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Rare Case of Acute Myocarditis Complicating Macrophagic Activation Syndrome: A Complex Clinical Conundrum

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Case Report

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ABSTRACT

Macrophagic Activation Syndrome (MAS) and myocarditis individually pose significant challenges to healthcare providers due to their complex pathophysiology and diverse clinical presentations. However, when these two conditions intersect, the immune system's dysregulation amplifies the inflammatory response, posing unique diagnostic and therapeutic dilemmas. The clinical presentation is nonspecific, showing no pathognomonic signs, the patient may present chest pain, shortness of breath, fever and signs of systemic inflammation, which calls for heightened awareness and a comprehensive approach to make the diagnosis and for better management.

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In the following paper, we report the case of a 23 years old man admitted to our hospital for dyspnea, and chest pain, associated to an altered general condition and fever, and in whom, a constellation of clinical features and laboratory findings, met the diagnostic criteria for MAS associated to a myocarditis. He was treated with high dose intravenous corticosteroid, and heart failure drugs, resulting in resolution of fever and dramatic clinical improvement.

Keywords: Hyperferritinemia; cytokine release storm; corticosteroid; myocarditis; macrophage activation syndrome (MAS).

1. INTRODUCTION

Macrophagic activation syndrome (MAS), also known as Hemophagocytosis syndrome or lympho-histiocyticis is a rare but potentially fatal disease. It was first described in 1939 by Scott and Robb-Smith in adults as a neoplastic proliferation of histiocytes. The mechanisms behind MAS are not completely understood, but recent advances in the genetic study of familial forms, with the discovery of the genes responsible, have completely altered our understanding of its pathophysiology [1-5]. It is often seen in the context of rheumatic diseases, such as systemic juvenile idiopathic arthritis and systemic lupus erythematosus, but can also occur secondary to infections or malignancies. Diagnosis is based on a combination of non-specific clinical and biological signs, requiring cytological or histological testing for hemophagocytosis and an exhaustive etiological investigation.

Myocarditis, on the other hand, is an inflammatory condition affecting the myocardium, the muscular tissue of the heart. It can result from various causes, including viral infections, autoimmune diseases, and drug reactions. The inflammation associated with myocarditis can impair cardiac function and lead to a spectrum of clinical manifestations, ranging from mild symptoms to life-threatening complications such as heart failure and sudden cardiac death.

Accurate diagnosis of a myocarditis complicating a MAS requires a high index of suspicion and a multimodal approach. Biological examinations may reveal elevated inflammatory markers, cytopenia and signs of myocardial damage. Advanced imaging modalities, such as cardiac MRI and PET scans, play a vital role in the diagnosis, providing valuable information on cardiac structure, function and inflammation statues.

The aim of our work is to report a case of a myocarditis complicating a Macrophagic activation syndrome collected in the Cardiology department of CHU Ibn Rochd, and compare it to data of the literature.

2. CASE PRESENTATION

A 23-year-old man with history of Rheumatoid Arthritis was hospitalized for acute dyspnea associated with moderate chest pain and fever. Pulse rate was 120 beats/min, arterial blood pressure was 110/50 mmHg, oxygen saturation: 96% and body temperature of 39.7°C were noted, associated with profuse sweating. Physical examination revealed bilateral crepitant rales. The electro-cardiogram showed sinus tachycardia with ventricular bigeminy. A chest radiograph disclosed cardiomegaly and interstitial syndrome. Blood analysis showed a high level of troponin at 60 times the normal, and an anemia with Hb at 11.2, PNN at 870, hyperferritinemia at 830 and elevated C-reactive protein at 400 mg/l.

The echo-cardiography found a dilated left ventricular, with altered systolic function (ejection fraction at 45%) and a moderate aortic regurgitation. The coronary angiography showed normal coronary arteries (Fig. 1).

Under the impression of myocarditis, we arranged cardiac MRI which disclosed a global left ventricular hypokinesia with an ejection fraction of 42%. It also showed hyperemia and sub-epicardial anterolateral wall delayed gadolinium enhancement (Fig. 2) which constitutes two criteria among three of lake Louise criteria, thus confirming the diagnosis of myocarditis. Etiological investigation including viral serologies yielded normal results.

