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Management Challenge of Coexistence of Macrophage Activation Syndrome, Systemic Lupus Erythematosus, and Hepatitis B: Case Report

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ABSTRACT

Hemophagocytic lymphohistiocytosis (HLH) is a rare and potentially fatal clinical and histological entity. Macrophage Activation Syndrome (MAS) is an HLH secondary to rheumatic and autoimmune diseases. Secondary MAS in systemic lupus erythematosus (SLE) is underdiagnosed. Its treatment is not yet standardized. The treatment of MAS in the context of SLE primarily involves corticosteroids and immunosuppressants, with the potential addition of Intravenous Immunoglobulins (IVIG) and biological treatments for refractory cases. Early detection and prompt intervention are crucial to reduce associated mortality. The presence of infection worsens the patient's prognosis. The coexistence of SLE and hepatitis B during MAS is rarely described in the literature, and its management remains debated. We report the case of a 42-year-old Malagasy woman presenting with SLE complicated by MAS at the time of diagnosis, associated with viral hepatitis B.

1 | Introduction

Hemophagocytic lymphohistiocytosis (HLH) is an aggressive life-threatening disease that involves uncontrolled activated lymphocytes and macrophages that secrete excessive cytokines [1]. HLH can be primary due to a genetic abnormality or secondary (sHLH) to a chronic rheumatic disease or autoimmune diseases, an infection, or cancers. According to Kaçar et al., secondary HLH appears to be more frequent than primary HLH [1]. Viral infections, including cytomegalovirus and herpes simplex virus, are common causes of sHLH [2, 3]. Viral hepatitis B is an extremely rare cause of sHLH [4] Macrophage activation syndrome (MAS) includes HLH secondary to chronic rheumatic diseases and autoimmune diseases [5]. MAS secondary to Systemic Lupus Erythematosus (SLE) is rare, with an incidence ranging from 0.9% to 4.6% [6]. The occurrence of MAS at the time of diagnosis is extremely rare [7]. The HLH-2004 protocols are the standard guidelines for the treatment of HLH, combining chemotherapy and immunotherapy with agents such as etoposide, dexamethasone, and cyclosporine A. These protocols have significantly improved patient survival, although toxicity and risk of infections remain major [8–10]. This protocol was also effective for the treatment of sHLH secondary to viral hepatitis B [4]. We report the case of a 42-year-old Malagasy woman presenting with SLE complicated by MAS at the time of diagnosis, associated with viral hepatitis B.

Summary

- Our patient's complex clinical presentation underlines the difficulty of managing MAS-SLE and the need for multidisciplinary management.
- This case report could be considered as additional data on secondary MAS at the time of diagnosis of SLE.
- Identification of elevated ferritin levels should be regarded as a warning sign, requiring urgent investigation for the diagnosis of MAS-SLE.

2 | Case History

Our 42-year-old patient was admitted to the rheumatology department in November 2022 for further management of febrile polyarthralgia and pancytopenia. Her history included 5 pregnancies, 4 parities, and 0 abortions, with pregnancy terminated at 21 amenorrhea weeks. She had no other particular personal or family history.

For about a month, her history was characterized by a fever associated with asthenia and inflammatory polyarthralgia (small, medium and large joints), without deformity. She subsequently reported chest pain, a productive cough with whitish sputum, predominantly nocturnal, progressively worsening exertional dyspnea, and edema of the lower limbs.

Clinical examination on admission revealed temperature at 37.2°C, tachycardia at 110 beats/min, arterial hypertension at 180/100 mmHg, and altered general condition with asthenia, SPI 3, and anorexia. She reported intermittent acrosyndrome of the hands and feet with no ulcer complications. Rheumatological examination revealed no true synovitis or tenosynovitis. Abdominal and cardiac examination revealed painful hepatomegaly, turgidity of the jugular veins, hepatojugular reflux, and bilateral, soft, painless, bucketing edema of the lower limbs. There was no evidence of deep venous thrombosis. Pleuropulmonary examination revealed a dullness and abolition of vesicular breath sounds, particularly on the right. Abdominal examination suggested mild ascites, with no splenomegaly. Mucocutaneous examination revealed no particular abnormalities. The lymph nodes were free.

Pre-admission laboratory tests revealed moderate pancytopenia, biological inflammatory syndrome, elevated D-dimer, hyper-creatininemia, hypertriglyceridemia, and normal liver function tests. Table 1 summarizes the laboratory tests before and during hospitalization.

