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Prognostic Factors and Outcomes of Adults With Hemophagocytic Lymphohistiocytosis

Sameer A. Parikh, MBBS; Prashant Kapoor, MD; Louis Letendre, MD; Shaji Kumar, MD; and Alexandra P. Wolanskyj, MD

Abstract

Objective: To describe the prognostic factors and outcomes of adults with hemophagocytic lymphohistiocytosis (HLH), a rare disorder caused by pathologic activation of the immune system.

Patients and Methods: The study population consisted of a consecutive cohort of adult (age ≥18 years) patients treated at Mayo Clinic in Rochester, Minnesota, from January 1, 1996, through December 31, 2011, in whom a diagnosis of HLH was suspected and subsequently confirmed by retrospective review using the HLH-04 diagnostic criteria.

Results: Of 250 adult patients suspected of having HLH, 62 met the HLH-04 diagnostic criteria and were included in the final analysis. The median age was 49 years (range, 18-87 years), and 42 (68%) were male. The underlying cause of HLH was malignant tumor in 32 patients (52%), infection in 21 patients (34%), autoimmune disorder in 5 patients (8%), and idiopathic disease in 4 patients (6%). After a median follow-up of 42 months, 41 patients (66%) had died. The median overall survival of the entire cohort was 2.1 months. The median overall survival of patients with tumor–associated HLH was 1.4 months compared with 22.8 months for patients with non-tumor–associated HLH (P=.01). The presence of a malignant tumor and hypoalbuminemia were significant predictors of inferior survival on multivariate analysis.

Conclusion: In this large series of adults with secondary HLH treated at a single tertiary care center, patients with low serum albumin levels and tumor–associated HLH had a markedly worse survival. Hemophagocytic lymphohistiocytosis remains elusive and challenging to clinicians who must maintain a high index of suspicion. The recent discovery of several novel diagnostic and therapeutic modalities may improve outcomes of adult patients with HLH.

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From the Division of Hematology, Mayo Clinic, Rochester, MN.

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening clinical syndrome characterized by extreme inflammation due to an uncontrolled, yet ineffective, immune response.[1] It was first reported approximately 60 years ago by Farquhar and Claireaux[2] in their case description of 2 infants who died of progressive cytopenias, hepatosplenomegaly, and fever. Autopsy findings revealed the presence of widespread infiltration of lymphocytes and histiocytes, leading to hemophagocytosis. Patients with HLH are categorized as having primary (familial) HLH or secondary (acquired) HLH. By definition, familial HLH occurs in infants and young children who have a family history of HLH or an underlying genetic defect that leads to dysfunctional cytotoxic T lymphocytes and natural killer (NK) cells.[3-7] On the other hand, acquired HLH occurs typically in adults because of a variety of underlying infectious, autoimmune, and malignant disorders.[8]

Outcomes for children with HLH have been studied through 2 pivotal clinical trials: HLH-94[9] and HLH-04.[10] The 5-year survival for children treated in the HLH-94 trial was 54%. The HLH-04 trial has completed accrual, and results are yet to be released. In contrast to primary HLH in children, there is a paucity of data in adult patients with acquired HLH. The cause, demographic characteristics, clinical features, and outcomes of adult patients with this condition are not well described. There have been a few[11-15] retrospective studies of adult patients diagnosed with HLH that address infection-associated HLH,[16] tumor–associated HLH,[17-22] or autoimmune-associated HLH[23-26] in isolation. To describe and compare clinical outcomes for the different causative conditions associated with this disease, we conducted a

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retrospective study of all adults (age ≥18 years) diagnosed with HLH (regardless of cause) at our center during the past 16 years.

METHODS

The Mayo Clinic electronic medical record database was queried for the terms *hemophagocytic syndrome*, *hemophagocytosis*, *hemophagocytic lymphohistiocytosis*, and *macrophage activation syndrome* from January 1, 1996, through December 31, 2011. All adult patients (age ≥18 years) whose medical records contained these terms were manually reviewed. The Mayo Clinic hematopathology database was also cross-referenced for the terms *hemophagocytic syndrome* and *hemophagocytosis* during the same period. All patients who satisfied the HLH-2004 criteria[27] for a diagnosis of HLH were included in this study (ie, 5 of 8 criteria). These criteria include (1) fever; (2) splenomegaly; (3) cytopenias in 2 or more cell lines; (4) hypertriglyceridemia (triglyceride level ≥265 mg/dL [to convert to mmol/L, multiply by 0.0113]) or hypofibrinogenemia (fibrinogen level ≤150 mg/dL [to convert to μmol/L, multiply by 0.0294]); (5) hemophagocytosis in the bone marrow, spleen, or lymph nodes; (6) hyperferritinemia (ferritin level ≥500 ng/mL [to convert to pmol/L, multiply by 2.247]); (7) impaired NK cell function; and (8) elevated soluble CD25. The study was approved by the Mayo Clinic Institutional Review Board.

For all patients included in the study, all relevant demographic, clinical, and laboratory parameters were abstracted from the medical record. A diagnosis of tumor–associated HLH was made on the basis of the HLH-04 criteria and the concomitant presence of cancer by histopathologic examination. Histologic subtypes of lymphoma were classified according to the 2008 World Health Organization criteria.[28] A diagnosis of infection-associated HLH was made on the basis of the presence of the HLH-04 criteria and the demonstration of active infection with viral, fungal, or bacterial presence, determined by culture of body fluids, polymerase chain reaction (PCR), or serologic testing. The diagnosis of autoimmune disorder–associated HLH was made when patients satisfied the American College of Rheumatology criteria for the diagnosis of an autoimmune disorder and an extensive search for other causes was unrevealing. Patients with familial HLH were excluded from this study. Information related to HLH-directed therapy, including corticosteroids, and immunosuppression with cyclosporine and/or etoposide was also documented.

Patient characteristics were summarized using median (range) for continuous variables and frequency (percentage) for categorical variables. The Fisher exact and Kruskal-Wallis tests were used to define differences between the categorical and continuous variables, respectively. Overall survival (OS) was estimated by the Kaplan-Meier method and defined as the time from the date of diagnosis until death or last follow-up. Patients alive at the last recorded follow-up were censored. Cox proportional hazards models were used to determine factors that affect OS. All statistical analyses were conducted using JMP statistical software, version 9 (SAS Institute Inc).

RESULTS

Baseline Clinical and Laboratory Characteristics

Of 250 medical records reviewed in which the diagnosis was listed, 62 patients met the stringent eligibility criteria for inclusion in the study. Table 1 outlines the baseline characteristics of our study population. The median age of patients was 49 years (range, 18-87 years), and 42 (68%) were male. Thirty-two patients (52%) were diagnosed with tumor–associated HLH. Of the remaining patients (n=30) with non-tumor–associated HLH, 21 (34%) had an infection, 5 (8%) had an autoimmune condition, and 4 (6%) had idiopathic HLH. One patient was diagnosed with familial HLH because of the presence of an XIAP deficiency. He was excluded from the final analysis. Except for a lower platelet count in patients with tumor–associated HLH compared with those in non-tumor–associated HLH (22×10^3/μL vs 70×10^3/μL, respectively [to convert to $\times 10^9$/L, multiply by 1]; P=.01), no significant differences in baseline characteristics were noted between the 2 groups. Table 2 lists the clinical and laboratory manifestations at presentation according to the HLH-04 criteria. Table 3 describes the underlying causes of HLH in this cohort of patients.