Conservative treatment with high dose intravenous corticosteroid was initiated, we prescribed a β-blocker (bisoprolol) and an ACE inhibitor (ramipril) with good clinical evolution and progressive improvement in dyspnea. An echocardiography was repeated after 6 months, showing a left ventricular of normal size and good global and segmental systolic function with an ejection fraction at 58% and a global longitudinal strain preserved at -15,7% and segmental strain slightly altered at anterolateral wall (Fig. 3).

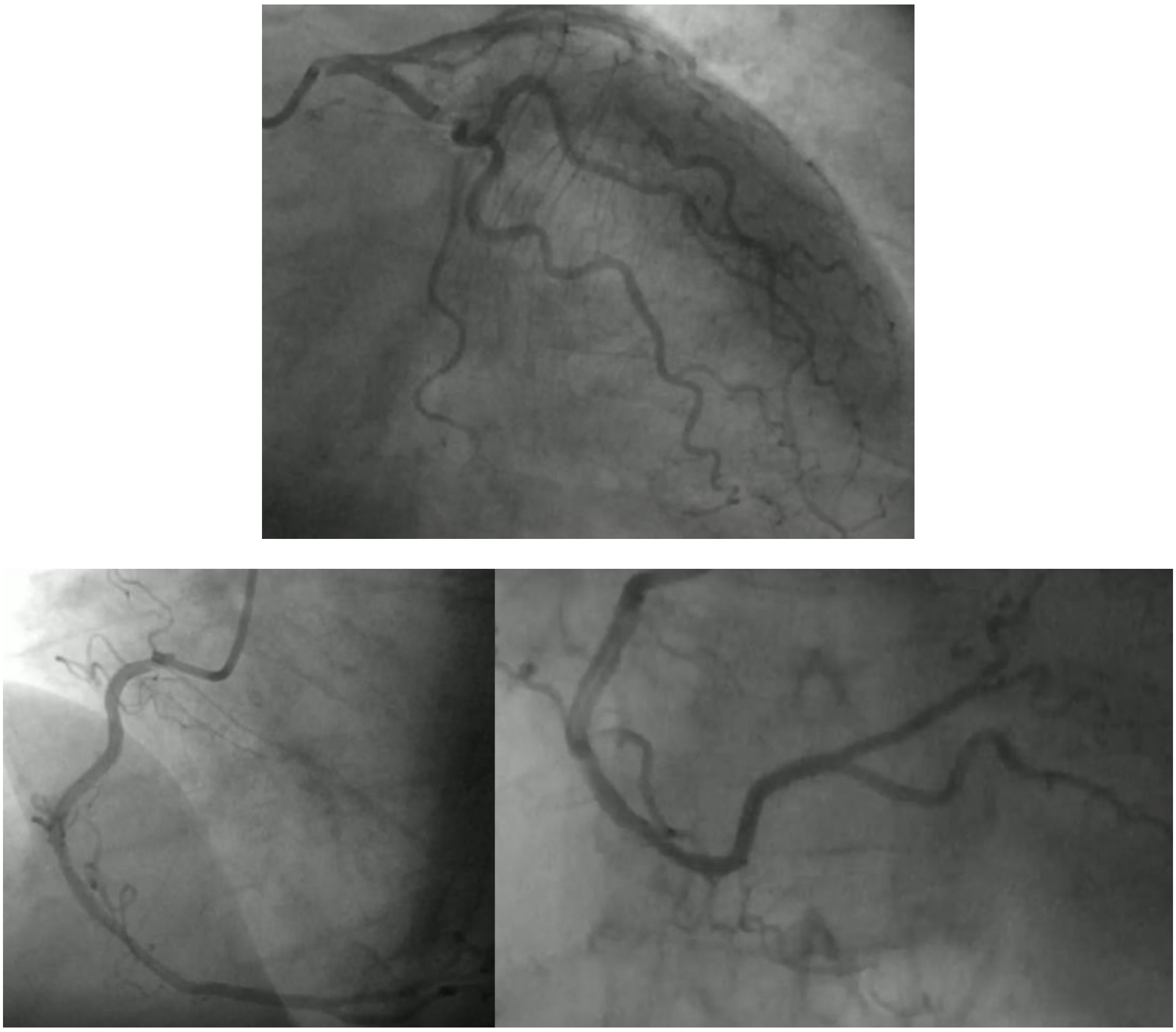

Fig. 1. The coronary angiography of the patient showing normal coronary arteries.

