Observational Study

Medicine

OPEN

Outcome of patients with primary and secondary hemophagocytic lymphohistiocytosis

A retrospective analysis from a tertiary care center

Abdul Muqtadir Abbasi, MBBS, FCPS[a], Mohammad Usman Shaikh, MBBS, FCPS[b], Muhammad Shariq, MBBS, FCPS[c], Muhammad Salman Arif, MBBS[a], Ainan Arshad, MBBS, FCPS[d], Ahmed Raheem, MSc, MPhil[e], Natasha Ali, MBBS, FCPS, MSc[b,*]

Abstract

Hemophagocytic lymphohistiocytosis (HLH) is a progressive and potentially life-threatening disorder. It is classified into primary and secondary HLH. The objective of our study was to determine the outcome of primary and secondary HLH in pediatric and adult patients based on HScore and treatment modality. We conducted a retrospective analysis done from July 2010 to June 2020. Variables analyzed included age, gender and history of death in siblings. HScore was used for disease classification while clinical and laboratory findings which were required to fulfill the HScore diagnostic criteria were also recorded. Continuous variables were summarized as median and categorical variables as frequencies and percentages. Categorical variables were compared using chi-square test and Fisher Exact test. Significance of different variables between primary and secondary HLH was calculated using independent-samples *t* test. A *P* value of $< .05$ was taken as significant. A total of 51 patients were included in the analysis (41 in primary and 10 in secondary HLH group). In primary HLH, 36 patients were in the pediatric age group and 12.2% had a history of death in sibling. All 41 patients had increased ferritin and decreased fibrinogen levels. The overall survival in primary HLH was 44%. In the secondary HLH group, viral infections were the most common etiology and ferritin was increased as well. The overall survival in secondary HLH was 60%. The median survival was 15 ± 4.8 months. The overall survival of both groups combined was 53%. Primary HLH should be considered in pediatric patients who present with pancytopenia and hepatosplenomegaly. In centers where genetic testing is not available, HScore along with serum ferritin and fibrinogen is a good substitute for disease classification.

Abbreviations: CMV = cytomegalovirus, HAART = Highly Active Anti-Retroviral Therapy, HIV = human immunodeficiency virus, HLH = hemophagocytic lymphohistiocytosis, ICD = international classification of diseases, sIL-2R = soluble interleukin 2 receptor.

Keywords: HLH, H-score, Pakistan, primary, secondary

1. Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a progressive and potentially life-threatening disorder secondary to abnormally increased activity of immune system with release of inflammatory cytokines.[1] It is a rare disease predominantly affecting infants; however, it can be observed at all ages. Pathogenesis primarily involves cytotoxic T cells, macrophages and natural killer cells.[2,3] Hyper activation of immune cells leads to multisystem organ dysfunction and eventually death. HLH is most commonly noted in response to some underlying triggers such as infections, autoimmune disorders or malignancies.[4–6] Most patients have an underlying etiology. However, children may also have an underlying genetic defect. Studies have been performed previously to look for underlying genetic abnormalities in adult patients with HLH as well. Zhang et al[7] conducted a study in 175 adults where 25 (14%) patients revealed missense and splice-site sequence variants in PRF1. Similarly, Chen et al[8] studied 6 genes in Chinese patients of whom 22 were aged > 18 years and in the cohort, 33% showed genetic variants of HLH. In contrast to pediatric patients, HLH in adults results from the combination of inherited genetic mutations and extrinsic triggers.

HLH is broadly classified into primary HLH with inherited genetic defects in genes affecting the cytotoxic pathways of T and NK cells and secondary or acquired HLH which includes

The authors have no funding and conflicts of interest to disclose.

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

[a] Department of Oncology, Aga Khan University Karachi, Karachi, Pakistan, [b] Department of Pathology and Laboratory Medicine/Oncology, Aga Khan University Karachi, Karachi, Pakistan, [c] Department of Pathology and Laboratory Medicine, Aga Khan University, Karachi, Pakistan, [d] Department of Internal Medicine, Aga Khan University Karachi, Karachi, Pakistan, [e] Department of Emergency Medicine, Aga Khan University Karachi, Karachi, Pakistan.

