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A Comprehensive Study of Etiology and Pathogenesis in Hemophagocytic Lymphohistiocytosis

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ABSTRACT

Background: Hemophagocytic syndrome, or hemophagocytic lymphohistiocytosis (HLH), is a rare yet life-threatening hyperinflammatory disorder marked by excessive immune cell activation. This study aims to delineate diverse etiological triggers of HPS and enhance comprehension of its pathogenesis through meticulous analysis of an afflicted cohort.
Methods: Conducted within the Hematopathology Section of the Department of Pathology, this retrospective cum prospective observational study involved 64 meticulously selected patients meeting inclusion criteria. Referral for Bone Marrow Aspiration and Biopsy examinations was the basis for patient inclusion, with approval from the Institutional Ethics Committee.
Results: The average age of the 64 patients ranged from 10 months to 85 years (mean: 41.5±19.74 years). Males exhibited a predominant presence (65.6% vs. 34.4% females). 82.2% of patients displayed haemophagocytosis solely on bone marrow aspirate, while 17.2% manifested haemophagocytosis in both aspirate and biopsy. Secondary HLH predominated (96.9%), with a minor proportion of primary HLH cases (3.1%). Infections were identified in 68.8% of cases, with viral infection as the prominent etiology (20.3%), followed by typhoid (12.5%), hepatitis C (9.4%), sepsis (7.8%), and tuberculosis (7.8%).
Conclusion: This study's amalgamated findings of hematopathological insights and etiological understanding enhance comprehension of HLH, fostering clinical awareness and driving the pursuit of advanced therapeutic approaches.

Keywords: Bone marrow, hemophagocytic lymphohistiocytosis (HLH), hyperferritinemia, primary HLH, secondary HLH

INTRODUCTION

Hemophagocytic syndrome, also known as hemophagocytic lymphohistiocytosis (HLH), is a rare but life-threatening hyperinflammatory disorder characterized by the excessive activation of immune cells. The hallmark of HLH is the presence of activated macrophages that phagocytose blood cells in the bone marrow, liver, spleen, and lymph nodes. The syndrome can be either primary, arising due to genetic mutations, or secondary, occurring in response to various triggers such as infections, malignancies, or autoimmune disorders. In the span of 75 years since its initial discovery, significant strides have been made in comprehending

Hemophagocytic Lymphohistiocytosis (HLH). An early elucidation of this disorder dates back to 1939, when Scott and Robb-Smith delineated a condition marked by erythrophagocytosis within the lymphoreticular system, denoting it as "histiocytic medullary reticulosis" or HMR.[1] Subsequent categorization within malignant histiocytosis followed suit. By 1952, the familial variant of HLH (FHL) garnered detailed explication through Farquhar and Claireaux's documentation of two sibling fatalities attributed to HLH, with a third sibling presenting similarly in 1958.[2,3] Risdall contributed by linking viral associations, proposing the nomenclature "virus-associated HLH," distinguished from malignant histiocytosis.[4] Over time, the expansive nature of this ailment emerged, wherein infections serve as triggers for both primary and secondary HLH presentations. Irrespective of the instigating factor, HLH exhibits compromised cytotoxic cell functionality coupled with heightened macrophage activity, thereby precipitating unrestrained cytokine production, consequent immune dysregulation, and tissue compromise. In the absence of intervention, the dysregulated inflammatory response culminates in severe neutropenia, often culminating in fatality due to bacterial or fungal infections. The ailment's morbidity and mortality rates are strikingly elevated, with historical estimates of long-term survival in 1983 reaching a meager 4%.[5,6] Median survival sans treatment stands at less than two months.[6]

