

Hemophagocytic Lymphohistiocytosis in Adults: Associated Diagnoses and Outcomes, a Ten-Year Experience at a Single Institution

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Abstract

Background: Hemophagocytic lymphohistiocytosis (HLH) is a syndrome of excessive systemic inflammation which causes tissue damage due to abnormal immune system activation and has a high fatality rate even with treatment. HLH continues to be a difficult diagnosis to make because of lack of awareness and its overlap with other illnesses. This disorder is well defined in pediatric patients under the age of 18, but there is also a paucity of data in the adult population. The goals of this study were to describe associated disorders, clinical course and outcomes, and to determine if additional clinical criteria can be used to help with the diagnosis of HLH in adult patients.

Methods: Patients' electronic medical records from 2007 to 2017 (who were ≥ 18 years old at the time of the search) were screened by ICD 9 and ICD 10 codes which contain the diagnosis of HLH or hemophagocytic syndrome, infection-associated. We identified 41 adult cases of HLH that were treated at our medical center over the course of 10 years and assessed these patients using both the historical and newly proposed diagnostic criteria. We also identified underlying diagnoses related to the development of HLH and fatality rates.

Results: Median age at diagnosis was 55 years old (18 - 87 years old) and 22 were male. Twenty-two had an infection, 16 with malignancy, seven had an autoimmune disorder and one with Sweet syndrome. Fifteen patients were treated with steroids alone, 18 with steroids and chemotherapy, three with steroids and antiviral agents, and two with chemotherapy alone. Sixteen (39%) died and 25 (60%) survived discharge. Seven patients died after discharge. Median survival of all patients was 1,095 days.

Conclusions: Our data show that HLH is primarily associated with infections and malignancies. Newly proposed diagnostic criteria are

not as specific, but can be helpful in making the diagnosis of HLH. We also showed that the fatality rate at our institution was lower than currently published rates of adult HLH.

Keywords: Hemophagocytic lymphohistiocytosis; Natural killer cells; Macrophages

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a syndrome of excessive systemic inflammation which causes tissue damage due to abnormal immune system activation [1]. This occurs through secretion of excessive amounts of cytokines leading to tissue destruction and organ failure [1]. It is thought to be caused by the absence of downregulation of activated macrophages and lymphocytes possibly by failure of natural killer (NK) cells and/or cytotoxic T cells to eliminate these activated macrophages [2, 3]. HLH is termed either being primary (familial) or secondary (acquired). Primary HLH is due to gene mutations that are responsible for an underlying immunodeficiency syndrome. Secondary HLH describes patients without a known genetic mutation that would predispose to HLH and they have a clear trigger for development of HLH. There can also be an overlap between these two designations because any illness that triggers secondary HLH can precipitate the condition in someone with a known genetic mutation.

Diagnosis of HLH can be difficult given that the clinical presentation is similar to that of sepsis, septic shock, or another systemic inflammatory condition. The criteria for diagnosis were initially developed by the Familial Hemophagocytic Lymphohistiocytosis study group in 1991 [4] which evaluated children under the age of 15 years old who developed HLH. The first treatment protocol (HLH-94) was developed by the same research group in 1994 [5]. The diagnostic criteria were modified and expanded in 2004 (HLH-2004).

The eight diagnostic criteria, of which five must be present to make the diagnosis, are [6]: 1) fever (temperature ≥ 38.5 °C); 2) splenomegaly; 3) cytopenias, of at least two cell lines: Hgb < 9 g/dL; platelet count $< 100,000/\mu\text{L}$; absolute neutrophil count $< 1,000/\mu\text{L}$; 4) hypertriglyceridemia (> 265 mg/dL) and/or hypofibrinogenemia (≤ 150 mg/dL); 5) hemophagocytosis in bone marrow, spleen, lymph node, or liver; 6) low or absent

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NK cell activity (< 10 lytic units); 7) ferritin \geq 500 $\mu\text{g/L}$; 8) elevated soluble CD25 (soluble IL-2 receptor) \geq 2,400 U/mL.

It is evident that these criteria on their own are not specific for HLH as many other conditions could cause similar abnormalities. Daver et al [7] added 10 variables to these to improve the diagnostic accuracy for HLH in potential malignancy associated cases. These criteria are: 1) hepatomegaly (clinically palpable liver); 2) monocytosis (absolute monocyte > 1,000/ μL); 3) renal failure (50% increase in creatinine over baseline); 4) elevated hepatic enzymes (\geq 2.5 times the upper limit of normal); 5) coagulopathy (prothrombin time \geq 1.5 times upper limit of normal and/or partial thromboplastin time \geq 1.5 times upper limit of normal, and/or D-dimer \geq 10.0 $\mu\text{g/mL}$); 6) hypoalbuminemia (< 3.5 g/dL); 7) elevated lactate dehydrogenase (LDH) (\geq 2.5 times upper limit of normal); 8) elevated β 2 microglobulin (\geq 2 mg/L).

