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Macrophage Activation Syndrome Complicating Rheumatoid Arthritis: A Case Report

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Abstract | **Case Report**

Macrophage activation syndrome (MAS) is a rare but potentially fatal complication that can occur during chronic inflammatory diseases such as rheumatoid arthritis (RA). We report the case of a 68-year-old female patient followed for progressive RA with severe joint involvement and subcutaneous rheumatoid nodules, complicated by MAS revealed by febrile pancytopenia. This case highlights the diagnostic challenges related to the non-specific presentation of MAS and emphasizes the importance of rapid management.

Keywords: Macrophage Activation Syndrome, Rheumatoid Arthritis, Pancytopenia.

INTRODUCTION

Macrophage activation syndrome (MAS), also known as secondary hemophagocytic lymphohistiocytosis (sHLH), is a severe and potentially fatal hyperinflammatory syndrome caused by uncontrolled activation of cytotoxic T lymphocytes and macrophages. This activation leads to a massive release of pro-inflammatory cytokines, resulting in multiorgan failure [1]. Although MAS is well described in systemic lupus erythematosus and adult-onset Still's disease, its occurrence in rheumatoid arthritis (RA) remains rare and likely underdiagnosed [1, 2]. Clinically, MAS often presents misleadingly, with non-specific signs such as persistent fever, pancytopenia, hepatosplenomegaly, elevated ferritin and triglycerides, and possible hepatic or neurologic involvement [2]. Due to this clinical polymorphism, diagnosis is often delayed, compromising timely treatment initiation. Diagnostic tools such as the H-score can now guide clinicians earlier toward MAS [1]. We present a case of MAS in a patient with active rheumatoid arthritis, illustrating the diagnostic complexity of this rare entity in autoimmune diseases.

CASE REPORT

We report the case of a 65-year-old woman with a 12-year history of seropositive, erosive rheumatoid arthritis, complicated by multiple rheumatoid nodules, particularly on the elbows and forearms. She was initially treated with methotrexate, then switched to leflunomide. Due to persistent inflammatory activity, tocilizumab was initiated six months prior to admission, in combination with low-dose corticosteroid therapy (5 mg/day prednisone).

The patient was hospitalized for a clinical presentation of general deterioration, including persistent fever at 39°C for five days, accompanied by profound fatigue, nausea, and anorexia. On admission, she was febrile (39.1°C), hypotensive (95/60 mmHg), and tachycardic (110 bpm), with oxygen saturation at 95% on room air. Clinical examination revealed a fatigued patient, conscious but confused, without any evident infectious focus. She presented with inflammatory subcutaneous nodules over the elbows, without signs of active peripheral arthritis.

Laboratory investigations showed:

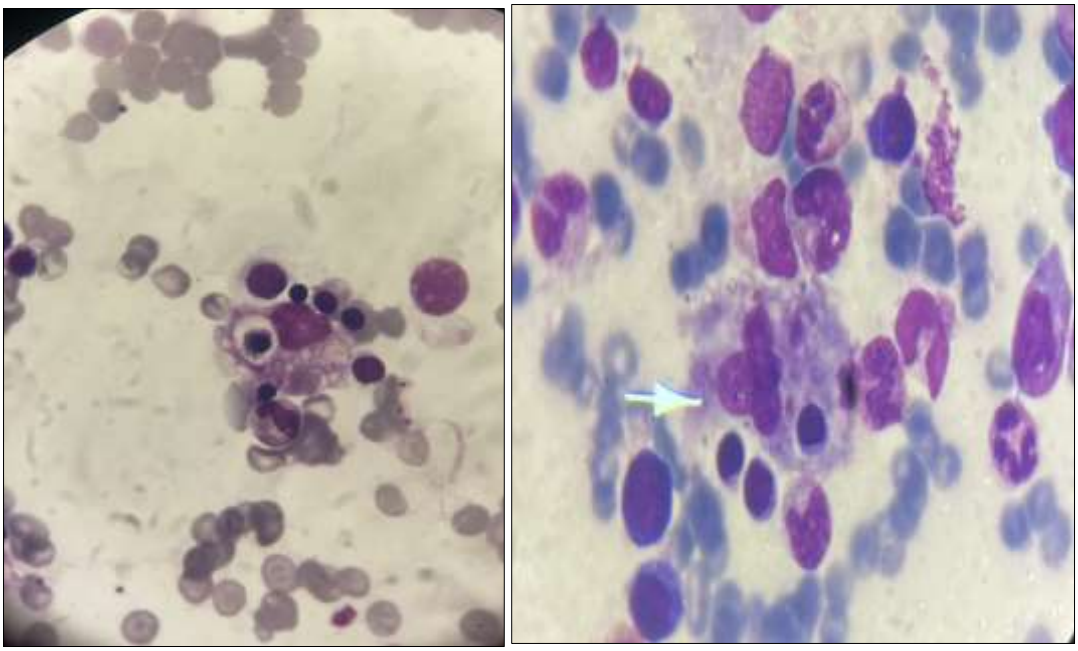
- Pancytopenia: hemoglobin 9.2 g/dL, leukocytes 2,900/mm³, platelets 52,000/mm³
- Marked inflammatory response: CRP 245 mg/L, ESR 85 mm/hr
- Hyperferritinemia: 4,300 ng/mL
- Hypertriglyceridemia: 3.8 mmol/L
- Elevated LDH: 580 U/L
- Moderately elevated liver enzymes: AST 85 U/L, ALT 72 U/L
- Low fibrinogen: 1.2 g/L
- Moderately elevated procalcitonin: 2.4 ng/mL