3 | Methods: Differential Diagnosis, Investigations and Treatment

Faced with these chronic multi-systemic clinical presentations and laboratory findings associating altered general condition, inflammatory polyarthralgia, intermittent acrosyndrome, polysseritis (ascites, pleurisy and probably pericarditis), pancytopenia, and biological inflammatory syndrome, the diagnostic hypotheses evoked were a relapsing dysimmune disease, a severe infection, or a hematological malignancy. Biological tests confirmed the persistence of the abnormalities found prior to admission (Table 1).

Additional laboratory tests revealed (Table 1): polyclonal hypergammaglobulinemia, hypoalbuminemia, hypoprotidemia, hyponatremia, 24 h proteinuria at 0.65 g, ferritinemia at 2675.56 ng/mL, normal prothrombin levels, activated partial thromboplastin time at 53.7 s. The Hbs Antigen was positive. The viral load could not be measured due to financial constraints. Other microbiological tests hepatitis B serology, HIV serology, acid-fast bacilli (AFB) search in sputum, COVID-19 polymerase chain reaction (PCR) were negative. The anti-nuclear antibody assay was positive at 1280, speckled, and anti-native DNA at 380 IU/mL. Myelogram showed a rich marrow with cell lysis and numerous macrophages. Chest X-ray revealed a right pleural effusion of moderate size and cardiomegaly with a cardiothoracic index of 0.6. Transthoracic echocardiography showed a 13.2 mm non-compressive pericardial effusion and dilated heart disease of ischemic origin, with a left ventricular ejection fraction of 35%.

At the end of this long investigation, we concluded to a macrophagic activation syndrome on the basis of HLH criteria in 2004 corresponding to 5 positives criteria out of 8 criteria (a fever, pancytopenia, hypertriglyceridemia, hyperferritinemia and presence of hemophagocytosis on myelogram) and a high HScore of 204, that is, a probability of 86 to 93%, secondary to active SLE with a SLEDAI 21 score meeting the criteria for EULAR/ACR classification in 2019, associated with viral hepatitis B whose activity could not be specified.

4 | Conclusion and Results: Outcome and Follow-Up

After a multidisciplinary consultation meeting, pulse methylprednisolone therapy at a dose of 2 mg/kg/d was started on day 21 of hospitalization. This treatment was combined with LAMIVUDINE 150 mg/d. Unfortunately, the patient died on day 2ème of the corticosteroid treatment following multivisceral failure.

5 | Discussion

We report a case of a patient diagnosed with SLE with fever, leukopenia, thrombocytopenia, pleurisy, pericarditis, polyarthritis, and renal involvement with 24-h proteinuria of 0.65 g/L [11], positive antinuclear antibodies, and anti-DNA antibodies with high activity since the SLEDAI score was 21 [12]. Our patient meets the 2019 ACR/EULAR criteria for SLE [13] with a score of 18. The SLE is associated with viral hepatitis B whose activity could not be determined and complicated by MAS. Macrophagic activation syndrome secondary to SLE is rare. Its prevalence is estimated at 0.9% to 4.6%. The diagnosis of MAS associated with SLE remains a challenge for the clinician, as MAS shares certain clinical and biological features similar to relapsing SLE [14–16]. Hyperferritinemia is considered the main significant parameter to distinguish between the two, with a sensitivity and specificity of approximately 100% [17]. It should alert clinicians to conduct a thorough and urgent investigation [6]. MAS rarely occurs at the onset of SLE [7]. Only Wang et al. reported that MAS was present

TABLE 1 | Summary of laboratory test results before and during hospitalization.

Paraclinical examinations	1 month before hospitalization	During hospitalization
Hemogram	Hemoglobin: 8.9 g/dL White blood cells: 2.80G/L Platelet: 103G/L	Hemoglobin: 8.9 g/dL White blood cells 3.28G/L Platelet 83G/L
Erythrocyte Sedimentation Rate	99 mm	85 mm
C-reactive protein (CRP)	62 mg/L	96 mg/L
Creatinine	159 μmol/L	141 μmol/L
Aspartate Aminotransferase (AST)		84 U/L
Alanine Aminotransferase (ALT)		90 U/L
Triglycerides	2.89 g/L	2.41 g/L
D-Dimer	9300 ng/mL	—
Liver check-up	Normal	Normal
Blood ionogram	—	Natrémie: 121 mmol/L Kaliémie: 4.9 mmol/L
Ferritin	—	2675.56 ng/mL
Blood protein electrophoresis	—	Hypergammaglobulinémie polyclonale Albuminémie: 13.42 g/L Proprotidémie: 43 g/L
24-h proteinuria	—	0.65 g/24-h
Prothrombin levels	—	100%
Activated partial thromboplastin time	—	53.7
Hepatitis B serology	—	Hbs Antigen Positive
Hepatitis C serology	—	Négative
HIV serology	—	Négative
RT-PCR COVID-19	—	Négatif
Septum examination acid-fast bacilli	—	Négative
Antinuclear antibody	—	1280, speckled
Anti-native DNA	—	380 UI/ml
Myelogram	—	Rich marrow, presence of cell lyses and numerous macrophages