Prospective data are still pending with regard to the validity of these additional criteria, but they do include variables that are more easily assessed.

We reviewed all cases of diagnosed HLH in our medical center between 2007 and 2017 to evaluate possible factors related to development of HLH in an adult population. There is only a limited amount of data about HLH in the adult population. The majority of the epidemiological data come from adult patients who already have a known malignancy and from single center studies [7-9]. Also the diagnostic criteria and treatment regimens in early studies only included patients less than 18 years old [10, 11]. Our primary purpose was to describe associated disorders, clinical course and outcome in adult patients with HLH.

Patients and Methods

Patients' electronic medical records, at Loyola University Medical Center, from 2007 to 2017 (who were \geq 18 years old at the time of the search) were screened by ICD 9 and ICD 10 codes which contain the diagnosis of HLH or hemophagocytic syndrome, infection-associated. The institutional review board approved the study based on these criteria and the study was conducted in compliance with all the applicable institutional ethical guidelines for retrospective research studies. Searching medical records based on the ICD9 and ICD 10 codes as noted above returned 50 results. Nine patients were excluded from additional analysis (four had incorrectly coded ICD codes, two due to being less than 18 years old at time of HLH diagnosis, two had been diagnosed with HLH at an outside institution and there were no records available, and two had diagnosis of adult Still's disease). Forty-one patients met the diagnostic criteria described by Daver et al [7]. We also collected data on age, sex, other comorbidities/known medical conditions, genetic testing for HLH and therapeutic interventions.

Results

This study included 41 patients as noted in Table 1. The median age at diagnosis was 55 years (range of 18 - 87 years

old) and 22 (54%) were male. All 41 patients had a ferritin level \geq 500 $\mu\text{g/L}$ (range 537 - 76,921, median 11,582). Thirty-two (78%) had temperature \geq 38.5 $^{\circ}\text{C}$, 29 (71%) had at least a bilinear cytopenia, 29 (71%) had hemophagocytosis on biopsy of bone marrow, 26 (63%) had hypertriglyceridemia and/or hypofibrinogenemia. Twenty-three of the 40 patients (56%) had splenomegaly (one patient previously had a splenectomy). Of the 18 patients who had NK cell activity evaluated, 15 (83%) showed low or absent activity. Of the 24 that were evaluated for CD25, 15 (62%) showed elevated levels \geq 2,400 U/mL.

Regarding the additional criteria proposed by Daver et al: 40 patients had hypoalbuminemia (one patient did not have albumin level evaluated); 25 (61%) had elevated hepatic enzymes; 23 (56%) had hepatomegaly; 21 (51%) had renal failure. Forty patients had differential on the complete blood count evaluated and eight (20%) had monocytosis. Thirty-nine patients (95%) had HgB < 9 g/dL; 31 (76%) had platelet count < 100,000/ μL ; nine (22%) had absolute neutrophil count (ANC) < 1,000/ μL ; 11 (27%) had coagulopathy. Of the 36 patients that had LDH levels done, 25 (69%) had an elevated level; none of the patients had β 2 microglobulin level evaluated.

The comorbid conditions of all of the 41 patients were evaluated (Table 2). There was overlap of comorbid conditions, such as having a malignancy as well as having an active infection. The most common precipitant of HLH was infection (54%). Of the infections documented viral infections were the most common (41%). In order of most to least common viral infections were Epstein-Barr virus (EBV), cytomegalovirus (CMV), hepatitis B, human herpes virus 6 (HHV6), influenza and finally parvovirus. Four patients (19%) had bacteremia and one patient (2%) had fungal infection. Malignancy was the second most commonly associated diagnosis with HLH (39%) with 11 cases of lymphoma, three of leukemia and two of solid organ malignancies. Nine patients (22%) had a history of an organ transplant and eight (19%) had a known autoimmune disorder.

In addition to the treatment directed against the underlying disease, 38 of 41 patients with HLH received immunosuppressive therapy (Table 3). This was typically done with corticosteroids with or without cytotoxic chemotherapy. A majority of patients were treated with corticosteroids (89%), six received additional etoposide and two received cyclosporine. The choice of chemotherapy regimens was dependent upon the type of malignancy. Those with bacterial or fungal infections were treated with antibacterial or antifungal agents, respectively, but not all patients with a viral infection were treated with antiviral therapy. Details of treatment regimens used are given in Table 3. Three patients received multiple types of chemotherapy and corticosteroid regimens, so the total number of the types of treatments does not equal the total number of patients treated. Intravenous immunoglobulin (IVIG) alone was used in a single patient due to the patient being in myasthenia crisis. The two were unable to tolerate the treatment for HLH.

