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Exploring the Clinical Spectrum and Hematological Patterns of Hemophagocytic Lymphohistiocytosis: A Comprehensive Study

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ABSTRACT

Background: Hemophagocytic Lymphohistiocytosis (HLH) presents a challenging disorder characterized by complex manifestations resulting from dysregulated immune responses. This study aims to enhance our understanding of the clinical and hematological spectrum of HLH, focusing on adult patients.

Methods: A retrospective-prospective observational study was conducted involving 64 adult HLH patients meeting HLH-2004 criteria. Comprehensive hematopathological assessments were performed, encompassing clinical parameters, hematological markers, and mortality rates. Data analysis utilized SPSS Version 20.0 for descriptive statistics.

Results: The most frequent clinical manifestations were fever (100%), splenomegaly (87.5%), bicytopenia (73.4%), hypertriglyceridemia (60.9%), hyperferritenemia (48.4%), hypofibrinogenemia (32.8%), and pancytopenia (26.6%). We observed that leucopenia was present in majority of patients (62.5%), and leukocytosis was present in 17.2% patients. About 65.6% had mild to moderate thrombocytopenia, followed by 14.1% patients with severe thrombocytopenia, 14.1% had normal platelet count and 6.3% had thrombocytosis.

Conclusion: The study revealed a diverse clinical spectrum within adult HLH patients, including universal fever, varied hematological irregularities, and mortality rates of 7.8%. These findings emphasize the complexity of HLH and the importance of early diagnosis and tailored interventions for improved outcomes. This study contributes valuable insights to the understanding of HLH's intricate clinical and hematological aspects, informing more informed diagnostic and therapeutic strategies for this complex disorder.

Keywords: Hemophagocytic lymphohistiocytosis (HLH), Clinical characteristics, Laboratory tests, Prognosis

INTRODUCTION

Hemophagocytic Lymphohistiocytosis (HLH) stands as a formidable challenge within the realm of medical understanding, characterized by its complex and often life-threatening manifestations. This rare and potentially fatal disorder arises from an aberrant immune response, resulting in the uncontrolled activation and proliferation of immune cells. As a subject of extensive medical investigation, the clinical spectrum of HLH encompasses a wide range of symptoms and presentations, necessitating comprehensive research to unravel its

intricate pathogenesis, diagnostic criteria, and therapeutic interventions.[1] The diverse array of clinical symptoms associated with HLH reflects the intricate interplay between immune dysregulation and the body's response to infections, malignancies, or other triggers. These symptoms may include fever, hepatosplenomegaly, cytopenias, neurological abnormalities, and coagulopathies.[2] Such a multifaceted presentation poses diagnostic challenges due to the potential overlap with other disorders, further emphasizing the need for a more comprehensive understanding of HLH's clinical nuances.

Whether primary or secondary, HLH is characterized by impaired control of cytotoxic cells during the initial immune response, leading to uncontrolled macrophage activity and hypercytokinemia.[3,4] This triggers an excessive inflammatory response known as a "cytokine storm", driving the main clinical and laboratory abnormalities of HLH and culminating in tissue damage and organ failure.[5] With an untreated median survival of less than 2 months, HLH carries a grim prognosis due to delayed diagnosis from nonspecific clinical findings and symptom overlap with other conditions.[6] Predominantly studied in pediatric patients, the diagnostic guidelines proposed by the Histiocytosis Society in 1991 and updated in 2004 were primarily derived from pediatric cases, even though they are also used for diagnosing adult HLH. However, these criteria's sensitivity and specificity in adults remain untested due to limited adult-focused research on HLH.[7,8] This study contributes to the understanding of adult HLH, by enrolling patients aged 18 and above who met the HLH-2004 criteria, the study maintains a homogeneous group while enabling exploration of additional clinical and laboratory features potentially useful for diagnosing or prognosticating adult HLH

Studying the clinical spectrum of HLH not only holds the potential to enhance diagnostic accuracy but also to guide treatment strategies. Timely intervention is crucial to prevent the often-devastating consequences of unchecked immune activation, such as multi-organ failure. Unravelling the underlying mechanisms that drive the disorder's varying clinical presentations could pave the way for targeted therapeutic approaches, moving beyond the conventional treatments that often involve immunosuppression and hematopoietic stem cell transplantation. In this pursuit, researchers, clinicians, and medical scientists are delving into the intricacies of HLH's immunopathogenesis, genetic predispositions, and molecular underpinnings.[9-11] Collaborative efforts to decipher the diverse clinical aspects of HLH are not only broadening our understanding of immune regulation but also raising hopes for more effective and personalized treatment strategies.