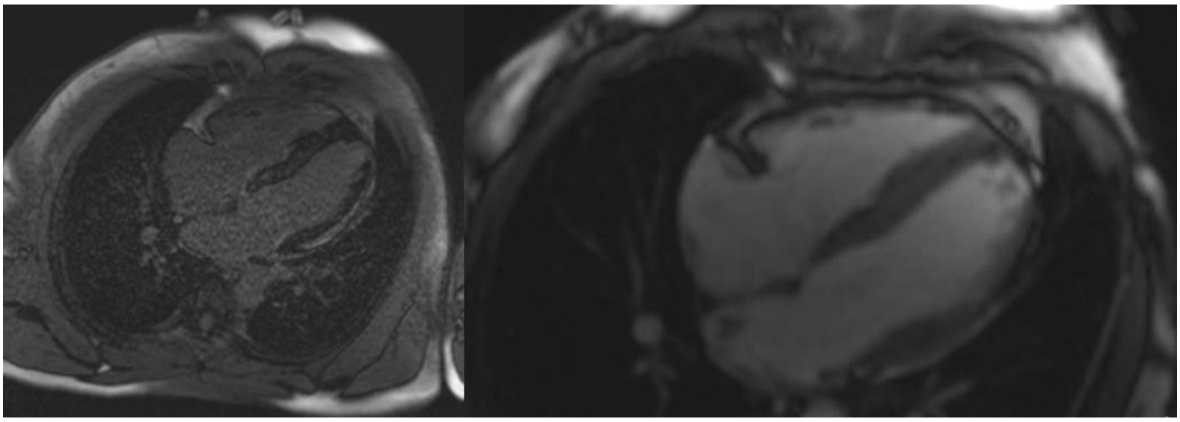

Fig. 2. Cardiac MRI of the patient showing signs of myocarditis

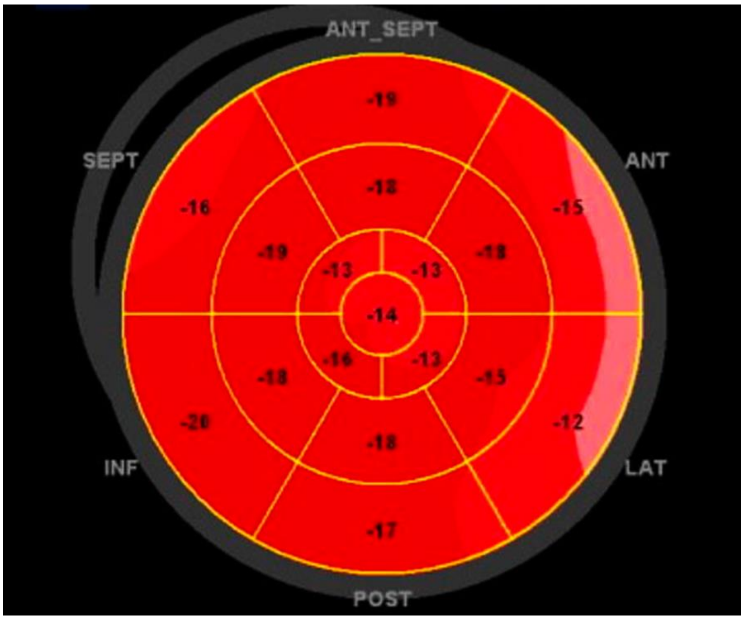

Fig. 1. The strain of the patient after 6 months

3. DISCUSSION

MAS is a multisystemic disease, linked to intense activation of the immune system, corresponding to more or less diffuse infiltration of tissues by activated macrophages responsible for a situation known as Cytokine Storm. It belongs to the group of non-malignant, non-Langerhansian histiocytoses [6].

