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CASE REPORT

Macrophage activation syndrome associated with systemic lupus erythematosus: a case report and brief literature review

Síndrome de ativação macrofágica associada ao lúpus eritematoso sistêmico: relato de caso e breve revisão de literatura

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ABSTRACT

Introduction: Macrophage Activation Syndrome (MAS) is a rare and underreported, potentially fatal condition characterized by immunopathological hyperactivation resulting in increased cytokines and immune-mediated damage in multiple organs. This syndrome develops from Hemophagocytic Lymphohistiocytosis (HLH), which can be either primary, associated with genetic abnormalities, or secondary, correlated with underlying disorders such as infections, autoimmune/rheumatological conditions, metabolic disorders, or neoplasms. **Objective:** To report the case of a patient diagnosed with HLH secondary to Systemic Lupus Erythematosus (SLE) during hospitalization, who developed Macrophage Activation Syndrome. **Methods:** This case report described a patient diagnosed with SLE who developed MAS during hospitalization in the Central-West region of Minas Gerais. This study highlighted the histopathological, laboratory, and clinical changes presented, as well as their response to the therapy employed. **Case Report:** A 58-year-old female patient presented with intermittent fever, night sweats, inflammatory polyarthralgia, and oral ulcers for three weeks prior to hospital admission. The patient had a history of diabetes and a presumed diagnosis of seronegative rheumatoid arthritis three years prior, with irregular treatment. She presented with pancytopenia on admission exams, in addition to elevated levels of inflammatory markers (including ferritin), positive hemolysis tests, negative viral serologies, and positive autoantibodies. An HScore was applied, with an initial score of 206, evolving to 241 after a bone marrow study. Furthermore, the patient had 29 points on the EULAR/ACR classification criteria, allowing for a diagnosis of SLE (Systemic Lupus Erythematosus). The management involved pulse therapy with methylprednisolone, followed by maintenance with corticosteroids, combined with hydroxychloroquine and azathioprine, with good clinical and laboratory response, as well as prevention of complications. **Conclusions:** Due to the severity and lethality of MAS, its early recognition is important. Suspicion should always be raised in patients presenting with rheumatological diseases, associated with cytopenias, fever, and increased ferritin. The HScore can be a useful risk stratification tool. Finally, although there is no standard therapy to manage such cases, the use of corticosteroids and immunosuppressants is routine and shows good results in previous case reports.

Keywords: Hemophagocytic lymphohistiocytosis; Systemic lupus erythematosus; Macrophage activation syndrome.

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RESUMO

Introdução: A Síndrome de Ativação Macrofágica (SAM) é uma entidade rara e subnotificada, potencialmente fatal, que tem como característica a hiperativação imunopatológica que resulta em aumento de citocinas e danos imunomediados em múltiplos órgãos. Essa síndrome se desenvolve a partir da Linfohistiocitose Hemofagocítica (LHH) que pode ser tanto primária — associada a anormalidades genéticas — quanto secundária: correlacionada a distúrbios subjacentes, como: infecções, quadros autoimunes/reumatológicos, metabólicos ou neoplasias. **Objetivo:** Relatar o caso de uma paciente diagnosticada com LHH secundária a Lúpus Eritematoso Sistêmico (LES) durante hospitalização, que cursou com a Síndrome de Ativação Macrofágica. **Métodos:** Trata-se de um relato de caso de uma paciente diagnosticada com LES, durante a internação em um hospital do Centro-Oeste de Minas Gerais, que apresentou SAM. Este estudo foi realizado evidenciando as alterações histopatológicas, laboratoriais e clínicas apresentadas, bem como sua resposta à terapia empregada. **Relato de Caso:** Paciente do sexo feminino, 58 anos, iniciou com quadro de febre intermitente, sudorese noturna, poliartralgia de ritmo inflamatório, e presença de úlceras orais, durante 3 semanas previamente à internação hospitalar. Paciente previamente diabética e com diagnóstico questionável de Artrite Reumatoide soronegativa há três anos, em tratamento irregular. Apresentou pancitopenia em exames admissionais, além de níveis elevados de provas inflamatórias (incluindo a ferritina), provas de hemólise positiva, sorologias virais negativas e autoanticorpos positivos. Foi aplicado o HScore com pontuação inicial de 206 e evolução para 241 após realização do estudo medular. Além disso, paciente com 29 pontos nos critérios de classificação do EULAR/ACR possibilitando o diagnóstico de LES. O manejo realizado se deu através da pulsoterapia com metilprednisolona, seguido da manutenção com corticosteroides, associado à hidroxicloroquina e azatioprina, com boa resposta clínica e laboratorial, além de prevenção de complicações. **Conclusões:** Devido à gravidade e letalidade da SAM, torna-se importante o seu reconhecimento precoce. A suspeita deve ser sempre levantada em pacientes que apresentam doenças reumatológicas, associadas a citopenias, febre e aumento de ferritina. O HScore pode ser útil como ferramenta de estratificação de risco. Por fim, apesar de não haver terapia padrão para manejo dos casos, o uso de corticosteroides e imunossupressores é rotineiro e apresenta bons resultados em relatos de casos anteriores.