Historically, the survival after the initial diagnosis of HLH has been very poor with mortality rates ranging from 52% to 75% [8, 12-14]. The median survival of malignancy-associated HLH ranged from 1.1 to 2.4 months [7] and in one study the

Table 1. Frequency of Individual Diagnostic Criteria

Criteria	No. (%) of patients ^a
Fever (temperature $\geq 38.5^{\circ}\text{C}$)	32/41 (78%)
Splenomegaly	23/40 (56%)
Cytopenias, of at least two cell lines:	29/41 (71%)
Hgb < 9 g/dL	39/41 (95%)
Platelet count $< 100,000/\mu\text{L}$	31/41 (76%)
Absolute neutrophil count $< 1,000/\mu\text{L}$	9/41 (22%)
Hypertriglyceridemia (> 265 mg/dL) and/or hypofibrinogenemia (≤ 150 mg/dL)	26/41 (63%)
Hemophagocytosis in bone marrow, spleen, lymph node, or liver	29/41 (71%)
Low or absent NK cell activity (< 10 lytic units)	15/18 (83%)
Ferritin ≥ 500 $\mu\text{g/L}$	41/41 (100%)
Elevated soluble CD25 (soluble interleukin-2 receptor) $\geq 2,400$ U/mL	15/24 (62%)
Hepatomegaly (clinically palpable liver or seen on imaging)	23/41 (56%)
Monocytosis (absolute monocyte $> 1,000/\mu\text{L}$)	8/40 (20%)
Renal failure (50% increase in creatinine over baseline)	21/41 (51%)
Elevated hepatic enzymes (≥ 2.5 times the upper limit of normal)	25/41 (61%)
Coagulopathy (prothrombin time ≥ 1.5 times upper limit of normal and/or partial thromboplastin time ≥ 1.5 times upper limit of normal, and/or D-dimer ≥ 10.0 $\mu\text{g/mL}$)	11/41 (27%)
Hypoalbuminemia (< 3.5 g/dL)	40/40 (100%)
Elevated lactate dehydrogenase (LDH) (≥ 2.5 times upper limit of normal)	25/36 (69%)
Elevated $\beta 2$ microglobulin (≥ 2 mg/L)	No patient was tested

^aTotals less than 41 indicated that not all patients were assessed/tested for that specific criterion.

median survival for non-malignancy-associated HLH was 47 months [8]. From our data, 16 patients (39%) died during hospitalization. Malignancy-associated HLH led to death in six of the 16 patients (37.5%). The causes of death are listed in the Table 4. The most common conditions that directly contributed to their death from most to least frequent were: sepsis (100%), pneumonia and/or respiratory failure (43.7%), directly related to malignancy (37.5%) and treatment toxicity (6%). Twenty-five patients (61%) survived and were discharged from the hospital. Details of follow-up data are limited. At the time of this report, 84% of the patients discharged from the hospital did not have any additional episodes of HLH.

Discussion

Within the limitation of our retrospective study, such as its retrospective nature, our data bring out certain features of HLH syndrome in adult patients, which add to the body of knowledge of this potentially fatal disorder. We show that this disorder is fairly common and it will behoove clinicians taking care of patients in the hospital setting to keep this disorder in the differential of seriously ill patients. The pre-existing illnesses that we saw were similar to those seen by others but had nine patients who had undergone a stem cell transplant for a hematologic malignancy or a solid organ transplant. This is surprising because most of these patients were receiving im-

mune suppressive therapy at the time of development of HLH syndrome.

We also report improved outcomes when compared to historical data. Previous reports show mortality rates ranging from 52% to 75% fatal [8, 12-14]. In patients with malignancy and HLH syndrome, the median survival ranged from 1.1 to 2.4 months [7] and in one study the median survival for non-malignancy-associated HLH was 47 months [8]. For our entire cohort, the median survival, at this current time and availability of medical records that could be reviewed, is 36.5 months.

Sixty-one percent of the patients in our study survived their initial hospitalization due to HLH. Of those who survived, 84% did not have recurrence of HLH that could be determined on the most current chart review. Of all patients who survived and were discharged from the hospital the median survival is 1,095 days. There were seven patients that survived their initial hospitalization and subsequently died following hospital discharge with a median survival of 240 days.