This exploration into the clinical spectrum of HLH serves as a reminder of the ongoing complexities within the medical field. With each discovery, we edge closer to unveiling the mysteries surrounding this disorder, inching towards improved patient outcomes, enhanced quality of life, and perhaps, one day, a definitive cure. As we embark on this journey of exploration and understanding, we are poised to make significant strides in comprehending HLH's clinical spectrum and translating this knowledge into meaningful clinical interventions.

METHODS

This study presents a retrospective cum prospective observational investigation conducted in the Hematopathology Section of the Department of Pathology, following approval from the Institutional Ethics Committee. A meticulously selected cohort of 64 patients meeting strict inclusion criteria formed the focus of this study. These cases were referred to the Hematopathology Division for comprehensive Bone Marrow Aspiration and Biopsy evaluations. Cases already under therapeutic intervention for hemophagocytic syndrome were excluded. Methodologically, a range of investigative techniques

including complete blood count analyses, peripheral blood smear assessments, Bone Marrow Aspiration and Biopsy studies were employed. Additional investigations such as ultrasonography, cytogenetics, and biochemical assays were performed when necessary.

The study utilized Leishman stain for peripheral blood film and Bone Marrow Aspiration staining, alongside hematoxylin and eosin technique for Bone Marrow Biopsy staining. Instruments like Edta-k2 vacutainers for complete blood counts, Salah's needles for aspirations, and Jamshidi's needles for biopsies were employed. Validation centered around heightened Reticuloendothelial activity and hemophagocytosis. Ethical protocols included obtaining informed consent from patients prior to procedures. Primary hemophagocytic lympho-histiocytosis cases underwent cytogenetic analysis. Comprehensive evaluation considered clinical parameters, biochemical indices, and thorough bone marrow examination emphasizing Marrow Hemophagocytosis.

Statistical analysis employed Microsoft Excel and SPSS Version 20.0 for continuous and categorical variables, presented as Mean±SD, frequencies, percentages, and bar diagrams. Ethical and integrity considerations were upheld, devoid of conflicts of interest. Financially, the study was self-driven without external funding, reflecting dedication to scholarly pursuits.

RESULTS

In this section, the results of the study will be described:

Within 64 patients studied, a concentration was noted in the 46-65 years category (39.1%). The ≤ 18 years and 19-45 years categories comprise 17.2% and 35.9%, respectively. Minor representation occurs in > 65 years (7.8%). Mean age: 41.5±19.74 (10 months to 85 years), providing comprehensive insights. Males dominate (65.6%, 42 individuals); females: 34.4% (22 individuals), highlighting pronounced male preponderance.

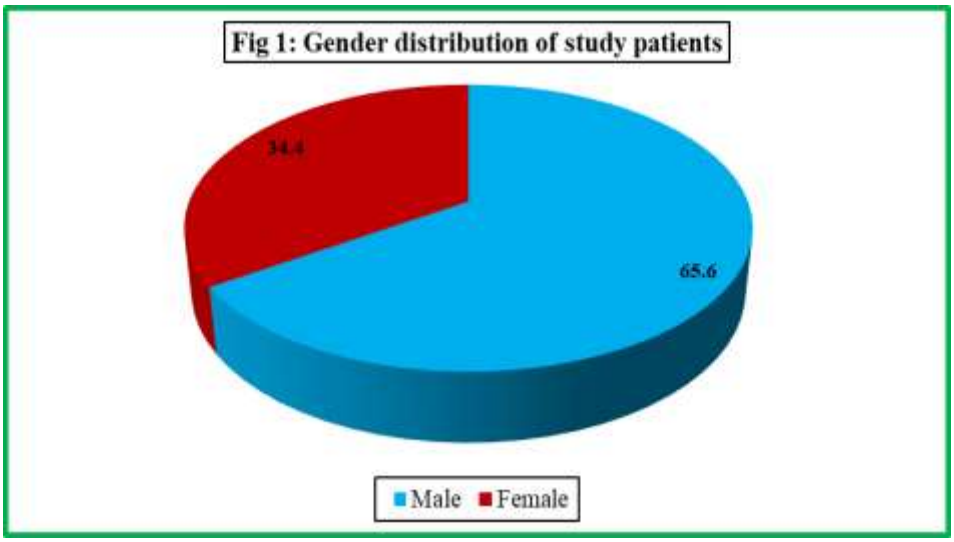

Table 1: Clinical presentation of study patients

Clinical presentation	Number	Percentage
Fever	64	100
Splenomegaly	56	87.5
Bicytopenia	47	73.4
Hypertriglyceridemia	39	60.9
Hyperferritenemia	31	48.4
Hypofibrinogenemia	21	32.8
Pancytopenia	17	26.6