Palavras-chave: Linfo-histiocitose hemofagocítica; Lúpus eritematoso sistêmico; Síndrome de ativação macrofágica.

Introduction

Hemaphagocytic Lymphohistiocytosis (HLH) is a rare and underreported, potentially fatal condition characterized by ineffective immunity, caused by immunopathological hyperactivation, resulting in elevated cytokine levels and immune-mediated damage in multiple organs[1-3].

HLH was first described in the literature in 1939 by Scott and Rob-Smith as "Disease of the reticuloendothelial system" and associated with inevitable mortality. Subsequently, in 1952, it was described by Farquhar and Claireaux and recognized as a hereditary immune dysregulatory disease of childhood, termed "hematophagocytic reticulosis". Risdall

was one of the first to describe HLH associated with a viral infection[4,5]. Back in 1991, Wong et al (1991)[6] reported cases of reactive hemophagocytosis in the bone marrow associated with Systemic Lupus Erythematosus (SLE) disease activity. After new cases associated with other autoimmune diseases were reported, the term "Autoimmune-associated Hemophagocytic Syndrome" was proposed[7]. HLH encompasses a wide range of conditions and can be classified as primary or secondary. Primary HLH is associated with genetic abnormality, including autosomal recessive familial HLH, and familial erythrophagocytic HLH. Secondary HLH is associated with underlying secondary disorders, such as infection, autoimmune/rheumatological, metabolic, or neoplastic conditions. Secondary HLH includes Macrophage Activation Syndrome (MAS), among other forms associated with immune-mediated rheumatic diseases. While primary HLH tends to manifest in childhood, secondary HLH has a progressive incidence with advancing age[3,4]. The incidence of primary HLH is estimated at approximately 1 case per 50,000 live births in countries like Sweden, with scarce data in Latin American countries. Regarding secondary cases, the incidence is approximately 4.2 cases per 1 million inhabitants per year[2].

The clinical presentation of HLH occurs acutely, with rapid progression to multiple organ failure. The main clinical manifestation is fever, frequently accompanied by hepatosplenomegaly, generalized lymphadenomegaly, encephalopathy, and hemorrhagic manifestations. In severe cases, there may be cardiac, pulmonary, and renal involvement. Laboratory findings most commonly include pancytopenia, elevated liver enzyme levels, hypertriglyceridemia, hypofibrinogenemia, and extremely high ferritin levels. The pathological hallmark is hemophagocytosis in the bone marrow, spleen, or lymph nodes; however, it is observed in only about 60% of patients, and its absence does not exclude the diagnosis[8-9].

MAS, considered a secondary form of HLH, is a rare and potentially fatal complication mainly associated with rheumatological diseases. It is predominantly observed in Systemic Juvenile Idiopathic Arthritis (SJIA) and adult-onset Still's disease, but it can occur in other rheumatological diseases such as SLE and Kawasaki disease. The term MAS is used to describe an hyperinflammatory state associated with autoimmune diseases. MAS differs from other HLH due to generally higher expected values of fibrinogen, platelets, and hyperferritinemia, as well as potentially more significant liver dysfunction. Its pathogenesis involves the excessive activation of macrophages and T lymphocytes, with a notable role for interferon gamma and interleukin 18. In adults, the syndrome is quite uncommon; the prevalence of MAS in SLE is estimated to range between 0.9 and 4.6%[8,9,11,12].

