

Hemophagocytic Lymphohistiocytosis, a Rare Presentation in Lupus Nephritis



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INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a rare immune disorder that is life threatening if not promptly diagnosed and treated. Its identification, however, remains a diagnostic challenge for clinicians, given the large overlap in presenting symptoms with other conditions, including autoimmune disease and infection. Further adding to the complexity is that HLH encompasses 2 separate forms of disease (Figure 1): primary or familial HLH (FHL), and secondary HLH (sHLH), which is often referred to as macrophage activation syndrome (MAS) when associated with rheumatological disease and which can occur in response to robust immunological activation.

Hemophagocytic lymphohistiocytosis syndrome is characterized by persistent fever, hepatosplenomegaly, and cytopenias.¹ Laboratory abnormalities include hyperferritinemia, hypertriglyceridemia, coagulopathy with hypofibrinogenemia, and hepatic dysfunction. Histopathology classically demonstrates hemophagocytosis in bone marrow and other involved tissues. However, histologic evidence of hemophagocytosis is detected in only a small proportion of cases at presentation, and its identification is neither sensitive nor specific for the diagnosis of HLH.² Revised HLH diagnostic criteria state that the presence of 5 of the following 8 features can be considered diagnostic: (i) fever, (ii) splenomegaly, (iii) cytopenia involving 2 of 3 lineages, (iv) hypertriglyceridemia and/or hypofibrinogenemia, (v) hemophagocytosis in bone marrow, spleen, or lymph nodes, (vi) reduced or absent natural killer (NK) cell activity, (vii) hyperferritinemia, and (viii) elevated soluble interleukin-2 (IL-2) receptor.³ However, these diagnostic criteria do not need to be fulfilled if a genetic diagnosis of HLH is made.

Primary HLH or FHL is a group of autosomal recessive immune disorders with an estimated incidence of 0.12 per 100,000 children per year.⁴ Nearly 70% of patients with FHL develop disease within the first year of life, with high mortality if unrecognized, and family history can often be negative. The various genetic defects associated with FHL have been linked to pathways involved in perforin-mediated cytotoxicity, which is central to the effector functions of cell-mediated immunity.⁵ Under physiologic conditions, cytotoxic cells, including NK cells and CD8⁺ T lymphocytes, engage virus-infected or tumor-transformed cells to induce apoptosis in these targets. Within the synapse formed between immune cells and target cells, lytic granules are released, which contain perforin and granzymes. Perforin is a key protein that forms pores in the target cell membrane, allowing for the entry of granzymes, which ultimately trigger programmed cell death.⁶ Genetic mutations in these cytolytic pathways lead to impaired cell-mediated cytotoxicity, and in HLH may lead to inappropriate survival of antigen-presenting target cells and subsequent persistent activation of effector cells with overproduction of proinflammatory cytokines or cytokine storm.⁷ Another proposed mechanism contributing to the overall immune activating state in HLH is based on the observation that perforin is involved in downregulating CD8⁺ T cells following an immune response.⁸ Therefore, abnormalities in this pathway may also result in failed suppression of activated cytotoxic T lymphocytes and prolonged proinflammatory cytokine production, macrophage activation, and hemophagocytosis.⁹

In contrast to primary HLH, sHLH occurs in all age groups and can be acquired in response to various immune system triggers, including infection, malignancy, and autoimmune disease.¹ Secondary HLH presents with a clinical syndrome similar to that of primary HLH, but

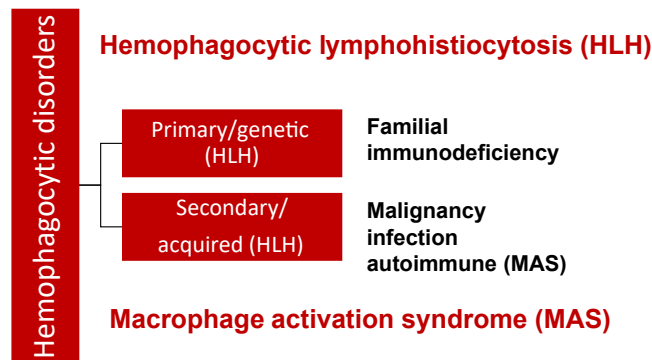


Figure 1. Overview of the terminology of hemophagocytic syndromes.

in some cases may be less pronounced and often mistaken for other illnesses, commonly leading to delays in diagnosis. Herpesvirus infections are the best-described infectious triggers for HLH, with Epstein–Barr virus the most common, although other viruses including HIV, influenza, and H1N1 have been reported to be associated. Malignancy-associated HLH typically occurs with hematological malignancies, and more specifically lymphomas and leukemias. Interestingly, heterozygous mutations in the genes associated with FHL may be present in as many as 40% of patients with secondary HLH.^{S1} The genetic defects in patients with secondary HLH are typically hypomorphic mutations.^{S2} Therefore an underlying genetic predisposition in the setting of an acute or chronic inflammatory condition may precipitate sHLH episodes.