**Correspondence: Natasha Ali, Department of Pathology and Laboratory Medicine/Oncology, Aga Khan University Karachi, P.O. Box 3500, Stadium Road, Karachi 74800, Pakistan (e-mail: natasha.ali@aku.edu).*

How to cite this article: Abbasi AM, Shaikh MU, Shariq M, Arif MS, Arshad A, Raheem A, Ali N. Outcome of patients with primary and secondary hemophagocytic lymphohistiocytosis: A retrospective analysis from a tertiary care center. Medicine 2023;102:43(e34898).

Received: 9 May 2023 / Received in final form: 7 July 2023 / Accepted: 3 August 2023

http://dx.doi.org/10.1097/MD.0000000000034898

patients who develop the syndrome in response to infections like, cytomegalovirus (CMV), Ebstein Barr Virus, bacteria and fungi. Malignancies such as lymphomas and autoimmune disorders (e.g., systemic juvenile idiopathic arthritis or systemic lupus erythematous) are also implicated as predisposing illnesses[6]

HLH, which manifests in the background of a preexisting rheumatological disorder, is also known as macrophage activation syndrome[9]

The commonly used diagnostic criteria was based on HLH-2004 guidelines[10] which required molecular genetic abnormality for primary familial HLH or 5 of 8 criteria which include fever; cytopenias, splenomegaly; hypertriglyceridemia, hypofibrinogenemia, elevated serum ferritin, elevated soluble interleukin 2 receptor (sIL-2R), hemophagocytosis in bone marrow spleen or lymph nodes, and low or absent NK cell activity.

However, recently, a new diagnostic scoring system for HLH,[11] the HScore was introduced for adults which was retrospectively also validated in 2 other cohorts of pediatric and adult patients. It was noted that HScore was more accurate when compared to HLH 2004 diagnostic criteria with sensitivity and specificity of 100% and 80% respectively for children and 90% and 79% for adults, respectively.

In this paper we have determined the outcome of primary and secondary HLH in pediatric and adult patients based on H sore and treatment modality.

2. Materials and methods

This study was performed at Aga Khan University Hospital Karachi, Pakistan using non-probability (nonrandom) consecutive sampling technique. It was a cross-sectional retrospective analysis done over a period of 10 years (July 2010 till June 2020). We included patients of all age groups who were diagnosed as HLH (primary and acquired) and macrophage activation syndrome secondary to autoimmune disorder using HScore which was calculated accordingly and the diagnosis of HLH was highly suggestive in patients with HScore ≥ 169. All other patients other than the diagnosis of HLH were excluded. Using ICD version 9 (diagnosis code 288.4), medical record data of patients was retrieved. Variables for analysis included age, gender and history of death in sibling. Clinical and laboratory findings which were required to fulfill the HScore diagnostic criteria e.g., history of intake of immunosuppressive drugs, body temperature (in Celsius), hepatomegaly, splenomegaly or both as hepatosplenomegaly, cytopenias, serum ferritin, triglyceride, fibrinogen, glutamic oxaloacetic transaminase and hemophagocytosis on bone marrow aspirate and trephine were also recorded. Other variables were etiological or precipitating factors such as viral infections, neoplasia, autoimmune disorders, and pharmacological interventions including cytotoxic drugs, the outcome and the median follow up. Continuous variables were summarized as median and categorical variables as frequencies and percentages. Categorical variables were compared by using chi-square test and Fisher Exact test. Significance of different variables between primary and secondary HLH was calculated by using independent-samples *t* test. A *P* value of < .05 was taken as significant. Survival graphs were calculated using the Kaplan–Meier method. IBM SPSS Statistics for Windows, Version 23.0. (IBM Corp, Armonk, NY) was used for the analysis. This study received exemption from institutional ethical review committee since we performed retrospective collection of data. All data supporting this study are provided in the results section of this paper.

3. Results

A total of 55 patients were identified during the study period. Four patients were excluded because they were lost to follow up after first encounter. The remaining 51 patients were included for further analysis. This cohort of patients was further divided into primary and secondary HLH. As the facility of genetic testing is not available at our institution, history, clinical examination, laboratory parameters, high HScore and the exclusion of secondary precipitating factors were used for the provisional diagnosis of Primary HLH.