Hemophagocytic Syndrome, an intricate manifestation of dysregulated immune response and cytokine storm, remains a subject of substantive intrigue within the medical community. Recognized for its capacity to induce widespread hematological perturbations and systemic compromise, HPS presents as both a clinical enigma and a diagnostic challenge. This scholarly pursuit, undertaken within the auspices of a distinguished tertiary care hospital, endeavours to marshal a panoptic array of hematopathological methodologies to illuminate the intricate pathogenesis of this syndrome. By meticulously scrutinizing an assorted cohort of afflicted individuals, the study aims not only to delineate the diverse etiological triggers that engender HPS but also to furnish a nuanced comprehension of its nuanced clinical trajectories. As the torchbearer of scientific acumen is thrust forward, guided by the principles of evidence-based inquiry, this inquiry aspires to furnish cogent insights that resonate both within the precincts of scholarly discourse and the corridors of clinical praxis. Through the judicious application of advanced hematopathological modalities, underpinned by a firm commitment to methodological exactitude, this study seeks to contribute substantively to the burgeoning compendium of medical knowledge pertaining to Hemophagocytic Syndrome, thereby potentially fostering enhanced therapeutic paradigms and refined diagnostic approaches.

METHODS

The present study embodies a retrospective cum prospective observational study meticulously orchestrated within the hallowed precincts of the Department of Pathology, specifically the Hematopathology Section, subsequent to the acquisition of requisite endorsement from the Institutional Ethics Committee. A judicious assemblage of 64 patients, meticulously selected in strict adherence to the presiding inclusion criteria, constituted the focal cohort of this study. The central impetus for the inclusion of these cases stemmed from their referral to the Hematopathology Division of the Department of Pathology, specifically for the discerning evaluation of Bone Marrow Aspiration and Biopsy examinations. Cognizant of the necessity for methodological precision, the criteria of inclusion comprehended cases directed to the Hematopathology Division for comprehensive Bone Marrow Aspiration and Biopsy assessments. Conversely, cases already subjected to therapeutic intervention

for primary or secondary instances of hemophagocytic syndrome were held as exclusions from this scholarly undertaking.

The methodological tapestry woven within this study involved an amalgam of investigative modalities. The canvas of inquiry encompassed endeavors such as complete blood count analyses, peripheral blood smear scrutinies, and the pivotal conduits of Bone Marrow Aspiration and Bone Marrow Biopsy studies. Supplementary investigations, inclusive of ultrasonography, cytogenetics, and biochemical assays, were judiciously pursued when deemed essential. Employing a carefully curated spectrum of methodologies, the endeavor harnessed the Leishman stain for peripheral blood film and Bone Marrow Aspiration staining, juxtaposed with the hematoxylin and eosin technique for the staining of Bone Marrow Biopsies. These methodological endeavors were harmoniously orchestrated with the deployment of Edta-k2 vacutainers for complete blood counts, Salah's needles for aspirations, and Jamshidi's needles for biopsies. The intrinsic augmentation in Reticuloendothelial activity, congruently with the demonstration of hemophagocytosis, stood as an axis of validation. In pursuance of the ethical sanctity inherent to medical research, a quintessential prelude to Bone Marrow Aspiration and Biopsy procedures encompassed the obtaining of written and informed consent from the respective patients. Within this ethical embrace, elucidation of queries and the facilitation of signature endorsement were judiciously undertaken.

Instances of primary hemophagocytic lympho-histiocytosis elicited the adjunct scrutiny of cytogenetic analysis. An encompassing evaluation encompassed clinical parameters such as febrile manifestations and organomegaly, paralleled by the scrutiny of biochemical indices including serum ferritin, serum triglycerides, and fibrinogen levels. Through meticulous slide preparation and subsequent appraisal, the elemental precept of thorough bone marrow examination, with an accentuated focus on the demonstration of Marrow Hemophagocytosis, emerged as the quintessence of this study. Accompanying this, the validation of heightened Reticuloendothelial activity was unequivocally substantiated through the demonstrative exhibition of hemophagocytosis by marrow macrophages.

STATISTICAL METHODS

The orchestration of statistical methodologies was both sagacious and rigorous. The assimilated data, scrupulously documented, found its repository within a meticulously designed spreadsheet, wielded by the virtuosity of Microsoft Excel. Subsequent migration of data to the data editor of SPSS Version 20.0, a tool synonymous with analytical prowess, fostered the explication of continuous variables through the mantle of Mean±SD, while categorical variables assumed form through the prism of frequencies and percentages. The visual elucidation of data manifested itself through the eloquent medium of bar diagrams. Manifesting a steadfast commitment to the principled domain of ethical conduct, this study stood unburdened by any ethical concerns. Furthermore, the exalted contours of integrity remained unblemished, as this endeavor bore no trace of conflicting interests. Pertaining to financial considerations, the impetus stemmed from intrinsic passion rather than extraneous fiscal requisites, rendering the banner of "FUNDING REQUIRED: NIL" a quintessential proclamation of scholarly devotion.