Secondary HLH as a complication of autoimmune disease is often termed MAS. In association with rheumatological conditions, sHLH has been described most commonly in systemic juvenile idiopathic arthritis and adult-onset Still disease.^{S3} Secondary HLH is also a reported severe complication of adult and childhood systemic lupus erythematosus (SLE), which may mimic disease flares at presentation, as many of the clinical findings in HLH are also features of SLE.^{S4–S6} In patients with SLE who develop sHLH, onset may be associated with a recent or current infection. Conversely, the development of sHLH may also be the inaugural presentation in a patient who is ultimately diagnosed with SLE.^{S7,S8} Published case series support that in patients with known SLE, the presence of unexplained fever, cytopenia, and highly elevated ferritin and lactate dehydrogenase (LDH) should alert to the possibility of sHLH. In this report, we describe a case of sHLH as a severe complication in an SLE patient with class III LN.

CASE PRESENTATION

A 35-year-old African American woman with asthma, Raynaud’s syndrome, SLE, and LN class III on maintenance therapy with mycophenolate mofetil (MMF),

low-dose prednisone, and hydroxychloroquine presented to our medical center for recurrent intermittent fevers. She had recently been on a cruise ship to the Mediterranean, at which time she was diagnosed with influenza A and treated with oseltamivir. Diagnostic workup was significant for acute kidney injury (serum creatinine increased from 0.9 to 4 mg/dl) with non-nephrotic proteinuria (urine protein/creatinine 1.5 g/g), pancytopenia (white blood cell count 1.8K/ μ l, neutrophils 96.3%, lymphocytes 1.9%, platelets 67 K/ μ l, and hemoglobin 6.4g/dl), liver dysfunction (alkaline phosphatase [ALP] 309 U/l, alanine aminotransferase [ALT] 49 U/l, aspartate aminotransferase [AST] 152 U/l), high triglycerides 209 mg/dl, high LDH 419 U/l, low fibrinogen 179 mg/dl, high ferritin 3678 (peaked at 11,000 mg/dl), high antibody to double-stranded DNA 3012 IU/ml, low serum complement (C3 = 18 mg/dl, C4 <8 mg/dl), C-reactive protein 8.6 (peaked at 172 mg/l), and erythrocyte sedimentation rate of 7 mm/h. She received broad-spectrum antibiotics for potential sepsis and high-dose i.v. steroid (methylprednisolone 1g/d for 3 doses) followed by prednisone taper for lupus flare. Mycophenolate was held because of concern for uncontrolled infection. i.v. Ig was not tolerated. The patient’s condition deteriorated, as she developed respiratory failure and kidney failure requiring transient dialysis, and experienced 2 cardiac arrests. Bone marrow biopsy was negative for hemophagocytosis; interleukin 2 receptor (IL2R) was elevated at 1613 pg/ml. Kidney biopsy showed active class III LN and acute tubular necrosis.

The patient was started on anakinra (interleukin-1–receptor antagonist). Her severe inflammatory process and illness gradually resolved. Within 2 months, she was back to her baseline with residual chronic kidney disease (new baseline serum creatinine 1.5 mg/dl) on MMF/prednisone and daily anakinra. The anakinra was discontinued after 6 months of treatment. Her SLE/LN and HLH remain in remission. Pertinent laboratory values at various time points from admission to 6 months can be found in [Table 1](#). The authors declare that they have obtained consent from the patient discussed in the report.