In 1991, the Histiocyte society brought together all the available publications to propose the first diagnostic criteria and define two distinct forms of the disease:

- “Primary” SAM, of genetic origin.
- “Secondary” SAM, acquired or reactionary, which most often occurs in a background of acquired immunosuppression with an identified, generally infectious, triggering factor.

At present, the pathophysiology of MAS is not fully understood. Numerous advances in the understanding of “primary” MAS have made it possible to propose explanations for the clinicobiological and evolutionary manifestations, although no certainty can be affirmed.

The central abnormality appears to be a cytotoxicity deficit in CD 8 and Natural Killer (NK) T lymphocytes, with no limitation in their ability to activate or produce cytokines. Under the effect of a particular infection, there is a normal but ineffective activation of the CD8/NK T lymphocyte system, leaving the causative agent and macrophages to persist, perpetuating the activation and proliferation of these same CD8 and NK T lymphocytes. The cytotoxic cells in turn stimulate macrophage activation, and the loop expands uncontrollably [7,8] (Fig. 4).

Clinically, the manifestations are not very specific, and it is their association that should prompt a diagnosis. At present, the Henter criteria are accepted as the diagnostic criteria for MAS, and the diagnosis of MAS is based on the presence of five of eight criteria: fever, splenomegaly, cytopenia (hemoglobin (Hb) < 9 g/dl, platelets < 100,000/mm3, neutrophils < 1,000/mm3), hypertriglyceridemia (> 3 mmol/l) and/or hypofibrinemia (< 1.5 G/l), hemophagocytosis marrow (or other tissues: lymph node, spleen, etc.), ferritin > 500 mg/mm3, ferritin > 500 mg/l, soluble CD25 > 2,400 U/ml and no or reduced natural killer (NK) activity [9,10]. The HScore can be used to estimate an individual's risk of having reactive hemophagocytic syndrome.

Cardiac dysfunction in MAS has been reported in a few case studies. However, no series has yet been published. Nevertheless, the prognosis of patients with cardiac disease associated with SAM is poor. A better description of this complication could lead to a better understanding of its pathophysiology and help clinicians to diagnose and manage it.