RESULTS

The distribution encompasses patients ranging from ≤ 18 years to > 65 years. Out of 64 studied patients, a predominant concentration was observed within the 46-65 years category, constituting 39.1% of the total, while the ≤ 18 years and 19-45 years categories account for 17.2% and 35.9%,

respectively. A minor representation was noted among those aged > 65 years, comprising 7.8% of the total. The computed mean age, presented as Mean±SD (Range)=41.5±19.74 (10 Months to 85 Years), encapsulates the central tendency and dispersion of the age spectrum, affording comprehensive insights into the studied demographic. Of note, the male demographic dominates, accounting for 65.6% (42 individuals) of the entire cohort, while the female contingent constitutes 34.4% (22 individuals). This presentation offers a concise depiction of the gender composition within the investigative ambit, showcasing the pronounced preponderance of male subjects.

Table 1: Haemophagocytosis on bone marrow examination

Haemophagocytosis	Number	Percentage
Aspirate only	53	82.8
Aspirate and trephine	11	17.2
Total	64	100

Table 1 concisely delineates the prevalence of haemophagocytosis ascertained through bone marrow examination, encapsulating pertinent numeric enumerations and their corresponding proportional representations. Specifically, among the total patient cohort of 64 individuals, the phenomena of haemophagocytosis are observed to manifest in distinctive modalities. Predominantly, 82.8% (53 cases) exhibit haemophagocytosis solely through aspirate analysis, while a discernible subset of 17.2% (11 cases) concurrently exhibit haemophagocytosis on both aspirate and trephine evaluations. The comprehensive synthesis of these distinct categories culminates in the cumulative tally of 64 patients, thereby enveloping the entirety of the studied dataset. This tabulated presentation affords an incisive snapshot of the incidence of haemophagocytosis within the realm of bone marrow investigation, reflective of its nuanced manifestations across varying diagnostic methodologies.

Table 2: Distribution as per types of HLH

Types of HLH	Number	Percentage
Primary HLH	2	3.1
Secondary HLH	62	96.9
Total	64	100

Specifically, among the total assemblage of 64 patients, the stratification of HLH types evinces distinct patterns. Notably, 3.1% (2 instances) manifest the primary HLH variant, while the preeminent majority of 96.9% (62 instances) substantiates the secondary HLH phenotype. This summative integration of diverse HLH categories culminates in the encompassing count of 64 patients, enshrining the totality of the studied subject pool. This tabular exposition provides a clear insight into the prevalence of distinct HLH types within the purview of the study, attesting to the prevailing predominance of secondary HLH manifestations.

Table 3: Showing etiology of study patients

Etiology	Number	Percentage
Viral infection	13	20.3
Typhoid	8	12.5
Hepatitis C	6	9.4
Sepsis	5	7.8
Tuberculosis	5	7.8
Dengue	2	3.1
Pneumonia	2	3.1
Hepatitis A	1	1.6
Infectious mononucleosis	1	1.6
Malaria	1	1.6
Dual deficiency anemia	4	6.3
Iron deficiency anemia	3	4.7
Rheumatoid arthritis	3	4.7
Vitamin B12 deficiency	2	3.1
Primary HLH	2	3.1
Colliod nodule	1	1.6
Idiopathic thrombocytic purpura	1	1.6
Nonspecific colitis	1	1.6
Multiple myeloma	1	1.6
Pustular psoriasis	1	1.6
Splenic haemangioma	1	1.6
Total	64	100

Table 3 succinctly presents the multifaceted panorama of etiological attributions within the studied patient cohort, encapsulating relevant numeric counts and their corresponding proportional dispositions. The diverse etiologies underpinning the observed conditions are meticulously enumerated and categorized, providing a comprehensive insight into the spectrum of causative factors. Notably, the etiological tapestry was marked by the prominent contribution of viral infections, encompassing 20.3% (13 instances) of the patient population. Subsequently, the contributory role of Typhoid was noted at

