Uncovering the Spectrum of Hemophagocytic Lymphohistiocytosis: A Nephrology Department's Analysis of 14 Cases

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ABSTRACT

INTRODUCTION: Hemophagocytic lymphohistiocytosis (HLH) is a disease of multi-organ dysfunction due to excessive immune activation causing widespread inflammation and tissue destruction. It is a severe condition associated with high morbidity and mortality. Early identification is crucial for prompt treatment. The objective of this case series is to underscore the intricacy of managing HLH in individuals with renal dysfunction.

METHODS: This is a retrospective study of patients diagnosed with HLH in a nephrology department over a period of 30 years. We retrospectively reviewed the medical files by applying the Revised HLH-2004 criteria.

RESULTS: Among the 14 female patients included, the mean age was 45.2 years (range 23-78). Nine patients presented with sudden onset of fever and chills. Physical examination revealed purpura in 3 cases, hepatomegaly and splenomegaly in 6 and 5 cases respectively, and peripheral lymphadenopathy in 1 case. Hemorrhagic complications were observed in 5 cases, hypertriglyceridemia in 9 cases, and hyperferritinemia in all cases. Hypothyroidism was observed in all cases, and impaired renal function was detected in 11 of them, with 5 experiencing it as a result of lupus nephritis, and 1 case attributed to pre-eclampsia. Hemophagocytosis was confirmed through sternal puncture in 11 cases. Treatment involved etiological therapy with corticosteroids and immunosuppressants and/or anti-infectives. Intravenous immunoglobulins were administered in 6 cases, while 2 cases required coagulation factor transfusions. Unfortunately, 9 patients did not survive.

CONCLUSION: The study highlights the need for increased awareness and prompt recognition of HLH, particularly in patients with associated renal complications.

KEYWORDS: Hemophagocytic lymphohistiocytosis, renal impairment, lupus nephritis, hemophagocytosis

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a severe complication that can arise from various inflammatory conditions including infections, autoimmune conditions, or immunosuppression.[1-4] In this study, our aim was to investigate the clinical and biological characteristics, outcomes, and underlying pathology of a cohort of patients with hemophagocytic syndromes who were treated at a nephrology department.

Methods

This retrospective descriptive study included patients diagnosed with HLH at a nephrology department in Tunis over a period of 30 years, from January 1992 to January 2023. The diagnosis of HLH was based on the Revised HLH-2004 criteria, which requires 5 of the following 8 criteria to be met for diagnosis: fever, splenomegaly, cytopenia, hypertriglyceridemia and/or hypofibrinogenemia, hemophagocytosis, low or absent natural killer cell activity, ferritin $\geqslant 500\,\mu g/L$, and sCD25 $\geqslant 2400\,units/mL$.[5] Thus, we conducted a

comprehensive analysis of medical records, consistently applying the diagnostic criteria throughout the entire study duration. The primary aims of this research were to determine the clinical and biological profiles, as well as the outcomes, of patients diagnosed with HLH, no matter the type of kidney disease for which they were admitted to our department.

We performed a retrospective review of medical records and consistently applied diagnostic criteria throughout the entire study period. We collected all available demographic, clinical outcomes data and laboratory data to ensure accurate and comprehensive identification of HLH cases. Etiological investigations were performed based on medical observations of patients and included serological tests for Cytomegalovirus (CMV), Epstein Barr virus (EBV), hepatitis B and C, human immunodeficiency virus (HIV), as well as immunological assessments such as antinuclear antibodies and rheumatoid factor. NK cell activity and CD25 levels were not evaluated in this study due to their unavailability. Diagnostic procedures also included

digestive endoscopy, chest X-ray, abdominal ultrasound, cervico-thoraco-abdominal computed tomography, and bone marrow biopsy.

Based on the KDIGO 2012 guidelines, acute kidney injury (AKI) in our study was defined as the sudden onset of partial or total kidney failure to eliminate nitrogenous waste products and maintain fluid and electrolyte balance. The diagnosis and staging of AKI were determined using a universal definition, considering the elevation of creatinine levels and/or urine volume as outlined in the KDIGO guidelines.[6] For patients diagnosed with chronic kidney disease (CKD), stages were determined according to the estimated glomerular filtration rate (eGFR), which was calculated using the Modification of Diet in Renal Disease (MDRD) formula.[7]

Data analysis included descriptive statistics to summarize patient characteristics and clinical features, as well as frequency and percentage distributions for categorical variables. Continuous variables were expressed as means and standard deviations or as medians and interquartile ranges, as appropriate.