at the onset of SLE in 54.65% of cases. The 2004 HLH diagnostic and therapeutic recommendations proposed diagnostic criteria with 8 items including fever, splenomegaly, bicytopenia, hypertriglyceridemia and/or hypofibrinogenemia, hemophagocytosis, low/absent NK cell activity, hyperferritinemia, and elevated levels of soluble interleukin-2 receptors. The diagnosis of HLH is made when the patient meets 5 of the 8 criteria [9]. These diagnostic criteria were found to be inappropriate for sHLH and difficult to apply in routine practice. In 2014, Fardet et al. proposed a scoring system called the HScore for sHLH, with the probability increasing with the score [18]. The elements included in the calculation were underlying immunosuppression, temperature, organomegaly (splenomegaly or hepatomegaly), the number of cytopenias, ferritin (ng/L), triglycerides (mmol/L), fibrinogen (g/L), AST (U/L), and hemophagocytosis on bone marrow examination. For example, a score above 250 indicates a probability of sHLH greater than 99%. Our patient met both the 2004 HLH criteria and had an HScore of 204, corresponding to a probability of 88%–93% of MAS. The positive serology for Hbs Antigen in our case is a confounding factor for the diagnosis of MAS-SLE. Indeed, viral infection is also a frequent cause of sHLH. However, viral hepatitis B is an extremely rare cause of sHLH [4]. Furthermore, viral infection could be a triggering factor or a complication of SLE [14–16, 19, 20]. It should be systematically screened before initiating immunosuppressive treatment [21]. In our case, viral hepatitis B was diagnosed in this context. To our knowledge, the association of two triggering factors for sHLH, as in our patient, is very rarely described. Wang et al. reported coinfection with MAS-SLE in 25% of cases [22]. The association of MAS-SLE and hepatitis B is exceptional [4]. Zeng et al. reported MAS-SLE induced after 19 months of treatment for chronic viral hepatitis B with anti-TNF alpha [23]. Management of secondary

MAS requires a multidisciplinary approach. It involves two components: symptomatic treatment and treatment of the causative agent. The HLH-2004 protocols are the standard guidelines for the treatment of HLH, combining chemotherapy and immunotherapy with agents such as etoposide, dexamethasone, and cyclosporine A. These protocols have significantly improved patient survival, although toxicity and risk of infections remain major concerns [9]. This protocol was also effective for the treatment of sHLH secondary to viral hepatitis B [4] In MAS-SLE, the efficacy of corticosteroids has been demonstrated in around two-thirds of cases, while immunosuppressive therapy has been proposed in the most severe forms and in cases of severe visceral involvement. Monoclonal antibodies are used in refractory forms [14–16, 19, 20, 24]. Some studies have shown that a combination with ETOPOSIDE or immunoglobulin may be beneficial [25, 26]. In the presence of even latent infection, antibiotic or antiviral treatment is proposed. In this case, immunosuppressive therapy is started at the same time as the infection is treated [19, 21]. In our case, treatment with intravenous corticosteroids combined with antiretroviral therapy was initiated after 21 days of hospitalization, a long diagnostic delay that testifies to the difficulty of diagnosis. For Zang et al. the initial treatment was an intravenous pulse of methylprednisolone at 200 mg per day for 5 days, followed by a combined treatment of etoposide (100 mg×3/week, accumulated 1000 mg), cyclosporine (50 mg, bid), cyclophosphamide (200 mg, qw), and entecavir with a favorable outcome [23]. Despite advances in the treatment of SLE, the vital prognosis of patients with MAS-SLE is guarded. In-hospital mortality remains high. Cohen et al. [25] in 2018 and Ahn et al. [27] in 2017 reported a death rate of 19% and 13% respectively for MAS-SLE versus 3% SLE without MAS. Several factors associated with poor prognosis were described, namely age greater than 50 years, profound cytopenia, ferritinemia greater than 50,000 μg/L, occurrence of disseminated intravascular coagulation, infections, high CRP, high SLEDAI score, low albumin level [14, 15, 24, 27]. Our patient had most of these factors. The longer delay in diagnosis and hepatitis B contributed to our patient's fatal outcome.