DISCUSSION

Secondary HLH is a severe and life-threatening complication of SLE. Here we have presented a case of a young woman with SLE and LN who developed a severe inflammatory illness consistent with HLH in the setting of a recent viral infection. Although her initial presentation was suspicious for sepsis and/or SLE flare, she was ultimately diagnosed with sHLH, given the presence of persistent fever, pancytopenia, elevated

Table 1. Pertinent laboratory values of case patient

Laboratory tests	Day of admission	Day 24: anakinra approved and started	D30: After 1 wk of anakinra	At 6-mo follow-up	Normal range
WBC	1.8	1.4	3.73	3.28	3.99–11.19 K/ μ l
Lymphocyte, %	1.9	7.4	6	13.4	
Neutrophils, %	96.3	79.5	78	51.6	
Platelets	67	26	96	171	150–393 K/ μ l
Hemoglobin	6.4	8.4	7	10.7	11.2–15.7 g/dl
Ferritin	3678	3000 ^a	3000	876	10–291 ng/ml
D-dimer	4.5	–	–	–	<0.50 μ g/ml
Fibrinogen	179	152	105	357	220–410 mg/dl
LDH	419	592	331	208	100–190 U/l
AST	152	31	35	19	14–40 U/l
ALT	49	24	36	10	9–48 U/l
Triglyceride	209	415	NA	70	<150 mg/dl
Ds DNA	3012	NA	40	358	\leq 4 IU/ml
C3	18	34	41	66	87–200 mg/dl
C4	<8	<8	NA	16	18–52 mg/dl
ESR	6	<1	<1	25	<20 mm/h
CRP	8.6	171.7	9.7	<1	<10 mg/l
Procalcitonin	0.62	–	–	–	0–0.5 ng/ml
IL2R	277 ^b	1613	NA	NA	\leq 1033 pg/ml
Serum creatinine	1.6	Hemodialysis	2.1 ^c	1.5	0.5–1.2 mg/dl
Urine protein/creatinine	1.4	1.5	1.5	0.088	g/g

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IL2R, interleukin-2 receptor; LDH, lactate dehydrogenase; NA, not available; WBC, white blood cell.

^aBetween day of admission and D24, ferritin rose as high as 11,000 ng/ml.

^bBetween day of admission and D24, procalcitonin rose to 18.7 ng/ml.

^cHemodialysis discontinued 1 week after starting anakinra.

triglycerides, low fibrinogen, hyperferritinemia, and increased soluble IL-2 receptor levels. Bone marrow biopsy did not reveal evidence of hemophagocytosis; however, it is not a necessary finding for HLH diagnosis, given its poor sensitivity. Furthermore, the patient continued to decline despite treatment for sepsis and active lupus nephritis, but responded to cytokine-directed therapy, thus further supporting the diagnosis of sHLH. Interestingly, her estimated sedimentation rate was persistently low.

Secondary HLH is an uncommon but severe complication of SLE. Often sHLH is difficult to distinguish from active SLE flare, given the common features of a hyperinflammatory state. In the largest published series, 89 adult SLE patients with sHLH were analyzed retrospectively. Differentiating features for HLH were high fever, elevated liver enzymes, specifically AST, increased LDH, hyperferritinemia, and severe neutropenia. These laboratory findings, however, may still be present in SLE flares.^{S4} Of note, in many of the reviewed cases, patients were not heavily immunosuppressed at the time of HLH diagnosis, as was the case in our patient who was receiving maintenance therapy with MMF and low-dose prednisone. In approximately 40% of cases of sHLH in SLE patients, a recent or current infection was identified, suggesting a potential trigger for onset of HLH. In 66% of cases, concomitant features of an active SLE flare were also present, and included elevated antibodies to double-stranded DNA,

hypocomplementemia, rash, arthralgia, and proteinuria of >1 g per day. It is certainly possible that the inciting event in many of these cases was a disease flare; however, sHLH driving disease activity from the overall state of immune activation may also contribute to these findings. Initial therapy in 90% of cases was corticosteroids, whereas subsequent treatments included a variety of immunosuppressants such as i.v. Ig, cyclophosphamide, etoposide, rituximab, and tocilizumab. Mortality in this review was reported at 4.9%.