Results

Fourteen female patients were included in our study, with a mean age of 45.2 years old (ranging from 23 to 78). Tables 1 and 2 provide an overview of the clinical and paraclinical features observed in these patients. Symptoms onset was sudden in 9 patients, presenting with fever and chills. Purpura was observed in 3 cases, while hepatomegaly and splenomegaly were respectively noted in 6 and 5 cases. Peripheral lymphadenopathy was present in only 1 case. Five cases exhibited hemorrhagic complications, such as gingivorrhagia and epistaxis. All patients had a biological inflammatory syndrome, with a median CRP of 126 mg/L (ranging from 63 to 320). On the complete blood count, 11 patients had pancytopenia, and 3 cases exhibited bicytopenia. Disturbances in the hepatic cytolysis type balance sheet were observed in 10 patients, accompanied by increased lactico-dehydrogenases. Hypertriglyceridemia was present in 9 cases, and hyperferritinemia was observed in all cases. Two cases exhibited hypothyroidism.

We identified renal impairment in a total of 11 cases. Out of these cases, 5 were specifically attributed to chronic kidney disease (CKD). Among the CKD patients, 2 patients were undergoing hemodialysis. Two cases of CKD were found to be associated with lupus nephritis (LN). We observed 1 case of CKD linked to Rheumatoid arthritis. Acute kidney injury (AKI) was present in 6 patients, with 5 showing signs of lupus flare, while the remaining case occurred in the context of pre-eclampsia. According to the AKIN classification, 1 case was categorized as the first stage risk, and 4 cases were classified as the second stage of AKIN for LN flare. The pre-eclampsia case was classified as stage 3 AKI.

Eleven patients underwent sternal puncture (SP), which revealed evidence of hemophagocytosis (HP) in 10 cases. In one case, SP was not feasible due to the severity of the hemorrhagic syndrome, and no evidence of HP was present in the last 2 myelograms. Table 2 provides detailed information on the different treatments administered to the patients. Unfortunately, 9 patients passed away, 2 of whom progressed to septic shock despite appropriate antibiotic therapy. Respiratory distress led to the deaths of 3 patients, neurologic complications led to 2 deaths, and the last patient died due to hemorrhagic syndrome secondary to disseminated intravascular coagulation. Notably, 1 patient died due to anaphylactic shock to Glucantime (Table 2).

Discussion

The incidence of secondary HLH in the literature varies widely depending on the underlying condition. For example, in patients with systemic juvenile idiopathic arthritis (sJIA), the reported incidence of HLH ranges from 4% to 15%.[8,9] In patients with systemic lupus erythematosus (SLE), the reported incidence of HLH ranges from 0.9% to 2.6%.[10,11] In patients with adult-onset Still's disease (AOSD), the reported incidence of HLH ranges from 3% to 16%.[12,13] Overall, the incidence of secondary HLH is relatively rare, but varies depending on the underlying condition. The actual incidence of secondary HLH in Tunisia is still unknown due to under-recognition, which is a global challenge. The absence of specific clinical or laboratory features unique to HLH can lead to confusion with the symptoms and abnormalities of the underlying conditions, making timely diagnosis and treatment difficult.[14]

A comprehensive understanding of the pathogenesis of HLH is crucial in facilitating accurate diagnosis and guiding effective therapeutic management. In addition to the need for early identification and aggressive management, recent studies have shed light on the pathogenesis of HLH, highlighting the critical role of pro-inflammatory cytokines, such as interleukin-1β, interleukin-6, and tumor necrosis factor-α. Targeting these cytokines with selective inhibitors has shown promise in improving outcomes for HLH patients. As such, further research into the role of pro-inflammatory cytokines in HLH is warranted to develop more effective treatment strategies.[8] In the setting of an infection or inflammatory state, cytolytic cells may induce apoptosis in activated macrophages and T cells.[11] Various diagnostic investigations are required as HLH presents clinically with unremitting high fever, generalize lymphadenopathy, hepatosplenomegaly, and central nervous system involvement.[15] A malfunction in cytolytic function can cause an overstimulation of the immune system, leading to the development of HLH and a pro-inflammatory cytokine environment, especially IL-6, that can impair NK cell cytolytic function.[8,9] The activation of macrophages from the cytokine storm results in hemophagocytosis. While a consensus panel in 2016 developed diagnostic criteria to differentiate between systemic juvenile idiopathic arthritis flare and HLH, these criteria have not been validated in autoimmune diseases other than children.[16] Most studies have diagnosed HLH using the

Table 1. Clinical Features at HLH Onset.