Methods

This study was conducted after the patient consented to participate in the case report by signing the Informed Consent Form (ICF) and after it was accepted by the Ethics and Research Committee for the development of this work under Opinion No. 7,791,908. A patient with SLE who presented with confirmed HLH during hospitalization in the state of Minas Gerais was included. For the diagnosis of the disease in question, the HScore tool (Appendix 1) was used, which estimates the probability of secondary HLH. Based on the review of the patient's medical records during her hospital stay and the analysis of the complementary examinations performed, the variables that make up the HScore were evaluated, namely: presence of immunosuppression, history of temperatures, presence of organomegaly, number of cytopenias, ferritin value, triglycerides, fibrinogen, aspartate aminotransferase, and presence of hemophagocytosis in bone marrow aspirate.

Case report

A 58-year-old female patient presented with intermittent high fever (38-39ºC), night sweats, asthenia, hyporexia, unquantified weight loss, and inflammatory polyarthralgia in her hands, wrists, feet, and ankles, with morning stiffness lasting more than 30 minutes daily and associated joint swelling, for three weeks prior to admission. She also reported oral ulcers and xerostomia.

She had a history of Diabetes Mellitus (DM), with the use of Gliclazide. In addition, she reported a questionable diagnosis of seronegative Rheumatoid Arthritis three years prior, with irregular treatment and follow-up. She had used methotrexate and prednisone, which were discontinued two months before the onset of current symptoms due to gastrointestinal intolerance.

The patient had one previous pregnancy, delivered via cesarean section, no history of abortions, and had been menopausal for approximately 10 years. She denied having had other surgeries. She had no history of smoking, alcoholism, or drug addiction. She also had no history of previous hospitalizations due to infectious diseases or a history of thromboembolic events.

Upon admission, the patient was in poor general condition, pale, and presented joint pain in the wrists, ankles, and knees, with signs of arthritis in the right ankle, and oral ulcers, without other lesions in the mucosa or skin. There were no alterations in the cardiorespiratory system. There was no palpable visceromegaly and lymphadenopathy on physical examination. On neurological examination, the patient did not present behavioral changes or altered levels of consciousness; however, a global reduction in muscle strength, grade 4, symmetrical, was noted. On the first day of hospitalization, she had a single episode of tonic-clonic seizure, which was promptly reversed. She did not show signs of meningeal irritation.

During admission exams, she presented with pancytopenia, with values shown in Table 1. Given the situation, an infectious condition was initially suspected, and empirical use of a 4th-generation cephalosporin antimicrobial was initiated for 7 days. Infectious screening

was also performed (abnormal elements and urinary sediments, urine culture, blood culture, and chest X-ray), which subsequently proved negative.

In addition to pancytopenia, as shown in Table 1, the patient exhibited a significant increase in ferritin (> 2,000), elevated C-Reactive Protein (CRP) and positive hemolysis tests, namely: elevated Lactate Dehydrogenase (LDH), reactive direct Coombs test, and decreased haptoglobin. Furthermore, she had hypertriglyceridemia, increased hepatic canalicular enzymes (Alkaline Phosphatase and Gamma GT), and transaminases (Aspartate Aminotransferase and Alanine Aminotransferase). There were no changes in renal waste products or liver function, and no hydroelectrolytic disturbances were identified.

Additionally, viral serologies were requested, which came back negative for HIV, Hepatitis A, B, and C. Chronic phase antibodies (IgG) for Epstein-Barr and Cytomegalovirus were present. Reactivity for syphilis was found with a positive Venereal Disease Research Laboratory (VDRL) test at a titer of 1:8. However, the Fluorescent Treponemal Antibody Absorption (FTA-ABS) test was nonreactive, indicating a likely false-positive in the non-treponemal test, since it showed no reaction. Furthermore, the presence of a positive Antinuclear Factor (ANF) at a titer of 1:640, Nuclear-Homogeneous (NH) standard, was also found.

Imaging exams were requested, and no acute ischemic changes or hemorrhagic foci were observed in the cranial tomography. Abdominal tomography revealed homogeneous splenomegaly (volume of 740 cm^3, reference value 340 cm^3).

Given the above data, the hypothesis of MAS was initially raised, since the patient had a score of 206 points on the HScore (appendix 1). This result corresponds to an 88-93% probability of hemophagocytic activity in a patient with rheumatological disease, such as SLE, and, to a lesser extent, a hematological or infectious disease.