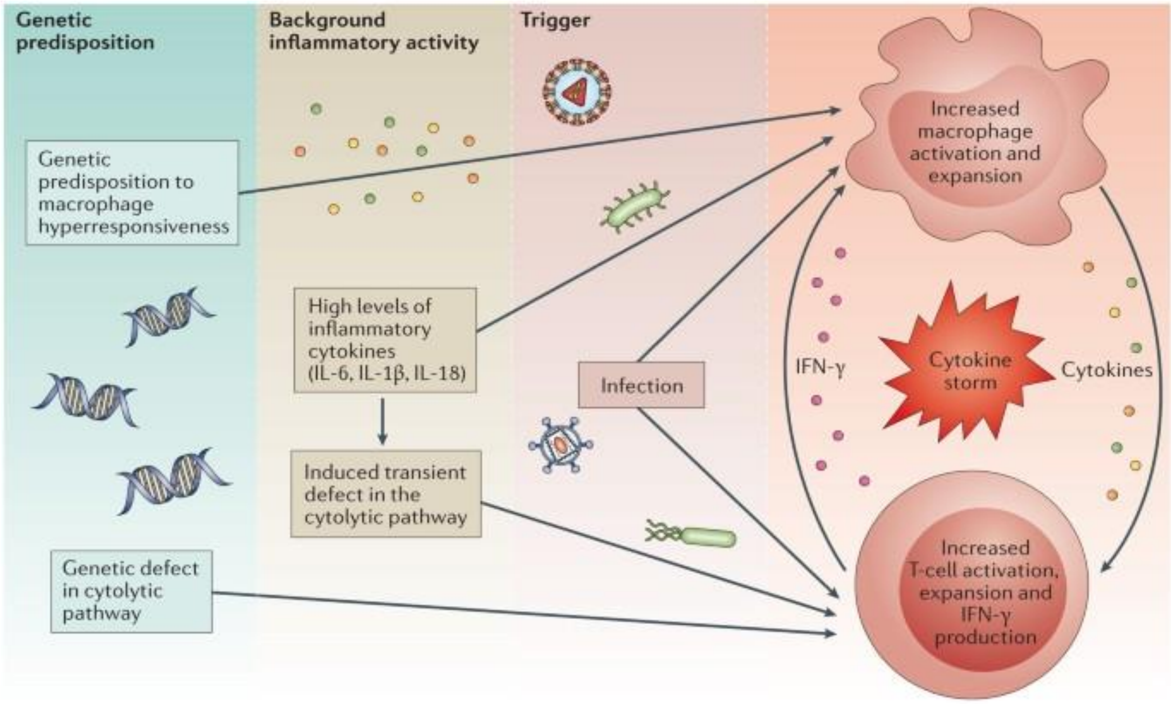

Fig. 2. Pathophysiology of macrophagic activation syndrome [11]

There's a fine line between septic heart disease and heart disease associated with MAS. This is particularly evident in MAS secondary to progressive infection. However, even when MAS complicates neoplasia or autoimmune disease, it is rarely possible to formally exclude a concomitant infection.

In 1991, Henter et al. reported for the first time the presence of imaged hemophagocytosis in the myocardium without associated cardiac dysfunction [12]. Since then, the pathophysiology of cardiac involvement in MAS has never been studied, partly due to its rarity. There are, however, several hypotheses, many of which derive from septic cardiomyopathy:

- As in sepsis, MAS is characterized by the deregulated synthesis and secretion of pro-inflammatory cytokines (the so-called “cytokine storm”). Among these cytokines, tumour necrosis factor (TNF)-α and interleukin (IL)-1β exert a myocardial depressant effect in-vitro [12,13]. Although a decrease in cardiac contractility has never been formally demonstrated in vivo, a pilot study of 10 septic shock patients treated with anti TNF-α showed an improvement in left ventricular function [14].
- Cytokine storms increase vascular permeability, leading to myocardial edema and consequent impairment of LV function. This edema could explain the appearance of left ventricular pseudohypertrophy described in some reported cases, but not found in our study [15,16].
- Viruses of the herpes family (mainly HHV-6), coxsackies, parvovirus B19 and adenovirus are frequently responsible for viral myocarditis [17]. Some viruses, such as adenovirus, can penetrate the cardiomyocyte via specific receptors and induce apoptosis [18]. Thus, viruses, as a trigger for MAS, can play a direct role in cardiac damage.
- Another purely mechanical hypothesis concerns heart-lung interaction in mechanically ventilated patients [19]. During positive pressure ventilation, there is a decrease in preload (responsible for a reduction in venous return) and an increase in LV afterload. Due to inter-ventricular dependence, LV preload decreases, as does DC.
- Finally, etoposide-VP16 can be directly responsible for cardiac damage. It has already been reported that etoposide-VP16 can induce coronary thrombosis or vasospasm, or even be responsible for direct myocardial cell toxicity [19,20].

Accurate diagnosis is paramount but can be elusive due to the similarities in clinical presentation and laboratory findings between acute myocarditis and MAS. Echocardiography is often the initial imaging modality used to assess cardiac structure and function. It can identify myocardial wall motion abnormalities, pericardial effusion, and signs of heart failure. Cardiac magnetic resonance imaging (MRI) provides detailed visualization of myocardial inflammation and edema, helping differentiate myocarditis from other causes of cardiac dysfunction.

Positron emission tomography (PET) scans with radiolabeled tracers can assess myocardial inflammation and aid in differentiating inflammatory processes from other etiologies. In cases where the diagnosis remains uncertain, or when there is a need for histopathological confirmation, endomyocardial biopsy may be considered.