In this table 1, we present the clinical presentation of study patients, showcasing the prevalence of different symptoms and abnormalities within the cohort. The data indicates that all 64 study patients (100%) experienced fever, establishing it as a universal symptom. Splenomegaly was evident in 56 patients (87.5%), underlining

its significant occurrence. Bicytopenia, characterized by deficiencies in two blood cell lines, was observed in 47 patients (73.4%). Hypertriglyceridemia was identified in 39 patients (60.9%), while hyperferritinemia was present in 31 patients (48.4%). Hypofibrinogenemia, signifying lower fibrinogen levels, was seen in 21 patients (32.8%). Pancytopenia, involving a deficit in all three blood cell types, manifested in 17 patients (26.6%). This breakdown of clinical manifestations offers valuable insights into prevalent symptoms and hematological irregularities, enhancing the diagnostic landscape of the studied condition.

Table 2: Hemoglobin (g/dl) of study patients

Hb (g/dl)	Number	Percentage
Severe anemia (<6 g/dl)	9	14.1
Mild to moderate anaemia (6-9) g/dl	44	68.8
Normal (>9)	11	17.2
Total	64	100

Table 2 summarizes the hemoglobin levels observed in the study patients, detailing the distribution across various ranges. Out of the total of 64 patients, 9 individuals (14.1%) displayed severe anemia with hemoglobin levels below 6 g/dl, indicating a significant anemic condition. A majority of patients, 44 (68.8%), exhibited mild to moderate anemia within the range of 6 to 9 g/dl, highlighting its prevalent occurrence. Moreover, 11 patients (17.2%) had normal hemoglobin levels exceeding 9 g/dl. This comprehensive breakdown underscores the distribution of anemia severity and normal hemoglobin concentrations within the studied cohort.

Table 3: Distribution of study patients as per WBC count

WBC Count	Number	Percentage
Leucopenia (<1000-3000)/µl	40	62.5
Normal leukocyte count (3000-3900)/µl	13	20.3
Leucocytosis (>3900)/µl	11	17.2
Total	64	100

Table 3 presents the distribution of study patients according to their white blood cell (WBC) counts, indicating the number and percentage of patients falling within specific ranges. Among the participants, 40 patients (62.5%) exhibited leucopenia, with WBC counts ranging from 1000 to 3000 cells per microliter. A total of 13 patients (20.3%) displayed a normal leukocyte count, falling within the range of 3000 to 3900 cells per microliter. Leucocytosis, characterized by WBC counts exceeding 3900 cells per microliter, was observed in 11 patients (17.2%). This data encapsulates the distribution of WBC counts within the studied group, shedding light on occurrences of leucopenia, normal leukocyte counts, and leucocytosis.

Table 4: Distribution of study patients as per platelet count

Platelet Count	Number	Percentage
Severe thrombocytopenia (<20000)/µl	9	14.1
Mild to moderate thrombocytopenia (20000-140000)/µl	42	65.6
Normal (150000-450000)/µl	9	14.1
Thrombocytosis (>450000)/µl	4	6.3
Total	64	100

In Table 4, we present the distribution of study patients categorized by their platelet counts, along with the corresponding numbers and percentages within each defined range. Among the participants, 9 patients (14.1%) demonstrated severe thrombocytopenia with platelet counts below 20000 cells per microliter. The majority of patients, totaling 42 (65.6%), displayed mild to moderate thrombocytopenia, with platelet counts ranging from 20000 to 140000 cells per microliter. Additionally, 9 patients (14.1%) exhibited a normal platelet count within the range of 150000 to 450000 cells per microliter. Thrombocytosis, denoting elevated platelet counts exceeding 450000 cells per microliter, was observed in 4 patients (6.3%). The table collectively covers all 64 study patients, providing a comprehensive depiction of platelet count distribution within the investigated cohort. Out of the total cases analyzed, 5 individuals succumbed to the condition, constituting a mortality rate of 7.8%. On the other hand, a significant majority of 59 cases (92.2%) exhibited resilience and survived the ordeal. These figures

emphasize the challenging and potentially life-threatening nature of HLH, while also highlighting the potential for positive outcomes through timely intervention and effective management strategies.