A total of 41/51 patients (80%) were identified as primary HLH. Thirty-six patients (87.8%) belonged to the pediatric age group category. Fever was not a presenting symptom and 12.2% patients revealed a history of death in siblings. Palpable hepatosplenomegaly was present on examination in 57% of patients. Laboratory findings showed presence of anemia and thrombocytopenia in all 41 patients. Bone marrow examination revealed hemophagocytosis in 17 (41.5%) patients. Among biochemical markers, all 41(100%) patients had a high serum ferritin level (more than 500 ng/mL). All patients revealed hypofibrinogenemia (<200 mg/dL). In primary HLH, the median HScore was 188 (109–270) and in secondary HLH, H-Score was 212 (133–271). H-Score of more than 169 was highly suggestive of HLH.[11] The minimum H-Score in our study was 109 while median HScore was 188; 30 patients with primary HLH (73%) had a score of > 169 (other parameters are shown in Table 1). The significant laboratory parameters for survival in these patients were serum ferritin and fibrinogen (Table 2; Fig. 1). Ten patients were diagnosed as secondary HLH and the etiology/precipitating factors in these 10 patients were viral infections (H1N1 influenza n = 2, CMV n = 1, human immunodeficiency virus [HIV] n = 1) diagnosed through polymerase chain reaction methodology, autoimmune disorders (Stills disease n = 3), lymphoproliferative

Table 1

Patients' demographic and laboratory features in primary HLH.

Characteristics	Total (%, n)
Total (n = 41)	
Age	
1–12 mo	53.7 (22)
13mo to 3 yr	9.8 (4)
4–10 yr	19.5 (8)
11–18 yr	4.9 (2)
19–37 yr	12.2 (5)
Female	31.7 (13)
Male	68.3 (28)
Male to female ratio	2.1
History of death of siblings	
Yes	12.2 (5)
No	48.8 (20)
Not documented	39 (16)
Laboratory parameters	Median (range)
Hemoglobin, g/dL	8.1 (4–11.9)
WBC (4–11 × 10^9/L)	5.1 (3.3–8.5)
Platelets (150–400 × 10^9/L)	43 (16–101)
Temperature, °C	37 (37–37.6)
AST, µ/L	228 (109–665)
Ferritin, ng/mL	6602 (1586–14,437)
Fibrinogen, mg/dL	101 (63–161)
Triglyceride, mg/dL	305 (262–386)
Hemophagocytosis features on bone marrow	41.5 (17)
H score	188.5 (109–270)
H score > 169	30/41 (73)
Outcome	
Survived	43.9 (18)
Expired	56.1 (23)
Follow up (wk)	11 (6–400)
Treatment	
HLH protocol	31.7 (13)
Steroids	61 (25)
Other immunosuppressive	7.3 (3)

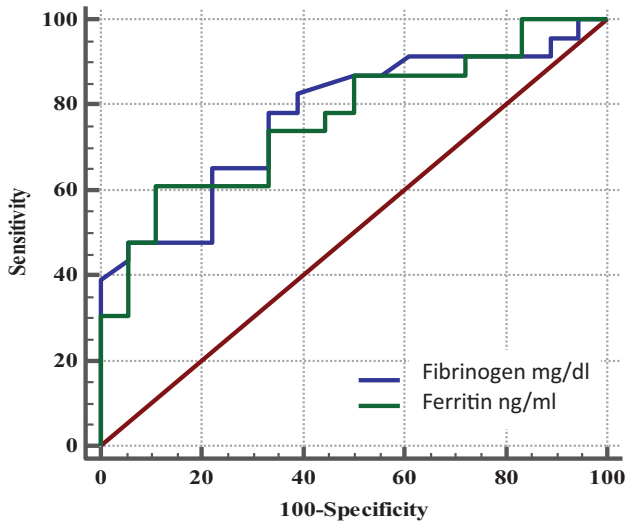
AST = aspartate aminotransferase, HLH = hemophagocytic lymphohistiocytosis.