Based on these findings, antibodies with greater specificity for SLE were assessed, as well as complement system markers. Of these, Anti-DNA was positive at a titer of 1:20. Consumption of complement components C3 and C4 was also positive. The following markers were not positive: Anti-RO, Anti-La, Anti-ribonucleoprotein (RNP), and anti-Smith antibody (SM), as well as Lupus anticoagulant and Anticardiolipin.

The classification criteria of the European League Against Rheumatism/American College of Rheumatology 2019 (EULAR/ACR 2019), Appendix 2, were applied. The patient presented 29 points of these criteria, which confers a higher probability of a SLE diagnosis. The patient scored in: Fever (2 points), Autoimmune hemolysis (4), Seizure (5), Oral ulcers (2), Joint involvement (6), C3 and C4 consumption (4), Anti-DSDNA (6). Bone marrow aspiration and immunophenotyping were performed on the patient, which revealed the presence of mild dysplasia, possibly reactive, and the absence of signs of primary bone marrow disease. The bone marrow biopsy revealed the presence of: hypercellular bone marrow, with hyperplasia of elements from the three myeloid lineages and foci of hemophagocytic activity (Figure 1). Thus, the HScore for MAS was recalculated, yielding a total of 241 points, indicating a probability greater than 95% of the presence of MAS in a patient with probable SLE.

Regarding management, pulse therapy with methylprednisolone 500mg was performed for 3 consecutive days (on the 14th day - D14 - of hospitalization. It was associated with an antiparasitic for prophylaxis of disseminated strongyloidiasis. After pulse therapy, the patient received prednisone at a dose of 0.5 mg/kg daily, combined with hydroxychloroquine 5 mg/kg/day and azathioprine 2 mg/kg/day. After these measures were taken, the patient showed gradual improvement in her general condition, as well as a reduction in arthralgia and no new fever spikes. Furthermore, progressive improvement in hematological parameters was observed, as shown in Table 1.

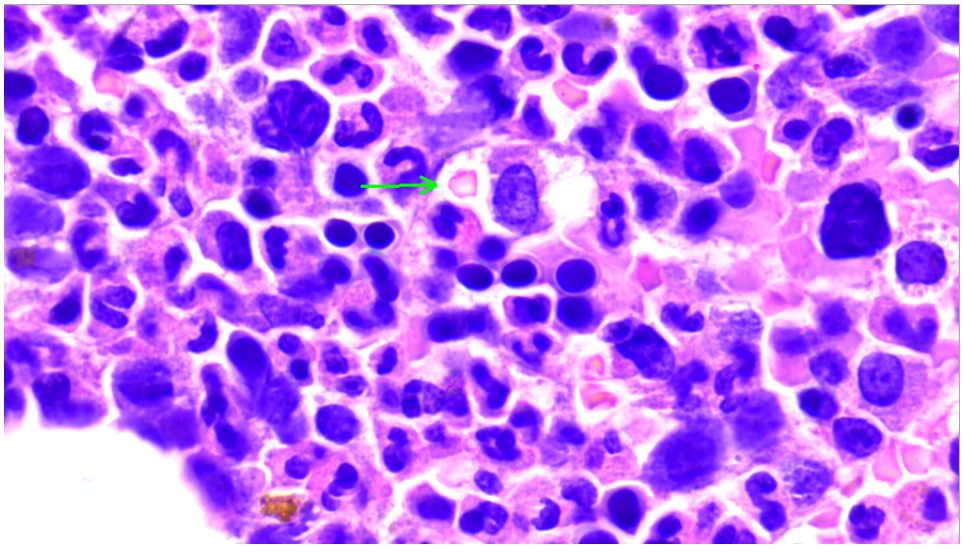


Figure 1. Hemophagocytosis

Source: Author's own elaboration.

After symptom control, the patient was discharged from the hospital with a referral for specialist follow-up, with consideration given to corticosteroid tapering and adjustment of the immunosuppressive therapy.