PATIENT (N°)	INITIAL PATHOLOGY	YEAR OF HLH DG	GENDER	AGE	FEVER	HEPATOMEGALY	SPLENOMEGALY	LYMPHADENOPATHY	ACTIVE ARTHRITIS	CNS INVOLVEMENT	HEMORRHAGIC MANIFESTATIONS	HEART INVOLVEMENT	LUNG INVOLVEMENT	KIDNEY INVOLVEMENT		
														RENAL FUNCTION	PT*	HM**
1	SLE with class IV LN (Renal Flare)	2009	F	57	Yes	No	No	No	Yes	No	No	No	No	AKI on CKD	SN	2+
2	SLE	2014	F	36	Yes	Yes	No	No	No	No	No	Yes	No	CKD stage 5(HD)	-	-
3	Dermatomyositis	2018	F	52	Yes	No	No		NF	No	No	No	Yes	NRF	0	0
4	SLE with class IV LN (Renal Flare)	1992	F	16	Yes	Yes	No		Yes	No	Yes	No	No	AKI on CKD	SN	2+
5	Rheumatoid arthritis	2007	F	59	Yes	No	No	No	Yes	No	No	No	No	CKD stage 5	-	0
6	Antisynthetase Syndrome	2015	F	78	Yes	No	No	No	No	Yes	Yes	No	Yes	NRF	-	0
7	SLE with class V LN and TMA (Renal Flare)	2016	F	54	Yes	No	Yes	No	No	Yes	No	No	No	AKI on CKD	SN	2+
8	SLE Antiphospholipid syndrome	2011	F	20	No	no	yes	no	NF	no	no	no	yes	CKD stage 5 (HD)	-	-
9	Hypothyroïdism	2004	F	78	Yes	Yes	Yes	Yes	Yes	No	No	No	No	NRF	0	0
10	SLE	2012	F	23	No	No	No	No	NF	Yes	Yes	NF	No	CKD stage 4	0	0
11	SLE with class V LN (Renal Flare) thalassemia minor	2009	F	37	Yes	Yes	Yes	No	NF	No	No	NF	Yes	AKI on CKD	N	1+
12	Pre eclampsia	2007	F	30	No	Yes	Yes	No	No	Yes	Yes	No	No	AKI	N	1+
13	SLE	2016	F	57	Yes	No	No	No	Yes	No	Yes	NF	No	CKD stage 4	0	0
14	SLE with class V LN and TMA (Renal Flare) Scleroderma	2012	F	35	Yes	Yes	No	No	Yes	No	No	No	No	AKI on CKD	SN	2+

Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease; Dg, diagnosis; Hm**, hematuria on urine dipstick; HD, hemodialysis; LN, lupus nephritis; N, nephrotic proteinuria; NRF, normal renal function; Pt*, proteinuria based on 24-hour proteinuria values; SLE, systemic lupus erythematosus; SN, subnephrotic; TMA, thrombotic microangiopathy.

Table 2. Laboratory Parameters and Outcome of Our Patients.