- Normal serum electrolytes and creatinine: 84 µmol/L, with estimated creatinine clearance of 70 mL/min

Blood cultures and an extensive infectious work-up including SARS-CoV-2 PCR, viral serologies (EBV, CMV, HIV, hepatitis B and C), and urine analyses were all negative. Bone marrow aspiration revealed activated macrophages exhibiting hemophagocytosis (Figures 1 and 2).

The H-score was calculated at 220, corresponding to a 93.5% probability of macrophage activation syndrome (MAS).

The diagnosis of MAS secondary to complicated rheumatoid arthritis was retained. The patient received intravenous methylprednisolone boluses (500 mg/day for 3 days), followed by oral corticosteroids at 1 mg/kg/day. The initial clinical course was favorable, with improvement in general condition, resolution of fever by day 3, and stabilization of laboratory parameters.



Figures 1 and 2: Images of hemophagocytosis by a macrophage cell seen under optical microscope

DISCUSSION

Macrophage activation syndrome (MAS) is a severe, potentially fatal complication of chronic inflammatory diseases, including connective tissue disorders. It is well recognized in systemic lupus erythematosus and systemic juvenile idiopathic arthritis but remains rarely reported in the context of rheumatoid arthritis (RA), which makes its diagnosis particularly challenging in this setting [1-3].

Our case falls within this uncommon framework. The patient, suffering from progressive RA treated with methotrexate and corticosteroids, developed an abrupt clinical picture characterized by high fever, deterioration of general condition, and pancytopenia. These signs, though nonspecific, are strongly suggestive of MAS when they occur together and warrant investigation for this syndrome [4]. The diagnosis was supported by a high H-score and confirmed by bone marrow analysis, which revealed numerous hemophagocytic images. It is now established that the central feature of MAS is a dysregulation of the cytotoxic immune response, leading to persistent activation of macrophages and T lymphocytes, with massive cytokine release (cytokine storm) [3-5]. This mechanism explains the multisystem clinical manifestations and characteristic laboratory abnormalities, including marked hyperferritinemia, hypertriglyceridemia, hypofibrinogenemia, and elevated lactate dehydrogenase (LDH). All these abnormalities were present in our patient, notably a ferritin level exceeding 2000 ng/mL, which strongly reinforced the suspicion of MAS.

The differential diagnosis of MAS in the context of RA under immunosuppressive therapy is challenging, as clinical manifestations can be mistaken for a severe disease flare or opportunistic infection [6]. However, certain features help distinguish MAS: the rapid onset of the clinical syndrome, the severity of cytopenia, and the disproportionately elevated ferritin levels. MAS induced or triggered by biologic agents (anti-TNF, tocilizumab, etc.) has also been reported in the literature. For instance, a similar case was described in a patient with axial spondyloarthritis treated with adalimumab [6]. This underlines the need for heightened vigilance in patients receiving biologic therapy, although

our patient was not on such agents at the time of presentation.

Management primarily relies on high-dose corticosteroid therapy, as initiated in our patient. In cases of treatment failure or unfavorable progression, additional immunosuppressants such as cyclosporine or etoposide may be required, but mortality remains high, especially when diagnosis is delayed or in the presence of severe co-infection [3, 4].

This case therefore highlights the importance for clinicians to consider MAS early in any unexplained febrile presentation in patients with RA, even in the absence of organomegaly. Prompt recognition of the clinical and biological profile, along with confirmation by bone marrow cytology, allows for the early initiation of appropriate treatment, which may improve prognosis.

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