Consequently, the patient was reassessed 3 and 7 weeks after discharge. In the first assessment, she already showed complete improvement of the joint condition and a reduction in muscle weakness. She did not have new febrile episodes. She was using prednisone 0.5 mg/kg/day (discharge dose), associated with azathioprine 2 mg/kg/day, and hydroxychloroquine 5 mg/kg/day. From a laboratory standpoint, she showed only monocytopenia due to anemia (Hb 11.6), normalization of C3, but persistently low C4 levels, transaminases within reference values, and partial improvement of the cholestatic pattern with Gamma GT (412 U/L) and Alkaline Phosphatase (112 U/L).

Regarding the second evaluation, 7 weeks after hospital discharge, the monocytopenia (anemia) present in the previous evaluation resolved. The cholestatic pattern continued to decline, with normalization of alkaline phosphatase and a decrease in gamma-GT (280 U/L). Furthermore, the improvement in joint function and muscle strength continued. Corticosteroid therapy was tapered at 0.3 mg/kg/day of prednisone, with a proposed reduction to 0.2 mg/kg/day for the next 15 days. Azathioprine and hydroxychloroquine were maintained at the previously mentioned doses. Therefore, the objective was to maintain regular follow-up with a specialist to taper corticosteroid therapy while actively monitoring disease activity.

Table 1. Tests performed on the patient during hospitalization.

	D1	D3	D5	D14	D17	D27	Reference values
Hemoglobin	9,0	8,4	7,9	8,1	9,2	10,2	12-16 g/dl
Total Leukocytes	1100	1800	2200	2330	3030	3800	4000-11000/mm³
Neutrophils	718	1269	1734	1790	1333	1876	1500-8000 /µL
Platelets	84000	90000	130000	186000	225000	272000	150-450.000/L
RCP	24	22		29			<10mg/L
Iron		48		44			50-150 mcg/dL
Haptoglobin		60		10			30-200 mg/dL
Vitamin B12		404		318			200-900 pg/mL
Transferrin Saturation Index		48		19			20-50%
Ferritin		2000		3390			10-200 ng/mL
Reticulocytes		0,9%		0,5%			0,5-2,5%
DHL		488		449			100-280 U/L
Direct Coombs		Reagent					Non-reactive
Indirect Coombs		1:32					Non-reactive
Alkaline Phosphatase					225	200	30-120 U/L
GT Range		722			884	889	5-43 U/L
AST		72		93	38	55	5-40 U/L
ALT		148		44	27	39	7-56 U/L
VHS		25					20 mm/h
Total bilirubin			0,53	0,5	0,36		0,2-1,2 mg/dL
Urea			13				10-50 mg/dL
Creatinine			0,63	0,37	0,37		0,6-1,2 mg/dL
Fibrinogen				314	362		200-400 mg/dL
Triglycerides			255	336			< 150 mg/dL
Folic Acid				5,81			3-20 ng/mL
VDRL				1:8			Non-reactive
FTA ABS IgM/IgG					NR		Non-reactive

Caption: D = Day of admission; CRP = C-Reactive Protein; LDH = Lactate Dehydrogenase; AST = Aspartate Aminotransferase; ALT = Alanine Aminotransferase; ESR = Erythrocyte Sedimentation Rate; VDRL = Venereal Disease Research Laboratory; FTA-ABS = Fluorescent Treponemal Antibody Absorption; NR = Non-reactive.

Discussion

Secondary MAS in SLE is a serious and potentially fatal complication. In these patients with SLE, MAS progresses rapidly, with a higher likelihood of early severe organ dysfunction. In advanced stages, treatment can be challenging, increasing the risk of mortality, estimated at approximately 4–19%[15-16].

Several sets of diagnostic and classification criteria are used to identify HLH. The HScore (see Appendix 1) is a validated tool for estimating the probability of secondary HLH. It is scored based on the presence of immunosuppression, body temperature, organomegaly, the number of cytopenias, ferritin, triglycerides, fibrinogen, aspartate aminotransferase. It is also considered the presence of hemophagocytosis in a bone marrow aspirate. The probability of diagnosing HLH varies according to the score, with scores ≤ 90 representing less than 1% probability and scores ≥ 250 indicating more than 99% probability of diagnosis[10].