Table 2

Variables affecting outcome in primary HLH.

	Survived (n = 24)	Expired (n = 27)	
Clinical parameters	**Median (25th–75th)**	**Median (25th–75th)**	***P* value**
Hgb, g/dL	7.68 ± 1.96	8.36 ± 1.98	.221
WBC ×10⁹/L	5.1 (3.35–8.55)	4.9 (3.3–8.5)	.985
Platelets × 10⁹/L	56.5 (17–108)	44 (21–101)	.947
Temperature, °C	37 (36.5–38.5)	37 (37–38)	.482
Triglyceride, mg/dL	343.61 ± 139.39	334.22 343.61 ± 120.12	.799
AST, µ/L	157 (82–270)	228 (117–673)	.159
Ferritin, ng/mL	4404 (1351–8395)	14,232 (4500–33,708)	.010*
Fibrinogen, mg/dL	152.5 (106–190)	86.65 (50–109)	<.001*
H score	188.62 ± 38.74	195.15 ± 42.38	.571

AST = aspartate aminotransferase, HLH = hemophagocytic lymphohistiocytosis.
**P* value of <.05



Variable	Fibrinogen	Ferritin
AUC [95% CI]	0.773 [0.615 to 0.889]	0.766 [0.607 to 0.884]
Cut off Criterion	≤108	>7964
Sensitivity [95% CI]	78.26 [56.3 - 92.5]	60.87 [38.5 - 80.3]
Specificity [95% CI]	66.67 [41 - 86.7]	88.89 [65.3 - 98.6]
+ LR [95% CI]	2.35 [1.2 - 4.7]	5.48 [1.4 - 21.1]

Figure 1. Sensitivity and specificity of serum fibrinogen and serum ferritin in the diagnosis of HLH. HLH = hemophagocytic lymphohistiocytosis.

Table 3

Laboratory features in secondary HLH (n = 10).

Laboratory parameters	Median [range]
Hgb, g/dL	7.8 [6.0–9.3]
WBC (4–11 × 10⁹/L)	4.6 [2.0–28.4]
Platelets (150–400 × 10⁹/L)	65 [15–399]
AST, µ/L	175 [70–571]
Ferritin, ng/mL	28,597 [2568–165,000]
Fibrinogen, mg/dL	162 [30–686]
Triglyceride, mg/dL	359 [145–582]
H score	212 [133–271]

AST = aspartate aminotransferase, HLH = hemophagocytic lymphohistiocytosis.

disorders (1 patient each for Hodgkin lymphoma and peripheral T cell lymphoma, lymph node biopsy proven) and immunodeficiency (Chediak Higashi syndrome n = 1 diagnosed on peripheral blood film findings).

There was a male preponderance with a male to female ratio of 7:3. Median age was 25.5 years (7 months–52 years). Serum ferritin was markedly elevated with a median level of 28,597 (2568–165,000) which was significantly high when compared to patients with primary HLH. The HScore was 212 (133–271) and 9 patients (90%) had an HScore of > 169. Out of the 10 patients, only 3 revealed hemophagocytosis on bone marrow examination (other parameters are given in Table 3).

Out of the 41 primary HLH patients, 38 patients received some form of treatment. Thirteen patients received HLH 2004 protocol while another 22 patients received steroids only. Statistically, high serum ferritin and low serum fibrinogen level were associated poor outcome (Table 2). Survival was better in patients who received HLH 2004 protocol when compared to those who received only steroids in this group (Fig. 2). Till the final analysis of this group, 18 patients (43.9%) were alive. The median survival of both groups combined was 15 ± 4.8 months (Fig. 3).

In the secondary HLH category, which consisted of 10 patients, 3 patients had presence of hemophagocytosis in bone marrow. HScore of > 169 was present in 9/10 patients (90%). Five patients received only steroids and 2, with lymphoproliferative disorder received steroids along with chemotherapy. The remaining 2 patients were started on HLH 2004 protocol. One patient was placed on HAART (highly active anti-retroviral therapy) for HIV infection. Four patients expired in secondary HLH group, one each with PTCL (peripheral T cell lymphoma), Chediak Higashi, HIV and Stills disease. These deaths occurred due to the underlying diagnosis, aggravated by HLH. Further details of secondary HLH patients are given in Table 4.