DISCUSSION

Hemophagocytic Lymphohistiocytosis (HLH) presents a complex and multifaceted clinical and laboratory spectrum, characterized by dysregulated immune responses and systemic inflammation. This disorder encompasses a wide range of clinical manifestations and hematological abnormalities, making its diagnosis and management particularly challenging. The present study delves into the intricate interplay between clinical presentations and laboratory findings, shedding light on the diverse aspects of HLH.

When analyzing the clinical presentation among the studied patients, a diverse array of clinical manifestations was evident, underscoring the multifaceted nature of HLH. The most prevalent clinical manifestation was fever, which was observed in 100% of the cases, followed by splenomegaly (87.5%), bicytopenia (73.4%), hypertriglyceridemia (60.9%), hyperferritinemia (48.4%), hypofibrinogenemia (32.8%), and pancytopenia (26.6%). Several studies, including those by Melissa et al, Iqbal et al, Li et al, and Sundari et al, have consistently reported fever as a common presenting symptom in HLH cases.[12-15] Fever's universal presence underscores its significance as a prominent diagnostic marker. Notably, studies by Melissa et al and Li et al reported fever in nearly 100% of HLH cases, aligning with our findings.[12,14] Notably, the recalcitrant nature of fever often renders antibiotic treatment ineffective. Splenomegaly, an enlargement of the spleen, was another frequently encountered manifestation (87.5%). These findings align with Zhang et al's observations of splenomegaly in 81% of their cases and Li et al's findings of splenomegaly in 72.9% of patients.[14,16] Laurence et al also reported splenomegaly in 65% of cases, while Melissa et al emphasized its presence in 100% of their patients.[12,17] The manifestation of splenomegaly carries prognostic implications and can aid in gauging the duration of the illness before diagnosis.

Bicytopenia (73.4%) and pancytopenia (26.6%) were prevalent hematological abnormalities. Yaseen et al and our study concurred on the prevalence of bicytopenia and pancytopenia among HLH cases. These hematological findings further emphasize the impact of immune dysregulation on bone marrow function. Bicytopenia and pancytopenia are frequent hematological manifestations, with similar observations made by Yaseen et al and corroborated by our study.[18] Bicytopenia, involving a decline in two out of three cell lines, often progresses to pancytopenia, where all three cell lines are affected. Hyperferritinemia, a hallmark of HLH, was observed in 48.4% of cases. Hyperferritinemia's correlation with macrophage activity and inflammation has been demonstrated in various studies, including Melissa et al, Chandra et al, and Verma et al.[12,19,20] Its role as a diagnostic and prognostic indicator underscores its clinical significance. Hypertriglyceridemia, seen in 60.9% of patients, mirrors findings by Sundari et al and Chandra et al.[15,19] Notably, it is often considered a hallmark of macrophage activation syndrome, which is closely related to HLH.

In the current study, hypertriglyceridemia was observed in 60.9% of the patients, aligning closely with the findings of Sundari et al, who reported hypertriglyceridemia in 59% of their patient cohort.[15] Similarly, Melissa et al and Chandra et al reported corresponding rates of hypertriglyceridemia, with 45% and 40% of their patients respectively exhibiting this abnormality, thereby reinforcing the consistency of our results with their observations.[12,19] Furthermore, our study identified hypofibrinogenemia in 32.8% of patients, mirroring the research by Sundari et al, who documented a hypofibrinogenemia

prevalence of 31% in their patient group.[15] Melissa et al and Chandra et al, in their respective studies, also reported a 40% occurrence of hypofibrinogenemia, lending further support to the concurrence of our findings with theirs.[12,19] It is noteworthy that in the context of adult hemophagocytic lymphohistiocytosis, an association with hypertriglyceridemia and/or hypofibrinogenemia is evident in at least 50% of cases. Although not stipulated as a diagnostic requirement, elevated liver function test results are observed in nearly all instances, underscoring the consistent patterns in this aspect of the disorder's presentation. The convergence of these observations across multiple studies emphasizes the importance of these laboratory parameters as potential indicators of the disease's severity and progression.