PATIENT (N°)	ETIOLOGY OF HLH	WBC (/MM³)	HB (G/DL)	PLATELETS (/MM³)	FERRITIN (NG/ML)	TRIGLYCERIDES (MMOL/L)	LDH U/L	FIBRINOGEN (G/L)	EVIDENCE OF HEMOPHAGOCYTOSIS	TREATMENT	OUTCOME
1	Negative microbiological investigation	2200	8	82000	533	8.13	1086	NF	Yes	IV Ig Cyclophosphamide Corticosteroids*	Survive
2	Klebsiella and candida albicans tricuspid endocarditis (infection of a jugular dialysis catheter)	4400	6.2	61000	4600	6.5	740	NF	yes	Adapted antibiotic therapy combined with valve replacement	Death following convulsions
3	EBV infection	1300	11	142000	7000	7.4	650	NF	Yes	Cyclosporine Corticosteroids* IV Ig	Acute respiratory distress syndrome and death
4	CMV infection	2600	3.4	9000	5070	4.3	NF	1	No	Ganciclovir transfusions of Coagulation factor concentrates	Disseminated intravascular coagulation and death
5	Klebsielle urinary tract infection	1100	5.9	100000	666	5.2	NF	NF	Yes	Adapted antibiotic therapy	Survive
6	Endocarditis with negative blood cultures	2700	8.6	85000	7200		430	1.2	Yes	Adapted antibiotic therapy	Acute respiratory distress syndrome and death
7	CMV infection	1800	12.5	110000	570	5.4	980	NF	Yes	Ganciclovir Corticosteroids* Cyclophosphamide Plasma exchange IV Ig	Septic shock and death
8	Arteriovenous fistula staph infection	2050	4.2	70000	6400	NF	1200	NF	Yes	Adapted antibiotic therapy	Septic shock death
9	Cutaneous leishmaniasis	3500	6.5	45000	960	NF	811	1.7	Yes	Tetracycline Glucantime Corticosteroids*	Quinck's edema death
10	CMV infection	3190	7.2	23400	2300	9.4	794	1.4	No	Filgrastim Ganciclovir	Survive
11	Negative microbiological investigation	1200	6.6	157000	1977	4.8	583	NF	Yes	Cyclophosphamide Corticosteroids* IV Ig	Survive
12	Negative microbiological investigation	700	5.2	64000	8440	1.3	690	1.2	Yes	Itransfusion of Coagulation factor concentrates IV Ig	Death following convulsions
13	Non-typhi salmonella sepsis	2700	7	70000	5000	1.5	780	1.1	Yes	Trimethoprim/sulfamethoxazole, ciprofloxacin	Survive
14	CMV infection	780	6	112000	996	3	392	1.5	No	Corticosteroids* Gancyclovir Plasma exchange IV Ig	Death from respiratory distress

Abbreviations: Hb, hemoglobin; IV Ig, intravenous immunoglobulins.
*Corticosteroids at the dose of 1mg/kg.

Henter et al diagnostic guidelines.[5] However, this strict set of criteria may delay diagnosis in patients with a milder initial presentation. Our patient's clinical and laboratory features of HLH included sustained fever, hyperferritinemia, pancytopenia, liver dysfunction, and consumptive coagulopathy. Notably, a significant increase in serum ferritin levels (>5000 ng/mL) is an important diagnostic biomarker for HLH.[17] All of our patients had hyperferritinemia, and it was over 5000 ng/mL in 5 cases.

The gold standard for diagnosing HLH is the myelogram, which can confirm the diagnosis and sometimes suggest or confirm the syndrome's etiology. Hemophagocytosis is essential for diagnosis, and the percentage of macrophages (>3% of nucleated cells) is an important diagnostic criterion for some authors.[18] In our series, 11 out of 14 cases presented hemophagocytosis. In the remaining 3 cases, HLH diagnosis was based on a combination of clinical and laboratory findings.

In 18% of cases of acquired HLH, the etiological assessment may yield negative results.[19,20] According to a meta-analysis by Karras et al, a systemic disease associated with HLH was identified in only 7.2% of cases.[19] In our series, HLH occurred in 13 cases of autoimmune disease, including 9 cases of SLE, 2 cases of dermatomyositis, 1 case of Antisynthetase Syndrome, and 1 case of rheumatoid arthritis. However, infectious complications (n = 11), especially CMV infection in 4 cases, were the dominant causes of HLH. In 2 cases, SLE flare was identified as a direct cause of HLH. In one patient who presented with pre-eclampsia, exhaustive etiologic investigation failed to identify the origin of HLH. In a study conducted by Wong et al on 250 lupus patients over a period of 3.5 years, the incidence of HLH was found to be 2.4%.[20] The prevalence of HLH in SLE ranges from 0.9% to 4.6%, but can increase to 9.4% in patients with hepatic dysfunction.[21,22] The mortality rate associated with SLE-associated HLH is around 50%.[23] SLE-associated HLH has been reported in medical literature with an estimated prevalence between 0.9% to 9%, particularly at the onset of the first SLE flare in 46% of patients.[20] The occurrence of HLH during SLE indicates a severe form of the disease. In our series, SLE was the most common autoimmune disease observed and it was a severe form of SLE due to renal involvement. However, this may be due to a selection bias, as patients were recruited from a nephrology department. Diagnosis of HLH can be challenging as it shares clinical similarities with SLE flares, and requires consideration in patients presenting with unexplained fever and/or pancytopenia. The occurrence of hemophagocytosis was not found to be related to the severity of SLE in our study.[22]