4. Discussion

HLH is a rare multi system, life threatening disorder characterized by extensive immune response with dysregulated macrophages and lymphocytes.[12] It predominantly affects pediatric age group and our study has shown similar distribution with 78% of patients being less than 18 years of age with a median age of 9 years at the time of presentation. Internationally, the male-to-female ratio is approximately 1:1, however in our study the ratio was 2.4:1 with male predisposition.

Genetic mutations are common in primary HLH[13] that usually manifest during infancy and childhood with predominant mode of inheritance being autosomal recessive. Currently we do not have the facility of mutational analysis of HLH at our center and there are financial constraints as well. However, in our cohort, 10% of patients had a history of death of a sibling in early childhood.

From clinical perspective, majority of the patients present with fever[12,14] in this disease however in our group, only 19% had fever. This can be attributed to the excessive use of antipyretics in our population prescribed by local general practitioners. On abdominal examination, 57% revealed hepatosplenomegaly, 14% had splenomegaly and 8% showed hepatomegaly only which is comparable to international medical literature.[15]

Cytopenias are a very common laboratory finding in HLH.[14] Most of these patients have anemia and thrombocytopenia, which was also noted in 94% and 82% respectively in our study. Leucopenia was a less frequent finding.[16]

Whenever there is a high index of suspicion of HLH, serum ferritin[17] is a very useful surrogate marker to guide the physician for further workup. Significantly raised ferritin levels have few differentials including poor iron chelation in β thalassemia

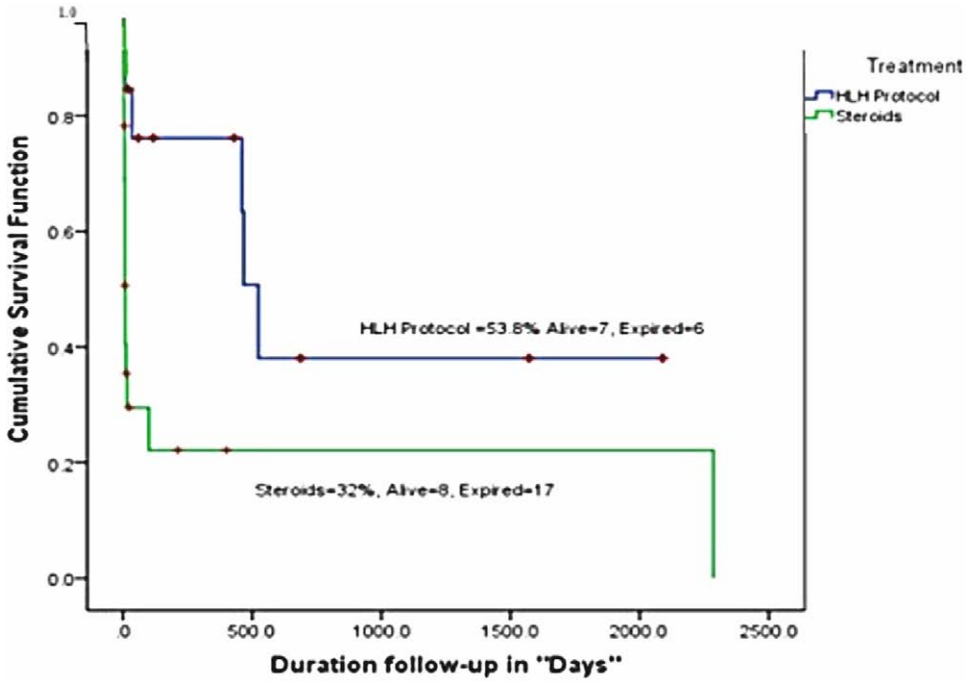


Figure 2. Survival of patients with Primary HLH (HLH 2004 protocol versus only steroids). HLH = hemophagocytic lymphohistiocytosis.

