Clinical Case Reports

Brazilian Journal of Case Reports

New-onset Systemic Lupus Erythematosus presenting with Macrophage Activation Syndrome and Diffuse Alveolar Hemorrhage: a case-based review

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Received on: Mar 22, 2022. Accepted on: Apr 12, 2022. Available online: Apr 19, 2022.

Abstract

Macrophage activation syndrome is a form of secondary hemophagocytic lymphohistiocytosis in the setting of autoimmune diseases. It's a rare, hyperinflammatory complication requiring prompt institution of therapy to prevent organ dysfunction and death. We report a young female presenting with macrophage activation syndrome with multiorgan failure and diffuse alveolar hemorrhage in the setting of inaugural systemic lupus erythematosus. The patient was successfully treated with steroids, plasma exchange and cyclophosphamide.

Keywords: Hemophagocytic lymphohistiocytosis; Macrophage activation syndrome; Systemic lupus erythematosus; Diffuse alveolar hemorrhage; Plasma exchange.

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a rare, life-threatening, hyperinflammatory, hyperferritinemic syndrome. Its pathophysiological hallmark is the persistent activation of macrophages and cytotoxic T cells leading to a proinflammatory cytokine storm [1]. Despite being more frequent in children, HLH can occur at any age and is almost uniformly fatal when untreated [2]. The most frequent triggers are infections (especially virus), malignancy, autoimmune diseases, drugs, and pregnancy [1, 3]. When induced by immune-mediated disorders, it's called macrophage activation syndrome (MAS) and is phenotypically indistinguishable from other forms. MAS is more commonly encountered in the pediatric setting of juvenile idiopathic arthritis but can also be seen in adult patients with Still's disease, systemic lupus erythematosus

ISSN: 2763-583X. doi: 10.52600/2763-583X.bjcr.2022.2.2.89-101. *This is an open access article under the CC BY license by Creative Common's Attribution 4.0 International License.*

(SLE), vasculitides and other immune disorders [4].

Patients typically present with a recurrent or refractory high fever of unknown origin. Additional signs and symptoms include neurologic impairment, fatigue, wasting, hepatosplenomegaly, lymphadenopathy, hemorrhagic diathesis and multiorgan failure. Laboratory features include cytopenias, elevated liver enzymes, abnormal coagulation parameters, histologic evidence of hemophagocytosis and elevated lactate dehydrogenase (LDH), ferritin and triglycerides [1, 4-5].

Given the variable and unspecific features mimicking several disease processes, HLH diagnosis remains challenging [4, 6]. It has been classically based on the pediatric HLH-2004 criteria, which require a molecular diagnosis consistent with HLH or fulfilling ≥5 of 8 criteria: fever; splenomegaly; cytopenias of at least two cell lines; hypertriglyceridemia and/or hypofibrinogenemia; hemophagocytosis in the bone marrow, spleen or lymph nodes in the absence of malignancy; low or absent NK cell activity; ferritin ≥500ng/mL; elevated soluble IL-2 receptor alpha (sCD25) ≥2400U/mL [7].

Worth noticing, this score has not been validated in the adult population and hemophagocytosis is neither pathognomonic nor required for the diagnosis. As such, HLH diagnosis should be considered in the setting of a compatible clinical presentation along with elevated inflammatory markers, even if 5 criteria are not met [4, 8]. Soluble CD25, present in the HLH-2004 criteria, has been recognized as a specific, sensitive, low-cost diagnostic test, with higher values associated with a worse prognosis [9]. CXCL9, an IFNγ-specific induced chemokine, is markedly elevated in HLH and may help in the differential diagnosis with other hyperferritinemic diseases [10]. Since these tests may not be readily available, pending results should not delay treatment initiation [4]. The HLH-probability calculator (HScore) is another diagnostic tool based on nine graded criteria, with higher scores reflecting an increasing likelihood of having HLH [11-12]. Serial ferritin measurements have been used as a marker of disease activity [13].

Optimal treatment of adult HLH remains unknown and its heterogeneity hinders the creation of a single treatment protocol. The 2019 expert opinion paper by La Rosée et al. [4], advocates that treatment should be tailored to control hyperinflammation and treat identified triggers, based on the HLH-94 protocol (the first international HLH study by the Histiocyte Society) as the recommended standard of care.[14, 15] In primary,

genetic forms of HLH, treatment with corticosteroids and etoposide is an effective first-line therapy. In refractory or relapsing HLH, combined chemotherapy and allogeneic hematopoietic stem-cell transplantation may be needed [4, 16].