In summary, we show that HLH syndrome, a potentially fatal illness, is fairly common in tertiary care setting. In addition to malignancies and viral illnesses, it can be seen after stem cell or solid organ transplants. Early suspicion of HLH syndrome appears to be critical, as it leads to prompt diagnosis and institution of treatment. The outcomes we report are better than those described in the past. Our findings suggest that prospective studies will have to be done to evaluate the

Table 2. Comorbid Conditions in Adult Hemophagocytic Lymphohistiocytosis Cases

Condition	Number of patients
Malignancy (n = 16)	
Lymphoma (n = 11)	
Peripheral T-cell lymphoma	3
Diffuse large B-cell lymphoma	2
Hodgkin lymphoma	2
Post-transplant lymphoproliferative disorder	2
Mantle cell lymphoma	1
T/natural killer cell lymphoma	1
Leukemia (n = 3)	
Acute lymphoblastic leukemia	1
Acute myeloid leukemia	1
Chronic lymphocytic leukemia	1
Solid organ cancer (n = 2)	
Renal cell carcinoma	1
Ovarian cancer	1
Infection (n = 22)	
Viral (n = 17)	
Epstein-Barr virus	8
Cytomegalovirus	5
Hepatitis B	1
Human herpes virus 6	1
Influenza	1
Parvovirus	1
Bacterial (n = 4)	
Vancomycin-resistant enterococci	2
Methicillin-resistant <i>Staphylococcus aureus</i>	1
Ehrlichiosis	1
Fungal (n = 1)	
Histoplasmosis	1
Autoimmune disorder (n = 8)	
Stills disease	4
Systemic lupus erythematosus	2
Myasthenia gravis	1
Sweet syndrome	1
History of transplant (n = 9)	
Liver	3
Bone marrow	2
Lung	2
Kidney	1
Heart	1
Aplastic anemia	1

Table 3. Treatment

Type of treatment	No. of patients
Corticosteroids alone	15
Corticosteroids along with chemotherapy (n = 18)	
Dexamethasone and etoposide	6
Cyclophosphamide, doxorubicin, vincristine and prednisone	2
Rituximab, etoposide, prednisolone, vincristine, cyclophosphamide, doxorubicin and intrathecal methotrexate	2
Dexamethasone, vincristine and dasatinib	1
Methylprednisolone, rituximab, etoposide and intravenous immunoglobulin	1
Methylprednisolone, methotrexate and tocilizumab	1
Methylprednisolone and rituximab	1
Methylprednisolone, tumor necrosis factor alpha inhibitor, cyclosporine, anakinra, tocilizumab	1
Methylprednisolone and cyclosporine	1
Cyclophosphamide, doxorubicin, vincristine, etoposide and prednisone	1
Dexamethasone, rituximab, doxorubicin, vinblastine, dacarbazine	1
Cisplatin, etoposide, gemcitabine, methylprednisolone	1
Anakinra and prednisone	1
Etoposide, prednisolone, vincristine, cyclophosphamide and doxorubicin for one cycle, then brentuximab	1
Corticosteroids along with antiviral	3
Cytotoxic chemotherapy alone	2
Azacitidine	1
Cladribine and cytarabine	1
Intravenous immunoglobulin alone	1
No treatment	2

efficacy of additional diagnostic criteria for HLH to improve our ability to initiate treatment sooner, specifically for adult patients. Also, additional treatment strategies will have to be investigated to see if there is improved efficacy from the established treatment regimen based on the HLH-2004 study as the most recent follow-up of that study showed no significant benefit to adding cyclosporine upfront, adding corticosteroids to intrathecal therapy, or a reduced time to hematopoietic stem cell transplant with these treatments [6]. A multicenter database would be valuable to continue to track not only outcomes for patients with HLH but also patterns of this disorder to know if there is a higher prevalence than what our historical

data show.

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None to declare.

Table 4. Clinical Outcomes, Remission Rate and Survival

Median survival, all patients (days)	1,095
Survived, initial hemophagocytic lymphohistiocytosis hospitalization	25 (61%)
Remission	21/25 (84%)
Died (due to any cause), following hospital discharge	7/25 (28%)
Median survival of those who died following hospital discharge (days)	240
Died, initial hemophagocytic lymphohistiocytosis hospitalization	16 (39%)
Sepsis or multi-organ failure	16/16 (100%)
Pneumonia and/or respiratory failure	7/16 (43.7%)
Malignancy-associated	6/16 (37.5%)

Conflict of Interest

None to declare.

Informed Consent

Informed consent was exempted due to the retrospective nature of the study and no patient identification information was utilized in determining the study results or in the review of the results.

Author Contributions

Sucha Nand developed the research study topic and was involved with the editing of the manuscript. Stephen Junic developed the IRB proposal, gathered patient data, performed all calculations, drafted the manuscript and submitted the manuscript once editing was completed.

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