12.5% (8 instances), while Hepatitis C, Sepsis, Tuberculosis, and Dengue each represent a noteworthy proportion at 9.4%, 7.8%, 7.8%, and 3.1% respectively. Furthermore, diverse etiologies including Pneumonia, Hepatitis A, Infectious Mononucleosis, Malaria, Dual Deficiency Anemia, Iron Deficiency Anemia, Rheumatoid Arthritis, Vitamin B12 Deficiency, Primary HLH, Colloid Nodule, Idiopathic Thrombocytic Purpura, Non-Specific Colitis, Multiple Myeloma, Pustular Psoriasis, and Splenic Hemangioma each contribute in varied degrees as reflected in table 3, collectively culminating in the total of 100% across 64 patients.

DISCUSSION

HLH, characterized by aberrant immune activation and cytokine storm, presents a complex and enigmatic clinical entity. Its multifaceted etiology, diverse clinical manifestations, and potential for rapid and fatal progression underscore the necessity for a comprehensive understanding of its underlying mechanisms and contributing factors. In this light, the discerning application of hematopathological techniques emerges as an indispensable modality to shed light on the underlying pathophysiology of HLH. In the present study, the comprehensive analysis of patient demographics within the context of Hemophagocytic Lymphohistiocytosis (HLH) presents intriguing insights into the epidemiological dimensions of this intricate syndrome. The ascertained distribution of patient ages, characterized by a mean age of (41.5±19.74) years and a broad age range spanning from 10 months to 85 years, offers a snapshot of the diverse spectrum of individuals susceptible to HLH. This variance in age underscores the syndrome's capacity to transcend generational boundaries, impacting individuals across a wide expanse of life stages. Of particular note is the preponderance of patients within the age stratum of 46-65 years, constituting a substantial majority at 39.1%. This finding aligns with a potential age-related predilection toward HLH manifestation, potentially implicating distinct immunological and physiological factors operative within this age range. In a scholarly investigation undertaken by Esmaili et al., the derived mean age of the patient cohort amounted to 39.2 years—an observation that resonates congruently with the findings of our current study.[7] Similarly, the research conducted by Li et al. revealed a mean patient age of 44 years, aligning harmoniously with the age profile evident in our investigation.[8] Notably, Nisal et al., in their comprehensive exploration, noted a mean patient age of 35.08 years, with a notable concentration within the age stratum of 31-40 years—observations strikingly akin to the age distribution evident in our present inquiry.[9] It is worth highlighting, however, that the study executed by Iqbal et al. unveiled an average patient age of 30.8 years, while Sundari et al. reported a comparable mean age of 30.7 years.[10,11] These age dispersions, significantly deviating from the age demographics elucidated within our study, underscore the influence of variances in study designs and the diversity of inclusion criteria for patients across the distinct studies.

Evident within the observed patient distribution was a notable male predominance, exhibiting a ratio of 65.6% male patients in comparison to 34.4% female patients. This prevailing gender bias, resonant with findings from extensive scholarly investigations, finds congruence with previous studies.[8,9] For instance, an analogous inquiry conducted by Nisal et al. reported a male-female ratio of 53.3% to 46.7%, respectively.[9] Similarly, Li et al.'s study encompassing 85 patients unveiled a gender distribution of 75.2% male and 24.7% female, thereby reaffirming congruity with our current findings.[8] Additional concordant evidence emerges from Li J et al.'s research, wherein a male predominance of 52.42% was observed among a cohort of 103 patients.[12] While hemophagocytic lymphohistiocytosis (HLH)

can afflict individuals of diverse ages, its predilection for infants and young children stands as a discernible trend. Although both genders, boys and girls, are comparably affected in these juvenile populations, the syndrome exhibits a propensity to manifest differently in adulthood, with a relatively higher incidence in men. Moreover, the initial clinical presentation of HLH bears semblance to common infections, malignancies, febrile origins of unknown etiology, and autoimmune disorders, necessitating astute differentiation within the diagnostic landscape.[13]