In the setting of MAS, no randomized controlled trials exist to provide a standard of care and treatment differs because inciting factors may be different from other forms of HLH [17-18]. Corticosteroids are the first-line treatment, often with high-dose pulse methylprednisolone (1 g/d for 3-5 consecutive days). Subsequent therapy should consider etoposide, cyclophosphamide, intravenous immunoglobulin, and cytokine-targeted therapies anakinra (IL-1-blockade) and tocilizumab (IL-6-blockade) [4, 19-20]. Plasma exchange (PEX) and hemoperfusion with cytokine adsorption columns have also been used as adjunctive measures [21].

In the specific setting of SLE-induced MAS, cyclophosphamide has been reported as highly effective [21-22].

Case report

A previously healthy caucasian woman in her late 20s presented with a 2-month history of fever (maximum of 39.8°C), malaise, anorexia, weight loss, and arthralgia of knees, wrists and hands. She was brought to the emergency room with severe neurologic impairment (9 points on the Glasgow Coma Scale). Blood pressure was 106/62mmHg, she had sinus tachycardia of 149 bpm and temperature was 34.5°C. Her skin and mucous membranes were pale and icteric. Dispersed ecchymosis was denoted, along with purpuric lesions on the lower limbs. Cardiac auscultation was unremarkable except for tachycardia. Pulmonary auscultation was remarkable for rhonchi and dispersed dry rales. Smooth, elastic lymph nodes of 2 cm were palpable in the axillary region. The abdomen was tender on the upper right quadrant, with palpable hepatomegaly. Asterixis was not present.

Progressive neurologic dys-function and hemodynamic instability ensued, and she was subjected to endotracheal intubation and vasopressor support. Initial laboratory evaluation (Table 1) showed lactic acidosis with acidemia, non-immune hemolytic anemia, thrombocytopenia, leukocytosis with neutrophilia, elevated inflammatory markers with a very high serum ferritin level, hepatocellular injury, coagulopathy, hypertri-glyceridemia, acute kidney injury (AKI) with bland urinalysis, negative serum hCG pregnancy test and negative PCR test for SARS-CoV-2.

Computed tomography (CT) scan showed signs suggestive of alveolar hemorrhage, hepatomegaly and multiple supra and infradiaphragmatic lymphadenopathies. Hemophagocytic lymphohistiocytosis was assumed, possibly in the setting of sepsis, lymphoproliferative disorder, or rheumatologic disease.

Subsequent workup (Table 1) showed low complement levels; positive ANA, anti-dsDNA and anti-Smith antibodies; negative ANCA, anti-GBM and antiphospholipid antibodies; negative serologic testing to Treponema pallidum, Human Immunodeficiency Virus, Hepatitis B Virus and Hepatitis C Virus; negative PCR testing to Cytomegalovirus, Epstein-Barr Virus and Parvovirus B19. Bronchofibroscopy confirmed the presence of alveolar hemorrhage. The diagnosis of inaugural SLE was made, presenting with MAS and Diffuse Alveolar Hemorrhage (DAH). Additional workup unavailable before initiation of disease-specific treatment included a lymph node biopsy, bone marrow examination and sCD25 blood measurement.

The results showed: a highly positive sCD25 of 11533 pg/mL [458-1997]; bone marrow with no signs of hemophagocytosis nor atypical cells, with myeloid hyperplasia characteristic of inflammatory states; immunophenotyping with elevated CD38 expression on T CD8+ cells, compatible with cytotoxic T cells activation; axillary lymph node incisional biopsy with necrotizing lymphadenitis compatible with SLE, and no signs of malignancy.

The patient fulfilled 5 of the 8 HLH-2004 criteria for the diagnosis of HLH and had an HScore of 239, indicating a 98-99% likelihood of hemophagocytic syndrome. These results, along with treatment response, supported our hypothesis of HLH in the context of SLE, known as SLE-associated MAS.

The patient was subjected to mechanical ventilation and vasopressor support at admission. Transfusion support with red blood cells, platelets, fresh frozen plasma (FFP) and fibrinogen were initiated. Given the sepsis-like presentation, empirical piperacillin-tazobactam plus vancomycin were started after blood and urine culturing.

After the diagnosis of SLE-associated MAS, we promptly started high-dose pulse methylprednisolone 1g in 3 consecutive days (followed by oral prednisolone 1mg/kg/d), and hydroxychloroquine 400mg/d. Given the critical condition and the presence of DAH, a decision to proceed with PEX was made.

We performed 5 consecutive daily sessions replacing 1.5 plasma

volumes with FFP. Rapid hemodynamic improvement allowed for the suspension of vasopressors 2 days after treatment initiation. Repeat CT scan showed resolution of DAH by day 3 but extubation was delayed due to a respiratory tract infection by multiresistant *P. aeruginosa* isolated in the bronchoalveolar lavage.

Blood and urine cultures were negative. Antibiogram-guided meropenem was initiated, allowing extubation at day 6. Neurologic impairment and AKI fully resolved. Hepatitis, coagulopathy, hematologic abnormalities, ferritin, triglycerides, and SLE activity markers improved slower.