6 | Conclusion

The clinical presentation of MAS-SLE is polymorphous. Its course is potentially fatal. Multidisciplinary management of the affected organs will increase the patient's chance of survival. Identification of elevated ferritin levels should be regarded as a warning sign, requiring urgent investigation for the diagnosis of MAS-SLE.

Author Contributions

L. N. Rakotonirina: conceptualization, formal analysis, writing – original draft, writing – review and editing. **M. O. Andrianiaina:** writing – original draft, writing – review and editing. **O. H. Rakotonirainy:** supervision, validation. **H. Ramanandafy:** validation, visualization. **N. H. Randriamifidy:** resources. **F. Rapelanoro Rabenja:** resources, supervision.

Ethics Statement

The authors thank the patient's family who provided written consent for this report. The article omits any personal information that might identify the patient. The names and dates on the chest CT scan have been redacted. The authors have included only the information necessary for scientific understanding.

Consent

Patient's family has provided written consent for the publication of this report in accordance with the journal consent policy.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

1. A. G. Kaçar and T. T. Celkan, "Hemophagocytic Lymphohistiocytosis," *Balkan Medical Journal* 39, no. 5 (2022): 309–317, https://doi.org/10.4274/balkanmedj.galenos.2022.2022-4-83.

2. A. Papazachariou and P. Ioannou, "Hemophagocytic Lymphohistiocytosis Triggered by Herpes Simplex Virus 1 and 2: A Narrative Review," *Hematology Reports* 16 (2024): 487–503.

3. L. Å. Rolsdorph, K. A. Mosevoll, L. Helgeland, and H. Reikvam, "Concomitant Hemophagocytic Lymphohistiocytosis and Cytomegalovirus Disease: A Case Based Systemic Review," *Frontiers in Medicine* 9 (2022): 819465, https://doi.org/10.3389/fmed.2022.819465.

4. N. S. Cyr, A. Douen, N. Sinha, N. St. Cyr, P. Farag, and M. Bernstein, "S2666 Hepatitis B—A Rare Cause of Hemophagocytic Lymphohistiocytosis," *American Journal of Gastroenterology* 115, no. 1 (2020): S1396, https://doi.org/10.14309/01.ajg.0000712712.84028.40.

5. C. B. Crayne, S. Albeituni, K. E. Nichols, and R. Q. Cron, "The Immunology of Macrophage Activation Syndrome," *Frontiers in Immunology* 10 (2019): 119, https://doi.org/10.3389/fimmu.2019.00119.

6. S. Vilaiyuk, N. Sirachainan, S. Wanitkun, K. Pirojsakul, and J. Vaewpanich, "Recurrent Macrophage Activation Syndrome as the Primary Manifestation in Systemic Lupus Erythematosus and the Benefit of Serial Ferritin Measurements: A Case-Based Review," *Clinical Rheumatology* 32 (2013): 899–904.

7. P. Poudel, T. Swe, and S. Rayancha, "A Rare Case of Macrophage Activation Syndrome Presenting as the First Manifestation of Systemic Lupus Erythematosus," *Journal of Investigative Medicine High Impact Case Reports* 6 (2018): 2324709618812196, https://doi.org/10.1177/2324709618812196.

8. J. Henter, A. Samuelsson-Horne, M. Aricò, et al., "Treatment of Hemophagocytic Lymphohistiocytosis With HLH-94 Immunochemotherapy and Bone Marrow Transplantation," *Blood* 100, no. 7 (2002): 2367–2373.

9. J. Henter, A. Horne, M. Aricò, et al., "HLH-2004: Diagnostic and Therapeutic Guidelines for Hemophagocytic Lymphohistiocytosis," *Pediatric Blood & Cancer* 48, no. 2 (2007): 124–131, https://doi.org/10.1002/pbc.21039.

10. K. McClain, "Treatment of Hemophagocytic Lymphohistiocytosis in the Era of New Biologics," *Pediatric Blood & Cancer* 67, no. 10 (2020): e28631, https://doi.org/10.1002/pbc.28631.

11. W. Gouda, A. Abdelaziz Alsaid, A. S. Abbas, et al., "Silent Lupus Nephritis: Renal Histopathological Profile and Early Detection With Urinary Monocyte Chemotactic Protein 1," *Open Access Rheumatology: Research and Reviews* 14 (2022): 161–170.