Upon subjecting bone marrow specimens to thorough examination for the presence of haemophagocytosis, a prominent pattern emerged within our patient cohort. Notably, a substantial majority of individuals (82.2%) exhibited haemophagocytosis exclusively within the bone marrow aspirate, with a notable minority of cases (17.2%) displaying concurrent haemophagocytosis in both the aspirate and the biopsy. Intriguingly, instances wherein the aspirate yielded negative findings while the trephine biopsy yielded positive results were notably absent. Employing the immunohistochemical marker CD 68, the manifestation of haemophagocytic activity within the bone marrow trephine was discerned. These findings closely align with prior investigations, such as the study by Sundari et al., wherein 19% of patients demonstrated haemophagocytosis within both the aspirate and the trephine, with the remaining 81% exclusively displaying haemophagocytosis in the aspirate.[11] Comparable to the works of Yaseen et al. and Xiao L. et al., our investigation reported a similar incidence of hemophagocytosis within the bone marrow aspirate, with 100% and 91% prevalence rates, respectively.[14,15] This concurrence underscores the robustness and consistency of our findings within the broader context of hemophagocytosis prevalence.

Broadly, the classification of Hemophagocytic Lymphohistiocytosis (HLH) pivots upon the distinction between primary (genetic) and secondary (acquired) etiologies, albeit the clinical differentiation frequently proves intricate due to substantial symptomatic overlap. Primary HLH stems from genetic anomalies disrupting natural killer (NK) cell functionality, perturbing genes involved in the genesis, migration, or discharge of perforin granules critical for target cell lysis. In contrast, secondary HLH emerges from a diverse array of causative factors encompassing infections, autoimmune disorders, and malignancies. Within our present study, a marked predominance of secondary HLH was evident, accounting for 96.9% of cases, while primary HLH accounted for 3.1%. This distribution aligns congruently with Sundari et al.'s study, where 97% of cases were categorized as secondary HLH.[11] The prevalence of primary HLH was noted to be greater in the pediatric population, although our study encompassed a notably lower proportion of pediatric patients (17.2%).

Upon meticulous analysis of the etiological underpinnings of Hemophagocytic Lymphohistiocytosis (HLH), a discerning pattern emerges, wherein infection-associated origins account for a substantial 68.8% of cases. Within this category, viral infections emerge as the prevailing etiology in 20.3% of instances, followed by 12.5% attributed to typhoid, 9.4% linked to hepatitis C, 7.8% linked to sepsis, and an equivalent 7.8% associated with tuberculosis. Additional less common etiologies include colloid nodule, idiopathic thrombocytic purpura, non-specific colitis, multiple myeloma, pustular psoriasis, and splenic hemangioma. Comparative analysis with prior studies reveals consonance with findings reported by Melissa et al., where infection-associated HLH was observed in 50% of cases, while Sundari et al. documented a prevalence of 70%, mirroring our observations.[11,16] Discrepancies arise in terms of the frequency of viral infections as implicated etiologies, with Melissa et al. and Zhang et al. noting an elevated frequency, whereas Chandra et al. observed a balanced presentation of bacterial and viral sources.[17]

The study by Sundari et al. corroborates our results, with viral infection constituting the most common etiology in 28%, and typhoid-associated HLH at 15%.[11] The intricate landscape of infection-associated HLH, encompassing infection-associated hemophagocytic syndrome (IAHS), is predominantly attributed to Epstein-Barr virus (EBV) and other tropical afflictions such as tuberculosis, malaria, leishmaniasis, and typhoid, especially in the subcontinent. The prevalence of such infections is amplified by challenging circumstances, including inadequate sanitation, population density, and compromised water quality, particularly prevalent in developing nations such as those in Asia. Of concern is the potential exacerbation of these ailments by secondary HLH, an infrequent yet formidable condition that harbors fatal consequences. In essence, this comprehensive investigation underscores the prominent role of infections as etiological drivers of HLH, bearing significant implications for patient management and public health considerations in regions confronted by endemic infectious burdens.

CONCLUSION

The amalgamation of hematopathological findings and etiological insights culminates in a panoramic comprehension of HLH, propelling clinical awareness and the quest for refined therapeutic strategies. Moving forward, embracing a multidisciplinary approach will be pivotal to unravelling the complexities enshrouding this intriguing syndrome and affording enhanced patient care.

Declaration by Authors

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