By day 11, despite improvement of HLH markers, and while still under meropenem, the patient presented fever, new-onset type 1 respiratory failure, marked hemoglobin drop, and negative C-reactive protein and procalcitonin. Repeat CT scan showed DAH once again. Disease activity was assumed. Intravenous cyclophosphamide was initiated and PEX was restarted for 5 more consecutive sessions.

The patient was discharged after 25 days with improved HLH and SLE markers (Table 1) and no clinical signs of disease activity. She underwent 10 in-hospital PEX sessions and 7 doses of 500mg IV cyclophosphamide every two weeks, with complete remission. Based on her age and non-adherence to anticonception methods, azathioprine was chosen as maintenance immunosuppression.

One year after the diagnosis, a slight, stable elevation of sedimentation rate and anti-dsDNA antibody persist, with no clinical signs or symptoms of disease activity under azathioprine, prednisolone and hydroxychloroquine.

Table 1. Laboratory results.

	Diagnostic workup	Day 10	Day 11	Day 25	1-year follow-up
Arterial gasometry (100% oxygen)	pH 7.27, PaCO2 17.8 mmHg, PaO2 64.8mmHg, HCO_3^- 8.1 mM, lactate 9.6 mM		Diffuse Alveolar Hemorrhage relapse – restart of plasmapheresis and initiation of cyclophosphamide		
Hemoglobin	6.1 g/dL	7.4 g/dL		8.2 g/dL	12.3 g/dL
Platelets	36000 /µl	220000/µl		285000/µl	230000 /µl
Leukocytes Neutrophils Lymphocytes	11600/µl 10790/µl 390/µl			6000/µl 3610/µl 1850/µl	5400 /µl 3920 /µl 990 /µl
Sedimentation Rate	54mm on 1st hour	44 mm on 1st hour		33 mm on 1st hour	48 mm on 1st hour
Peripheral blood smear	No schistocytes				
prothrombin time INR aPTT Fibrinogen	17.5s 1.52 39.3s 56 mg/dL				

d-dimer	4.79 µl/mL				
Direct/indirect antiglobulin (Coombs) testing	Negative/negative				
Haptoglobin	<10mg/dL	105 mg/dL			
Iron Ferritin Transferrin saturation	112 µl/dL 11719 ng/mL 95.5%;	1298 ng/mL		773 ng/mL	
total/direct bilirubin	9.3/6.84 mg/dL	2.5/2.03 mg/dL			
Aspartate aminotransferase Alanine aminotransferase	2207 UI/L 234 UI/L	102 UI/L 39 UI/L		41 UI/L 40 UI/L	17 UI/L 15 UI/L
Alkaline phosphatase	253 U/L	200 U/L			52 U/L
Albumin	1.7 g/dL	2.8 g/dL		4.1 g / dl	4.5 g/dl
Lactate dehydrogenase	1569 U/L	457 UI/L			225 UI/L
Triglycerides	346 mg/dL	472 mg/dL			46 mg/dL
Creatinine	2.7 mg/dL	0.8 mg/dL		0.5 mg/dL	0.6 mg/dL
Urea	97 mg/dL			46 mg/dL	33 mg/dL
Na^+	138 mM			137 mM	139 mM
K^+	4.6 mM			3.8 mmol/L	4 mmol/L
Serum hCG pregnancy test	negative				
C-reactive protein	10.23 mg/dL			0.56 mg/dL	0.39 mg/dL
Procalcitonin	7.05 ng/mL				
Urinalysis	bland			bland	bland
C3 complement fraction [90-180] C4 complement fraction [10-40]	24 mg/dL 8.1 mg/dL	81 mg/dL 11.2 mg/dL		107 mg/dL 20 mg/dL	113.00 mg/dL 16.60 mg/dL
ANA [≤ 1/160] Anti-dsDNA [<10] Anti-Smith ANCA Anti-GBM	1/2560 263 UI/mL Positive Negative Negative			6.50 UI/mL	15.00 UI/mL
Anti-cardiolipin Anti-B2GP1 Lupus anticoagulant	Negative Negative Negative				
Anti-Treponema pallidum Anti-HIV 1 and 2 HbsAg / Anti-Hbs Anti-HCV	Negative Negative Negative / Positive Negative				
PCR to CMV PCR to EBV PCR to Parvovirus B19 PCR to SARS-CoV-2	Negative Negative Negative Negative				
Soluble CD25 [458-1997]	11533 pg/mL				

Legend: ANA, antinuclear antibodies; ANCA, Antineutrophil Cytoplasmic Antibodies; aPTT, activated Partial Thromboplastin Time; B2GP1, beta2-glycoprotein I; CMV, Cytomegalovirus; dsDNA, double-stranded DNA; EBV, Epstein-Barr virus; GBM, glomerular basement membrane; HbsAg, Hepatitis B virus surface antigen; HCV, Hepatitis C virus; HIV, Human Immunodeficiency Virus; INR, international normalized

Discussion and Conclusion

SLE-associated MAS is a rare, life-threatening condition occurring in 0.9 to 4.6% of SLE patients [8]. Gavand et al. [22] reported a median age of 32 years, with MAS as the inaugural SLE manifestation in 46% of cases.