Early diagnosis of MAS is particularly challenging, since there are no characteristic clinical manifestations or specific laboratory findings. In addition, overlap with other diseases makes diagnosis even later, which increases its lethality[2]. SLE is an autoimmune disease that affects multiple systems, including the skin, serous surfaces, joints, kidneys, and central nervous system. In SLE, MAS may be associated with or mimic acute exacerbation of the disease, as both pathologies share some common characteristics, such as fever, splenomegaly, lymphadenopathy, and blood cytopenias. In general, MAS can occur in association with the first SLE flare-up[13], as observed by Ammouri Wafa et al. (2022)[17], in which 35% of patients who presented with MAS were in the context of a first SLE flare-up16, and also by Pierre-Edouard Gavand et al. (2017)[18], in which 45% presented as a primary diagnosis of the rheumatological disease in association with the hyperinflammatory state.

Clinical and laboratory signs may overlap between SLE and MAS. Wenxun Lin's et al. (2024)[15] study compared characteristics between patients with MAS secondary to SLE and with isolated SLE. It was observed that patients with MAS had an earlier age of onset, however, there was no significant difference in gender distribution. The incidence of hepatomegaly and splenomegaly was significantly higher in the SAM secondary to SLE group. Furthermore, patients with MAS presented a higher proportion of neurological and psychiatric involvement compared to patients with isolated SLE. Moreover, there was a significant increase in the mortality rate in the MAS secondary to SLE group[15].

Fever is an extremely common symptom among patients with MAS secondary to SLE and can be attributed to the inflammatory cytokine storm. Although it can be observed in almost all patients with MAS, it cannot be considered a specific symptom of this condition, since it can be associated with SLE flare-ups or concomitant infections[15,17].

Hematologic involvement is very common in SLE, but pancytopenia or involvement of two cell lineages, mainly anemia and thrombocytopenia, are more frequent in MAS associated with SLE[17]. Increased ferritin levels are less frequent in cases of isolated SLE than in MAS[20]. Regarding anemia, hemophagocytosis is not the only mechanism involved; the storm of secreted cytokines also causes inhibition of hematopoiesis. In patients with MAS, coagulopathy may occur, including prolongation of Prothrombin Time (PT) and Activated Partial Thromboplastin Time (aPTT), fibrinogen tends to be reduced, and D-dimer may be elevated. Furthermore, liver damage, with increased transaminases, tends to be presente[17].

Ferritin is a sensitive test for MAS and should be checked in all patients with new, ongoing, or worsening symptoms suggesting MAS. The lower cutoff limit is typically 500 µg/l. However, according to Liu et al. (2017)[21], optimized ferritin cutoff values from 662.5 ng/ml enhance its positive predictive value for the pathology. Nevertheless, ferritin levels in MAS can reach values exceeding 5,000 µg/l, reinforcing the diagnostic hypothesis of Macrophage Activation Syndrome[19,21].

In addition to ferritin, low levels of high-density lipoprotein (HDL) are predictive factors of MAS secondary to SLE and represent an independent prognostic factor. Elevated triglyceride levels are not specific to MAS but are frequently included in diagnostic criteria. In patients with MAS secondary to SLE, low HDL levels are more common than hypertriglyceridemia[15,18,19].

Patients with MAS secondary to SLE have higher levels of C-reactive protein (CRP), and a cutoff value of 90 mg/L has been proposed to distinguish these conditions. Elevated CRP levels may be associated with primary disease activity or secondary infections. Monitoring dynamic changes in CRP levels may help differentiate between MAS and disease activity[15]. However, in the context of Macrophage Activation Syndrome, elevated CRP levels, when present, are associated with an independent risk factor for ICU admission[18].

A decrease in erythrocyte sedimentation rate (ESR) is also characteristic of MAS. This reduction may reflect hypofibrinogenemia secondary to fibrinogen consumption and liver dysfunction. Reduced ESR can help differentiate MAS from worsening SLE. Suspicion of MAS may arise when ESR is low and ferritin is elevated[19].

Histopathological evidence of hemophagocytosis cannot be a sole diagnostic criterion for MAS but it is useful in the differential diagnosis. Hemophagocytosis in bone marrow aspirates may not be present at symptoms onset, and its absence does not rule out the diagnosis[19]. It is important to emphasize that hemophagocytosis can be observed in other conditions, such as Langerhans cell histiocytosis; therefore, the analysis of other clinical/laboratory parameters is important[23].