12. R. Seror, "Évaluation Thérapeutique Dans le Lupus Érythémateux Systémique," *Lupus érythémateux* 209 (2021): 2021.

13. M. Aringer, K. Costenbader, D. Daikh, et al., "2019 European League Against Rheumatism/American College of Rheumatology Classification Criteria for Systemic Lupus Erythematosus," *Arthritis and Rheumatology* 71 (2019): 1400–1412.

14. P.-E. Gavand, I. Serio, L. Arnaud, et al., "Clinical Spectrum and Therapeutic Management of Systemic Lupus Erythematosus-Associated Macrophage Activation Syndrome: A Study of 103 Episodes in 89 Adult Patients," *Autoimmunity Reviews* 16 (2017): 743–749.

15. H. Lu, F. Simonetta, K. Samii, et al., "Syndrome d'activation macrophagique," *Forum Med Suisse* 17 (2017): 981, https://doi.org/10.4414/fms.2017.02981.

16. A. Wafa, H. Hicham, R. Naoufal, et al., "Clinical Spectrum and Therapeutic Management of Systemic Lupus Erythematosus-Associated Macrophage Activation Syndrome: A Study of 20 Moroccan Adult Patients," *Clinical Rheumatology* 41 (2022): 2021–2033.

17. W. Gouda, F. Alsaqabi, A. Moshrif, A. S. Abbas, T. M. Abdel-Aziz, and M. A. Islam, "Macrophage Activation Syndrome Triggered by Systemic Lupus Erythematosus Flare: Successful Treatment With a Combination of Dexamethasone Sodium Phosphate, Intravenous Immunoglobulin, and Cyclosporine: A Case Report," *Journal of Medical Case Reports* 15 (2021): 497.

18. L. Fardet, L. Galicier, O. Lambotte, et al., "Development and Validation of the HScore, A Score for the Diagnosis of Reactive Hemophagocytic Syndrome," *Arthritis and Rheumatology* 66 (2014): 2613–2620.

19. D. Hayfa, J. Fatima, M. Ghribi, et al., "Syndrome d'activation macrophagique et lupus érythémateux systémique," *La Revue de Médecine Interne* 38 (2017): A177–A178.

20. Y. R. Kim and D.-Y. Kim, "Current Status of the Diagnosis and Treatment of Hemophagocytic Lymphohistiocytosis in Adults," *Blood Research* 56 (2021): S17–S25.

21. R. Watanabe, T. Ishii, and H. Harigae, "Pretreatment Screening for Hepatitis B Virus Infection in Patients With Systemic Lupus Erythematosus," *Tohoku Journal of Experimental Medicine* 237 (2015): 9–15.

22. J. Wang, W. Rong, and H. Yan, "Eighty-Six Cases of Clinical Characteristics and Outcomes of Systemic Lupus Erythematosus-Associated Macrophage Activation Syndrome: A Meta-Analysis Study," *Immunology & Inflammation Diseases* 12 (2024): e1364.

23. Z. Zeng, W. Tu, B. Ji, et al., "IFN-α Induced Systemic Lupus Erythematosus Complicated With Hemophagocytic Lymphohistiocytosis: A Case Report and Literature Review," *Frontiers in Immunology* 14 (2023): 1223062, https://doi.org/10.3389/fimmu.2023.1223062.

24. A. Aziz, E. E. Castaneda, N. Ahmad, et al., "Exploring Macrophage Activation Syndrome Secondary to Systemic Lupus Erythematosus in Adults: A Systematic Review of the Literature," *Cureus* 13, no. 10 (2021): e18822, https://doi.org/10.7759/cureus.18822.

25. E. M. Cohen, K. D'Silva, D. Kreps, K. D'Silva, M. B. Son, and K. H. Costenbader, "Arthritis and Use of Hydroxychloroquine Associated With a Decreased Risk of Macrophage Activation Syndrome Among Adult Patients Hospitalized With Systemic Lupus Erythematosus," *Lupus* 27, no. 7 (2018): 1065–1071, https://doi.org/10.1177/0961203318759428.

26. P. La Rosée, A. Horne, M. Hines, et al., "Recommendations for the Management of Hemophagocytic Lymphohistiocytosis in Adults," *Blood* 133 (2019): 2465–2477.

27. S. S. Ahn, B.-W. Yoo, S. M. Jung, S. W. Lee, Y. B. Park, and J. J. Song, "In-Hospital Mortality in Febrile Lupus Patients Based on 2016 EULAR/ACR/PRINTO Classification Criteria for Macrophage Activation Syndrome," *Seminars in Arthritis and Rheumatism* 47 (2017): 216–221.