Intramedullary hemophagocytosis can be found in other hematological disorders, and is therefore necessary but not sufficient for the diagnosis of MAS; it must be associated with the above-mentioned clinical and biological signs. Other cytological and/or histological tests may reveal active hemophagocytosis, but are less effective. bone marrow biopsy, for example, can help in the diagnosis and reveal of the etiology of the MAS (lymphoma, tuberculosis).

It's essential to consider other conditions that can present with similar clinical features, including viral myocarditis, autoimmune diseases (e.g., systemic lupus erythematosus), and other forms of systemic inflammatory syndromes.

Once the diagnosis is confirmed or strongly suspected, treatment should be initiated promptly. Managing acute myocarditis complicating MAS requires a multidisciplinary approach involving cardiologists, rheumatologists, and intensivists. Treatment aims to suppress the exaggerated immune response while addressing cardiac inflammation and dysfunction.

Etiological investigation is essential, as the cornerstone of treatment is the management of the triggering factor. However, in cases of diagnostic doubt, or when the efficacy of treatment of the cause is likely to be delayed (as in the case of treatment of tuberculosis or lymphoma), the cytokine storm should be rapidly inhibited. To date, there is no consensus on the treatment of secondary SALH. This is mainly due to the absence of prospective trials comparing different therapies [21].

Etoposide (VP16) at a dose of 150 mg/m² is the treatment of choice for secondary MAS, especially in cases of severe SALH. Etoposide is a type 2 topoisomerase inhibitor that rapidly regulates CD8+ LT activity [22]. When the infection is associated with EBV, it has shown superior efficacy to other historical chemotherapies [23]. However, no prospective studies in adults have evaluated the efficacy of VP16. VP16-induced apoptosis is not limited to CD8+ LTs alone, and leads to transient aplasia, increasing the risk of infection.

Since the advent of monoclonal antibodies, Rituximab, an anti-CD20, has shown remarkable efficacy in EBV infections by eliminating the B lymphocyte viral reservoir. The effect on viral load only seems to be effective after 2 weeks of treatment. It is therefore the treatment of choice for EBV-induced MAS, in association with VP16 [24].

Other possible treatments for MAS include intravenous immunoglobulins and corticosteroids. These molecules have shown relative efficacy, but carry a risk of therapeutic failure in almost 50% of cases [25]. Ruxolitinib is an inhibitor of Janus kinase (JAK), which is involved in the cellular signaling pathway responsible for inflammation, via activation of STAT proteins.

A mouse model study showed a significant increase in survival in mice with MAS treated with Ruxolitinib [26]. Since these publications, this treatment has been used in several cases of refractory MAS, with promising safety and efficacy data [27].

Studies showed that IL1β inhibition via anakinra (an IL1β receptor antagonist) can be used in the treatment of acute myocarditis in the context of various diseases where the inflammatory pathway is activated such as Macrophagic activation syndrome, mediterranean fever, adult Still's disease, but also autoimmune diseases such as rheumatoid arthritis [28,29]. But large-scale trials on higher-risk patients are needed to assess the potential benefit of this treatment.

The prognosis for patients with acute myocarditis complicating MAS depends on various factors, including the extent of cardiac involvement, the severity of systemic inflammation, and the timeliness of intervention. Long-term management focuses on monitoring cardiac function, preventing disease flares, and addressing potential complications such as heart failure and arrhythmias. Long-term management focuses on disease monitoring, preventing relapses, and optimizing cardiac function.

4. CONCLUSION

The convergence of Macrophagic Activation Syndrome and myocarditis represents a challenging clinical scenario that demands vigilance, prompt recognition, and targeted intervention. Collaboration among healthcare professionals and ongoing research efforts are essential for improving diagnostic accuracy, refining treatment strategies with tailored therapeutic interventions, and ultimately enhancing outcomes for affected individuals. By unraveling the complexities of this intersection, we can strive towards better outcomes and improved quality of life for patients with these overlapping conditions. A prospective study comparing septic cardiomyopathy with SALH is needed to determine whether these are two distinct entities, or whether they share a common pathophysiology.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscripts.

CONSENT

As per international standards or university standards, patient written consent has been collected and preserved by the author.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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