Despite the severity and potential lethality of MAS, there are no specific treatment guidelines in the literature, and the level of evidence on available outcomes remains low. Though not supported by substantial evidence, high-dose glucocorticoids are the primary treatment for MAS triggered by rheumatological diseases[14,21].

In their literature review, Baldo et al. (2025)[14] observed that glucocorticoids were frequently used to treat MAS.

Among the available options, methylprednisolone or prednisolone were used in 90% of cases. Glucocorticoids were mainly used in conjuction with other medications, and only 14% of MAS cases were treated as monotherapy.

Currently, there are no clinical trials supporting guidelines for treating MAS. Treatment is primarily based on clinical experience or reference to treatment methods used for other types of HLH. Methylprednisolone at a dose of 10–30 mg/kg/day, maximum of 1 g/day for 1 to 3 days, followed by 1 mg/kg/day intravenously or orally, is reported in almost 60% of studies. Cyclosporine (2–7 mg/kg/day) was the most frequently used medication, in addition to glucocorticoids, with an overall favorable efficacy and safety profile. Anakinra is the most commonly used biological treatment for MAS, especially in SJIA. Other therapeutic options reported in the literature include etoposide (50–150 mg/m²/dose, 1–2 doses/week), intravenous immunoglobulin (IVIG) (0.4–1 g/kg/day for 2 to 5 days), and plasmapheresis[14,21,24].

Anakinra is a recombinant interleukin-1 (IL-1) receptor antagonist that acts by competitively blocking the binding of the pro-inflammatory cytokines Interleukin-1α and Interleukin-1β to the type I interleukin-1 receptor, which is expressed in various tissues. In this context, Anakinra functions as an immunomodulatory agent targeting IL-1, a cytokine central to the pathophysiology of MAS (systemic inflammatory disease). Anakinra is primarily used in cases associated with systemic juvenile idiopathic arthritis (SJIA) and adult-onset Still's disease, especially when there is failure or an insufficient response to corticosteroids and cyclosporine[25-27].

Carter et al. (2019)[28] suggest a treatment protocol for MAS involving the administration of intravenous methylprednisolone (1 g/day for 3 to 5 days) combined with intravenous immunoglobulin G (1 g/kg/day for 2 days) as first-line therapy. If there is clinical worsening, the second-line therapy suggested by the authors indicates the use of biologics, such as Anakinra (1 to 8 mg/kg/day). Finally, if the disease remains refractory, third-line therapy with etoposide is recommended (150 mg/m2 twice a week for 2 weeks, followed by once a week for 6 weeks). Additionally, cyclosporine (2 to 7 mg/kg/day) can be used as a parallel treatment for early MAS or to prevent recurrence[24]. This suggested therapy aligns with recommendations from other authors, such as Liu et al. (2017)[21] and Gavand[18].

However, it is important to emphasize that in the present clinical case, cyclosporine was not used due to its unavailability at the hospital at the time of hospitalization, preventing its use despite preliminary evidence supporting its adjuvant efficacy. On the other hand, azathioprine, although not considered first-line in the specific management of MAS, is widely indicated in the treatment of systemic SLE, mainly as a corticosteroid-sparing agent, which was used for the management of MAS in the patient in the case report in question[30]. Given the temporary unavailability of cyclosporine, treatment with azathioprine associated with glucocorticoid was instituted, aiming not only to achieve general immunosuppressive control of the underlying disease (SLE) but also to reduce steroid dependence, in accordance with available therapeutic guidelines for SLE and its secondary complications[31].

Conclusion

In summary, due to the severity of MAS and its potential lethality, early recognition and intervention are crucial. The diagnosis of MAS can be challenging, as it may mimic or represent the initial manifestation of SLE. Therefore, in patients with rheumatological diseases, MAS should be considered whenever fever is present in associated with bicytopenia or pancytopenia, elevated markers such as ferritin, and organ dysfunction, especially hepatic dysfunction. The HScore may be a useful tool for risk stratification in MAS.

Finally, although there is no standard therapy for managing cases, the use of corticosteroids and immunosuppressants is routine and shows good results, as reported in previously cited cases. This is especially true in scenarios where early diagnosis is made.

Author's contributions

We describe contributions to the papers using the taxanomy (CRediT) provided above: *Conceptualization, Investigation, Writing – review & editing*: IB Lopes. *Investigation, Methodology, Supervision, Writing – original draft*: M de F Lopes. *Data curation, Investigation, Project administration, Writing – original draft*: PC Morato Filho.