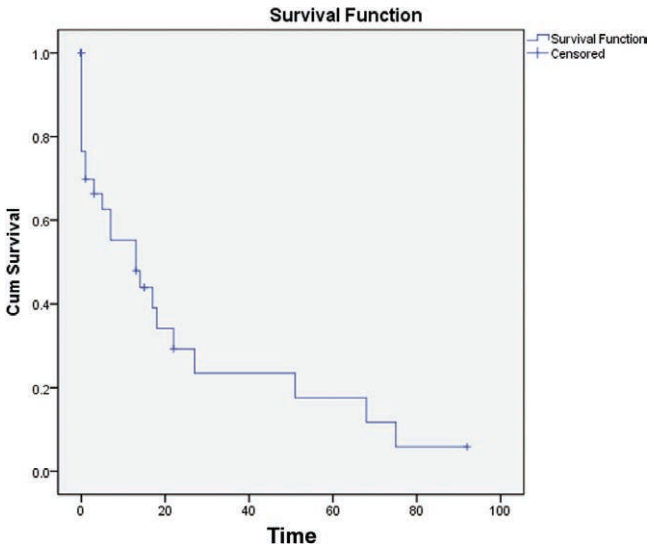


Figure 3. Overall survival.

major and acute hepatic failure.[18] Otherwise raised serum ferritin level has increased sensitivity and specificity for HLH.[19] In the HLH-94 study, ferritin levels greater than 500 ng/mL were seen in 93% of HLH patients.[20] In 98% of our patients combining both primary and secondary HLH, serum ferritin was > 500 ng/mL and 60% had levels of more than 5000 ng/mL.

Almost all patients have evidence of liver dysfunction in HLH that is evident on baseline laboratory investigations.[21] Hypertriglyceridemia and hypofibrinogenemia is also very common in HLH[22] and our patients showed similar pattern. Hemophagocytosis was found in approximately half of our patients, which is a common finding on bone marrow examination but it is not pathognomonic of HLH.[23]

HScore of > 169 was found in 30/41 (73%) of primary and 9/10 (90%) of secondary HLH patients. In the past, most institutes used HLH-2004 based diagnostic criteria,[10] which required molecular genetic abnormality for primary familial HLH or 5 of 8 criteria which include fever; cytopenias, splenomegaly; hypertriglyceridemia, hypofibrinogenemia, elevated serum ferritin, elevated sIL-2R, hemophagocytosis in bone marrow spleen or lymph nodes, and low or absent NK cell activity. However, in third world countries like ours, laboratory testing facility of genetic markers like sIL-2R and NK cell activity are not available. In addition, patients have severe financial constraints. In contrast most variables included in HScore are readily available and its usefulness is well established.[11,24]

Secondary HLH was seen in 10 patients. Common causes reported in medical literature include lymphoproliferative disorders, autoimmune diseases and viral infections.[4] Our study found similar etiologies in our patients with viral infections being the most common among them.

Early studies on outcome showed worse prognosis and high fatality rate in children with primary HLH who received no treatment.[25] Long-term follow-up studies from the HLH-94[26] and 2004 trials[27] revealed an estimated 5-year survival of approximately 50%. However, long term survival is only possible with allogeneic bone marrow transplant.[28] Secondary HLH which is more commonly seen in adult also carries high mortality rate ranging from 26.5% to 74.8%.[29] Mortality rate has been shown to be somehow lower when HLH is associated with autoimmune disorders (8–22%), while, it is very high when it is associated with lymphoproliferative disorders. In our study, the combined overall survival of both primary and secondary HLH was 53%. The survival rate was 43.9% in primary HLH while 60% in secondary HLH respectively.

We had a high percentage of missing data for history of death in siblings and the median follow-up period is relatively short. Both of these are limitations of our study

5. Conclusion

Primary HLH is a rare disease with relatively increased prevalence in pediatric age group and should be considered in any pediatric patient who presents with pancytopenia and hepatosplenomegaly. For initial screening, serum ferritin and serum

Table 4

Patient characteristics and outcome of secondary HLH (n = 10).