We report a case of a previously healthy young woman presenting with a

severe inflammatory syndrome that progressed to multiorgan failure in the setting of new-onset SLE-associated MAS. High fever, a presenting sign in our patient, has been consistently regarded as the most common manifestation, approaching 100% in most studies [5, 22-26].

Since most MAS features can also occur in SLE, this condition can be challenging to distinguish from a lupus flare. In this regard, ferritin, which has been constantly reported as above 1000ng/mL and sometimes above 10000ng/mL [5, 22-29], may be the most differentiating feature, suggesting that the ferritin cut-off value in the HLH-2004 criteria may be increased to allow for better specificity. In the presented case, the highly elevated ferritin, AST, hypertriglyceridemia, LDH and hypofibrinogenemia, were the main clues for the diagnosis of HLH, despite the initial sepsis-like presentation.

Given the patient's age, a primary genetic HLH was unlikely (functional and genetic testing are not generally recommended in this population given its low sensitivity to detect abnormalities), mandating a thorough investigation of triggers [4]. Given the exuberant lymphadenopathies, the lymph node biopsy was mandatory to exclude underlying lymphoproliferative disorder. Bone marrow evaluation, an integral part of the diagnostic investigation of hemophagocytic syndromes, was characteristic of inflammatory states, as is the case of HLH. Hemophagocytosis is neither sensitive nor pathognomonic and was not seen in this case. Ultimately, the immunologic study was pivotal in identifying SLE as the trigger. The elevated sCD25 later confirmed the diagnosis of MAS-HLH.

Lung involvement by HLH has long been reported, with rates of 14.6 to 75% [21-22, 25, 27]. In SLE, DAH has been reported in 0.6 to 5.4% of patients [30-31]. The retrospective multicenter study by Blay et al. is the largest study to evaluate DAH in SLE and reported this feature in 2.2% of childhood-onset SLE patients. More importantly, it was the first study to demonstrate that DAH, despite not being a disease activity score descriptor, is associated with serious, high mortality SLE flares [32].

Our patient exhibited lung involvement in the form of DAH. This was our main rationale for adding PEX to the glucocorticoid pulses, since it's been advocated as second-line therapy for severe complications of SLE, as of the American Society for Apheresis 2019 guidelines [33]. There have been reports of the additive use of PEX in MAS, with positive results, but never as monotherapy [20, 34].

In a report from Lorenz et al., steroid-refractory MAS cases were

subsequently treated with PEX, and all patients ended up needing additional escalation of immunosuppressive therapy. However, the high fevers were blunted, suggesting that PEX might be used as a supportive measure to temporarily disrupt the systemic cytokine storm and serve as a bridge for cell-targeted therapies to act, but should not be considered a promising strategy on its own [21].

Indeed, that was the case with our patient, as fever, ferritin and other markers of HLH rapidly improved with methylprednisolone and PEX. One week later, under oral prednisolone, fever and DAH resumed, motivating the initiation of cyclophosphamide, which has proven successful and has been considered effective in several SLE-associated MAS reports [21-26].

Positive reports with the IL-1-receptor antagonist anakinra [35] may pave the way to the evolving area of cytokine-targeted therapy in SLE-associated MAS patients.

In conclusion, MAS remains challenging to diagnose and treat. The lack of validated criteria for adults, along with unspecific features, often delays the diagnosis. Prompt initiation of treatment is of utmost importance to prevent organ dysfunction and death. Optimal management remains unclear and randomized controlled trials are lacking.

Attention should be given to treating the underlying trigger. In the specific setting of SLE-associated MAS, cyclophosphamide remains effective and should not be delayed. Most patients seem to have severe SLE organ manifestations that, by themselves, would be an indication to use this drug.

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Conflict of interest: The authors declare no conflicts of interest.

Acknowledgements: All authors were involved in the patient's care, treatment decisions and writing the manuscript.

Funding: No financial support was received for this manuscript.

How to cite this article: Cruz GC, Sousa M, Vilela S, Gouveia R. New-onset Systemic Lupus Erythematosus presenting with Macrophage Activation Syndrome and Diffuse Alveolar Hemorrhage: a case-based review. Brazilian Journal of Case Reports. 2022 Jan-Mar;02(2):89-101.