In a matched case-control study retrospectively comparing adult SLE patients with and without sHLH, it was observed that SLE patients presenting with sHLH were more likely to have higher SLE disease activity index (SLEDAI) scores and renal involvement, and less likely to manifest with arthritis and to be on hydroxychloroquine therapy.^{S9} Again in this study, patients with SLE who developed sHLH demonstrated significantly elevated ferritin levels, marked cytopenia, liver dysfunction, and increased inflammatory markers. In another retrospective review of febrile hospitalized SLE patients with features of sHLH, lower C-reactive protein and C3 complement levels were additional distinguishing features. Hospital mortality was reported to be significantly higher in SLE patients with sHLH, with an odds ratio of 64.5.^{S10} Therefore, although the differentiation of SLE disease and sHLH can be difficult, there are helpful laboratory features to aid clinicians in distinguishing the 2 diseases. The early recognition and

Table 2. Teaching points

1.	Hemophagocytic disorders are classified as either primary or secondary
2.	Prompt diagnosis of HLH or sHLH is imperative due to high mortality if untreated
3.	HLH may be mistaken for sepsis or autoimmune disease flare due to symptom overlap
4.	Hyperinflammatory conditions not responsive to usual therapy should prompt consideration for HLH or sHLH
5.	Anti-IL-1 therapy should be considered in SLE/IN patients with sHLH

HLH, hemophagocytic lymphohistiocytosis; sHLH, secondary HLH; SLE, systemic lupus erythematosus.

diagnosis of sHLH in patients with SLE is imperative, given the significant differences in patient management and outcomes (Table 2). Preliminary guidelines have been proposed for the diagnosis of sHLH in juvenile SLE, but no criteria to date exist for adult patients.^{S6}

Macrophage activation and subsequent hemophagocytosis and cytokine overproduction are hallmarks of sHLH.^{S1} As described above, defects in cytotoxic pathways involving NK cells and T lymphocytes ultimately lead to prolonged stimulation and macrophage activation, likely through interferon- γ (IFN- γ) signaling. The role of hemophagocytic macrophages in the pathophysiology of sHLH has not yet been clearly elucidated. Hemophagocytosis is typically a late feature of sHLH and is only pathologically evident in 60% of cases.^{S11} In contrast, pro-inflammatory cytokine production markedly increased in the acute phase of sHLH and is mediated largely by activated macrophages. Implicated pro-inflammatory cytokines in the pathophysiology of sHLH include tumor necrosis factor (TNF), interleukin (IL)-6, and IL-1.^{S12,S13} Enhance release of these cytokines by activated macrophages potentiates a cascade of downstream inflammatory signaling and cytokine storm. This hyperinflammatory state eventually leads to hemodynamic instability, multi-organ failure, and, if left untreated, potentially death.^{S14}

Given the rarity of cases, there are no randomized controlled trials to guide management of sHLH. Corticosteroids are commonly used as first-line treatment, but with the improved understanding of the role of cytokine storm in disease progression and the development of biologics, cytokine-directed therapies are an evolving class of therapy (Table 2). Our patient was successfully treated with anakinra, an anti-IL-1 therapy. Anakinra is recombinant human IL-1RA and is a competitive inhibitor of endogenous IL-1 receptor for IL-1 α and IL-1 β . Anakinra has been used successfully in treating patients with systemic juvenile idiopathic arthritis, including cases complicated by sHLH, as well as adult-onset Still disease, and rheumatoid arthritis, albeit with modest effectiveness.^{S15–S17}

Cytokine-targeted therapy is an emerging area of investigation in the management of SLE, and IL-1 has been implicated in lupus pathogenesis, given the association of

genetic polymorphisms at the IL-1 gene cluster with disease.^{S18} The evidence supporting use of anakinra in the treatment of SLE, however, is limited. In 1 study, 2 patients with refractory SLE received anakinra, with improvement in myositis and polyarthritis.^{S19} In a case series, 4 patients with severe lupus arthritis were successfully treated with anakinra. The treatment was found to be safe and well tolerated, and followed by clinical and serological improvements.^{S20} At present, the limited evaluation of anakinra in SLE precludes any meaningful conclusions regarding efficacy and duration of therapy.

In conclusion, we have presented a case of severe sHLH in a patient with SLE and lupus nephritis who was successfully treated with anakinra. Prompt recognition of sHLH in this patient likely contributed to the positive outcome in this case. In patients with SLE and other autoimmune diseases, severe inflammatory illnesses refractory to typical disease therapy should prompt consideration for associated sHLH and initiation of targeted therapy if diagnosed (Table 2).

DISCLOSURE

All the authors declared no competing interests.

SUPPLEMENTARY MATERIAL

[Supplementary File \(PDF\)](#)

[Supplementary References](#)

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