	Age (yr)	Gender	Diagnosis	Treatment	Outcome
1	39	Male	Hodgkin's lymphoma	Chemotherapy and steroids	Alive
2	52	Male	PTCL	Chemotherapy and steroids	Expired
3	7	Male	Chediak higashi	HLH 2004	Expired
4	32	Female	H1NI	Steroids	Alive
5	7 mo	Male	H1N1	Steroids	Alive
6	14	Male	HIV	Steroids and HAART	Expired
7	25	Male	CMV	HLH 2004	Alive
8	44	Male	Stills disease	Steroids	Alive
9	14	Female	Stills disease	Steroids	Expired
10	26	Female	Stills disease	Steroids	Alive

CMV = cytomegalovirus, HAART = Highly Active Anti-Retroviral Therapy, HIV = human immunodeficiency virus, HLH = hemophagocytic lymphohistiocytosis, PTCL = peripheral T cell lymphoma.

fibrinogen levels are useful. HScore is a reliable scoring system for further characterization. Primary HLH carries very high mortality and HLH 2004 protocol can provide survival advantage. Secondary HLH is rare but more common in adults with steroid therapy being the mainstay of treatment.

Author contributions

Conceptualization: Abdul Muqtadir Abbasi, Mohammad Usman Shaikh, Natasha Ali.
Data curation: Muhammad Salman Arif, Ainan Arshad.
Formal analysis: Ahmed Raheem.
Methodology: Abdul Muqtadir Abbasi, Muhammad Shariq, Ainan Arshad.
Project administration: Ainan Arshad.
Software: Ahmed Raheem.
Supervision: Mohammad Usman Shaikh, Muhammad Shariq, Ainan Arshad, Natasha Ali.
Validation: Ahmed Raheem, Natasha Ali.
Writing – original draft: Abdul Muqtadir Abbasi.
Writing – review & editing: Abdul Muqtadir Abbasi, Mohammad Usman Shaikh, Muhammad Shariq, Muhammad Salman Arif, Ahmed Raheem, Ainan Arshad, Natasha Ali.