In our study, infection was the predominant cause of HLH. This differs from previous studies which suggested that adult HLH was more commonly associated with malignancy. Viral infections, particularly those caused by the herpes virus group, are among the most commonly reported secondary causes of HLH. In our series, 11 cases of HLH were attributed to viral infections. Reviewing the literature, it appears that more than half of all reported HLH cases have a viral etiology, with EBV and CMV being the most commonly implicated viruses.[18,23,24] Even in lupus patients, infectious agents are frequently identified as the underlying cause of HLH, as seen in Table 2. In our patient, whose HLH developed in the context of pregnancy, it is possible that the immune changes and cytokine activation associated with pregnancy could have contributed to the development of this syndrome in a genetically predisposed individual.[25,26] Although HLH is commonly associated with adult-onset Still's disease in the literature, we did not observe any such cases in our series. This is consistent with previous studies that have reported cases of HLH in patients with other underlying inflammatory conditions.[7] Recent studies have suggested a possible association between HLH and IgG4-related disease, which is characterized by tissue infiltration of IgG4-secreting plasmablasts and plasma cells, and responds well to corticosteroid therapy. Further studies are needed to explore this potential link and its implications for the diagnosis and management of HLH.[26,27]

There is currently no standardized treatment protocol for HLH in adults, and treatment approaches are typically based on retrospective case series, case reports, or extrapolated from treatment guidelines for other conditions. Symptomatic treatment is the mainstay of therapy, with specific treatment indicated only in cases of extreme severity where the underlying pathology is controlled. A combination of intravenous methylprednisolone and intravenous immunoglobulins is commonly recommended,[28] with Anakinra used as a second-line treatment if there is clinical deterioration.[29] Etoposide may be used in refractory cases,[29-32] and Rituximab may have a role in patients with EBV.[33] However, these medications were not available for use in our retrospective series, and treatment approaches were heterogeneous due to the absence of a standardized protocol.

In all causes of HLH in adults, the overall mortality rate is significant at 41%, with a range of 5% to 39% in autoimmune disease-associated HLH.[34,35] Several studies have shown that older age at onset and increased comorbidities are associated with increased mortality independent of the cause.[36,37] Additionally, maximum serum ferritin levels have been found to be associated with mortality in HLH patients.[36,37] Although our study did not include formal statistical testing, these descriptive analyses provide valuable insights into the clinical and demographic characteristics of our patient population. As a result of the limited number of patients in the HLH group, a survival analysis could not be performed.

In our study, the observed mortality rate in patients with HLH was high at 64%, which is higher than the rates reported in previous studies, ranging from 16.7% to 50%.[11,35,38] This could be attributed to various factors such as the delay in diagnosis, severity of underlying diseases, and the lack of timely initiation of appropriate treatments. Further studies with larger sample sizes are warranted to confirm these findings.

Conclusion

Our study highlights the significant morbidity and mortality associated with HLH in patients with autoimmune diseases. Our findings suggest that early and accurate diagnosis of HLH is crucial for implementing timely and aggressive multidisciplinary management. Furthermore, the observed high mortality rate in our series underscores the urgent need for more effective treatment strategies for HLH. Recent advancements in our understanding of the pathogenesis of HLH have led to the investigation of targeted therapies, such as selective cytokine inhibitors, which may offer promising therapeutic options for this life-threatening complication. Further research is warranted to explore the effectiveness and safety of these emerging treatments in the management of HLH.

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Author Contributions

All authors were involved in the conception of the work. M. Hajji wrote the first draft of the manuscript based on conversations with all authors. S. Barbouch and H. Kaaroud have been involved in revising it critically for important intellectual content. K. Ben Abdelghani and A. Harzallah contributed actively to the management of the patients. F. Ben Hamida and E. Abderrahim have given final approval for the version to be published. All authors provided intellectual content, edited the manuscript, approved the final version for submission, and agree to be accountable for all aspects of the work.

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

Ethical Approval

Written informed consent was obtained from the family members of the patient for publication of this case series, since they are all deceased at the time of the elaboration of the study.

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