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Appendix 1:

Hscore[10]

Variables		Score
Fever	<38,4°C	0
	38,4°C - 39,4°C	33
	>39,4°C	49
Organomegaly	Absent	0
	Hepatomegaly or Splenomegaly	23
	Hepatomegaly and Splenomegaly	38
Cytopenia*	One cell lineage	0
	Two cell lineages	24
	Three cell lineages	34
Triglycerides(mg/dl)	<132.7	0
	132.7-354	44
	>354	64
Fibrinogen (mg/dl)	>250	0
	<250	30
ASL (UI/L)	<30	0
	>30	19
Ferritin (ng/dl)	<2.000	0
	2.000-6.000	35
	>6.000	50
Hemophagocytosis	Absent (or not tested))	0
	Present	35
Immunosuppression**	Absent	0
	Present	18

*Defined as a hemoglobin level < 9.2 g/dL and/or a white blood cell count < 5,000/mm³ and/or a platelet count < 110,000/mm³.

**Human immunodeficiency virus (HIV) positive or receiving long-term immunosuppressive therapy (i.e., glucocorticoids, cyclosporine, azathioprine).

Source: Adapted from Fardet L, Galicier L, Lambotte O, Marzac C, Aumont C, Chahwan D, et al. Development and validation of the HScore, a score for the diagnosis of reactive hemophagocytic syndrome. Arthritis Rheumatol. 2014;66(9):2613-20.

Appendix 2:

Eular/ACR 2019 - European League Against Rheumatism/American College of Rheumatology; SLE = Systemic Lupus Erythematosus[29]

Clinical domains			Score
Constitutional	Fever	>38°C	2
Hematologic	Leukopenia	<4.000 cel/mm³	3
	Thrombocytopenia	<100.000 cel/mm³	4
	Autoimmune hemolysis	[d]	4
Neuropsychiatric	Delirium		2
	Psychosis		3
	Seizure (generalized or focal)		5
Mucocutaneous	Non-scarring alopecia		2
	Oral ulcers	[e]	2
	Subacute or discoid cutaneous lupus erythematosus		4
	Acute cutaneous lupus		6
Serositis	Pleural or pericardial effusion		5
	Acute pericarditis		6
Musculoskeletal	Joint involvement	[f]	6
Kidney	Proteinuria (> 0.5 g/24 hours)		4
	Renal biopsy class II or class V lupus nephritis		8
	Renal biopsy class III or class IV lupus nephritis		10
Immunologic domains			
Antiphospholipid antibodies	Anticardiolipin antibodies or Anti-β2 glycoprotein I antibodies or Lupus anticoagulant		2
Complement system proteins:	Low C3 or low C4		3
	Low C3 and low C4		4
SLE-specific antibodies:	Anti-dsDNA antibody or Anti-Smith antibody		6

[a] Patients are only eligible for these criteria if they have a positive ANA ≥ 1:80.

[b] Criteria do not need to occur simultaneously. Only the highest-weighted criterion within a single domain should be used. SLE must be the most likely explanation for each criterion.

[c] Each criterion is assigned a weight of 2 to 10. If the patient's total score is 10 or higher, and at least one clinical criterion is met, the disease is classified as SLE.

[d] Evidence of autoimmune hemolysis (such as the presence of reticulocytosis, low haptoglobin, elevated indirect bilirubin, elevated lactate dehydrogenase) and direct antiglobulin test (direct Coombs test).

[e] This criterion can be observed during physical examination or when reviewing a photograph.

[f] Joint involvement is defined as synovitis in ≥ 2 joints characterized by swelling or effusion, or tenderness in ≥ 2 joints with at least 30 minutes of morning stiffness.

ANA = antinuclear antibodies; anti-dsDNA = double-stranded DNA antibodies (dsDNA).

Source: Adapted from Mehta P, Cron RQ, Hartwell J, Manson JJ, Tattersall RS. Silencing the cytokine storm: the use of intravenous anakinra in haemophagocytic lymphohistiocytosis or macrophage activation syndrome. Lancet Rheumatol. 2020;2(6):e358-e367. doi:10.1016/S2665-9913(20)30096-5.

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