References

[1] Filipovich A, McClain K, Grom A. Histiocytic disorders: recent insights into pathophysiology and practical guidelines. Biol Blood Marrow Transplant. 2010;16(1 Suppl):S82–9.
[2] Hayden A, Park S, Giustini D, et al. Hemophagocytic syndromes (HPSs) including hemophagocytic lymphohistiocytosis (HLH) in adults: a systematic scoping review. Blood Rev. 2016;30:411–20.
[3] Pachlopnik Schmid J, Côte M, Ménager MM, et al. Inherited defects in lymphocyte cytotoxic activity. Immunol Rev. 2010;235:10–23.
[4] Otrock ZK, Eby CS. Clinical characteristics, prognostic factors, and outcomes of adult patients with hemophagocytic lymphohistiocytosis. Am J Hematol. 2015;90:220–4.
[5] Strenger V, Merth G, Lackner H, et al. Malignancy and chemotherapy induced haemophagocytic lymphohistiocytosis in children and adolescents – a single centre experience of 20 years. Ann Hematol. 2018;97:989–98.
[6] Davì S, Minoia F, Pistorio A, et al.; Paediatric Rheumatology International Trials Organisation, the Childhood Arthritis and Rheumatology Research Alliance, the Pediatric Rheumatology Collaborative Study Group, and the Histiocyte Society. Performance of current guidelines for diagnosis of macrophage activation syndrome complicating systemic juvenile idiopathic arthritis. Arthritis Rheum. 2014;66:2871–80.
[7] Zhang K, Jordan MB, Marsh RA, et al. Hypomorphic mutations in PRF1, MUNC13-4, and STXBP2 are associated with adult-onset familial HLH. Blood. 2011;118:5794–8.
[8] Chen X, Wang F, Zhang Y, et al. Genetic variant spectrum in 265 Chinese patients with hemophagocytic lymphohistiocytosis: molecular analyses of PRF1, UNC13D, STX11, STXBP2, SH2D1A, and XIAP. Clin Genet. 2018;94:200–12.
[9] Bracaglia C, Prencipe G, De Benedetti F. Macrophage activation syndrome: different mechanisms leading to a one clinical syndrome. Pediatr Rheumatol Online J. 2017;15:5.
[10] Henter JI, Horne A, Aricó M, et al. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer. 2007;48:124–31.
[11] Fardet L, Galicier L, Lambotte O, et al. Development and validation of the HScore, a score for the diagnosis of reactive hemophagocytic syndrome. Arthritis Rheumatol. 2014;66:2613–20.
[12] Janka GE, Lehmberg K. Hemophagocytic lymphohistiocytosis: pathogenesis and treatment. Hematology Am Soc Hematol Educ Program. 2013;2013:605–11.
[13] Miao Y, Hua-Yuan Z, Chun Q, et al. Pathogenic gene mutations or variants identified by targeted gene sequencing in adults with hemophagocytic lymphohistiocytosis. Front Immunol. 2019;10:39–5.
[14] Carcillo JA, Podd B, Simon DW. From febrile pancytopenia to hemophagocytic lymphohistiocytosis associated organ dysfunction. Intensive Care Med. 2017;43:1853–5.
[15] Ramos-Casals M, Brito-Zerón P, López-Guillermo A, et al. Adult haemophagocytic syndrome. Lancet. 2014;383:1503–16.
[16] Niece JA, Rogers ZR, Ahmad N, et al. Hemophagocytic lymph histiocytosis in Texas: observations on ethnicity and race. Pediatr Blood Cancer. 2010;54:424–8.
[17] Surupa B, Biplab M, Santanu B, et al. Hyperferritinemia in hemophagocytic lymphohistiocytosis: a single institution experience in pediatric patients. Indian J Clin Biochem. 2018;33:108–12.
[18] Prieto J, Barry M, Sherlock S. Serum ferritin in patients with iron overload and with acute and chronic liver diseases. Gastroenterology. 1975;68:525–33.
[19] Allen CE, Yu X, Kozinetz CA, et al. Highly elevated ferritin levels and the diagnosis of hemophagocytic lymph histiocytosis. Pediatr Blood Cancer. 2008;50:1227–35.
[20] Trottestam H, Horne A, Aricò M, et al.; Histiocyte Society. Chemoimmunotherapy for hemophagocytic lymphohistiocytosis: long-term results of the HLH-94 treatment protocol. Blood. 2011;118:4577–84.
[21] Li J, Wang Q, Zheng W, et al. Hemophagocytic lymphohistiocytosis: clinical analysis of 103 adult patients. Medicine (Baltimore). 2014;93:100–5.
[22] Okamoto M, Yamaguchi H, Isobe Y, et al. Analysis of triglyceride value in the diagnosis and treatment response of secondary hemophagocytic syndrome. Intern Med. 2009;48:775–81.
[23] Lim SH, Park S, Jang JH, et al. Clinical significance of bone marrow hemophagocytosis in adult patients with malignancy and non-malignancy-induced hemophagocytic lymphohistiocytosis. Ann Hematol. 2016;95:325–35.
[24] Debaugnies F, Mahadeb B, Ferster A, et al. Performances of the H-score for diagnosis of hemophagocytic lymphohistiocytosis in adult and pediatric patients. Am J Clin Pathol. 2016;145:862–70.
[25] Sung L, King SM, Carcao M, et al. Adverse outcomes in primary hemophagocytic lymphohistiocytosis. J Pediatr Hematol Oncol. 2002;24:550–4.
[26] Henter JI, Samuelsson-Horne A, Aricò M, et al.; Histocyte Society. Treatment of hemophagocytic lymphohistiocytosis with HLH-94 immunochemotherapy and bone marrow transplantation. Blood. 2002;100:2367–73.
[27] Bergsten E, Horne A, Aricó M, et al. Confirmed efficacy of etoposide and dexamethasone in HLH treatment: long-term results of the cooperative HLH-2004 study. Blood. 2017;130:2728–38.
[28] Fu L, Wang J, Wei N, et al. Allogeneic hematopoietic stem-cell transplantation for adult and adolescent hemophagocytic lymphohistiocytosis: a single center analysis. Int J Hematol. 2016;104:628–35.
[29] Parikh SA, Kapoor P, Letendre L, et al. Prognostic factors and outcomes of adults with hemophagocytic lymphohistiocytosis. Mayo Clin Proc. 2014;89:484–92.