). This often explains the noisy nature of the clinical picture presented by patients (7) as seen in our patient who presented with a variety of clinical symptoms.

The diagnosis of MAS was based on a set of clinical, biological and cytological signs. These clinico-biological signs are not in themselves specific to MAS, but their association was strongly suggestive of this diagnosis. Indeed, MAS is based on constellation of clinical, biological and cytological or histological signs (8). It is most often a picture of fever and weight loss associated with organomegaly, with the presence of bi- or pancytopenia, cytolysis and/or cholestasis, hyperferritinemia and haemostasis disorders.

The reference test for the diagnosis of MAS is the myelogram, which makes it possible to confirm the presence of haemophagocytosis on the one hand and to confirm the underlying etiology on the other hand. However, the presence of haemophagocytosis on cytological or histological samples is not sufficient to make the diagnosis of MAS (9). Thus, several diagnostic criteria have been proposed (10). Currently, the most widely used are those proposed by Henter in 1991 (11), which were revised and retained by the Histiocyte Society (1). In our case however, the myelogram did not show image of haemophagocytosis.

In addition to the so-called primitive MAS associated with genetic factors, the secondary MAS found in adults are often of infectious etiologies. Among the infectious aetiologies is *Mycobacterium tuberculosis*, which has already been reported by some authors in the United States, Europe and Africa (5). In the case of MAS of infectious etiology, it is sometimes difficult to attribute the occurrence of macrophage activation to a causal infection. On the one hand, the infectious agent could just play the role of triggering MAS, often in a particular immunological field. On the other hand, the immunosuppression that results from MAS can promote secondary superinfections, sometimes making etiological diagnosis impossible (12,13). In all cases, the underlying pathology must be sought out and treated. Our patient had multifocal tuberculosis (pleural, cardiac, hepato-splenomegaly, and cutaneous).

Rapid initiation of appropriate anti-infective therapy is a determining prognostic factor in the case of MAS of infectious etiology (14). There are few and very heterogenous publications in the literature on the clinical characteristics of patients with MAS of infectious aetiologies and treatments administered. Most of the proposed treatment options are based on protocols used in the familial forms of lymphohistiocytosis or based on pathophysiological and pharmacological assumptions. However, the management of infectious MAS revolves around three axes (5); symptomatic treatment and management of organ failure, aetiological treatment of the causative infectious agent, and specific immunomodulatory treatment of haemophagocytosis. The management of infectious MAS often requires rigorous management and close monitoring because of rapid deterioration that may occur in the patient condition. The underlying pathology must be relentlessly sought out and treated, which can sometimes be hinder the successful treatment of MAS.

As for the specific treatment of MAS, the use of etoposide, a selective cytotoxic compound of the monocyte lineage, seems to be the determining factor for the success of MAS treatment, as it can very quickly block macrophage activation within 24 to 48 hours. This drug must however be administered early (5). The initiation of immunosuppressive therapy in addition to the continuation of the first-line treatment can improve the prognosis of MAS, and the patient may also benefit from blood transfusion support.

Conclusion:

MAS is a life-threatening condition that is often associated with infections such as tuberculosis. Careful clinical examination and appropriate laboratory investigations can help make the diagnosis. Prompt treatment of the underlying pathology and etoposide therapy can improve the management of MAS.

Contributions of authors:

AC and ASD were involved in the main methodology of the study. MT, ID and ASK were responsible for literature review on the subject. MD critically reviewed and corrected the manuscript. All authors approved the manuscript submitted for publication.

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Conflict of interest:

Authors declare no conflict of interest

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