In the current study, an analysis of 64 patients reveals a significant distribution of anemia severity. Among these patients, 14.1% exhibited severe anemia, while a substantial majority (68.8%) presented with mild to moderate anemia. This finding aligns with previous studies conducted by Iqbal et al. and Sundari et al., where they similarly reported that over 66% of their subjects displayed mild to moderate anemia.[13,15] Notably, hemophagocytic lymphohistiocytosis (HLH) has been observed to associate with various conditions, such as acute myeloid leukemia, aplastic anemia, and tuberculosis.[21,22] Aplastic anemia, in particular, stands as an immune-mediated disorder characterized by heightened apoptosis of bone marrow stem cells, driven by the release of numerous cytokines from activated T-cells that hinder hematopoiesis. Within the context of HLH, a systemic stimulation of histiocytes and macrophages triggers heightened phagocytosis of hematological components. This intricate interplay points towards genetic, infectious, neoplastic, and immunological factors as contributors to the hyperinflammatory syndrome. Prolonged fever, cytopenias, hepatosplenomegaly, and the distinctive presence of activated, morphologically benign macrophages engaging in hemophagocytosis emerge as primary clinical indicators of HLH. These observations collectively emphasize the intricate interplay between clinical and hematological aspects, underpinning the multifaceted nature of HLH.

In the present study, leucopenia was a prominent feature observed in the majority of patients (62.5%). Furthermore, 20.3% of patients exhibited a normal leukocyte count, while 17.2% demonstrated leukocytosis. These findings are consistent with previous research, such as the study by Sundari et al, who reported similar proportions of leucopenia (59%), normal leukocyte count (22%), and leukocytosis (19%) in their patient population.[15] Similarly, Li et al found that 77.5% of their patients exhibited leucopenia, aligning closely with our study's observations.[14] However, Iqbal et al contradicted these findings, as their study identified leukocytosis as the most common laboratory finding in HLH patients.[13] The prevalence of leucopenia in HLH has clinical implications, as it deviates from the leukemoid reaction commonly associated with increased white blood cell counts. Notably, the rarity of leukemoid reactions in HLH, despite leucopenia being a common symptom of typical scrub typhus, highlights the distinct pathophysiological mechanisms underlying these conditions. Turning to thrombocytopenia, our study revealed that 65.6% of patients experienced mild to moderate thrombocytopenia, whereas 14.1% exhibited severe thrombocytopenia. Additionally, 14.1% demonstrated a normal platelet count, and 6.3% displayed thrombocytosis. These observations correspond with similar findings reported by Sundari et al and Iqbal et al, where a majority of their patients exhibited mild to moderate thrombocytopenia (63% and 70% respectively).[13,15]

Among studied patients, a total of five individuals succumbed to the disorder, resulting in an overall mortality rate of 7.8%. Within this mortality subset, three adult patients met their unfortunate fate due

to sepsis, contributing to an adult mortality rate of 5.66%. Of notable interest, two of these deceased patients fell under the category of primary HLH and were below the age of 18. An in-depth analysis of our data unveiled a noteworthy finding in the pediatric age group, where the mortality rate for HLH reached 18.18%. This aligns with existing studies that have consistently reported mortality rates for pediatric patients ranging from 13% to 28%.[23-25] In contrast, the trajectory of adult HLH progression has proven to be notably challenging and, at times, unpredictable. The fatality rates in this subset exhibit wide variability, spanning from 8% to as high as 60%, as reported in various scholarly sources.[26-28] Our findings harmonize with well-documented reports that establish sepsis, hemorrhage, and multiorgan failure as the predominant culprits behind the mortality patterns observed in HLH. These leading causes of mortality mirror our own study's outcomes, further validating the consistency of our observations with established medical insights. This alignment of findings underscores the critical role of these factors in shaping the trajectory of HLH-related mortality.

CONCLUSION

This comprehensive study highlighted the diverse clinical and hematological spectrum associated with Hemophagocytic Lymphohistiocytosis (HLH). Fever emerged as a universal symptom among all 64 study patients, underscoring its fundamental role as a diagnostic indicator. Splenomegaly, bicytopenia, hypertriglyceridemia, hyperferritinemia, hypofibrinogenemia, and pancytopenia were prevalent manifestations, shedding light on the extensive range of hematological irregularities characterizing HLH. The study also revealed the spectrum of anemia severity, ranging from severe anemia to normal hemoglobin levels, providing a comprehensive understanding of the hematological impact. Leucopenia, normal leukocyte counts, and leucocytosis showcased distinct distributions within the patient cohort, contributing to our comprehension of immune responses in HLH. Similarly, platelet counts exhibited a wide range, emphasizing the variable impact of thrombocytopenia and thrombocytosis on patient profiles. Most notably, the study disclosed a mortality rate of 7.8%, with 5 individuals succumbing to the condition. Conversely, a significant majority exhibited resilience, highlighting the critical role of early diagnosis and tailored interventions in enhancing patient outcomes. Collectively, these findings enrich our understanding of the clinical and hematological intricacies of HLH, contributing to more informed diagnostic and therapeutic approaches in the management of this complex disorder.

Declaration by Authors

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