CLINICAL RESEARCH STUDY

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Reactive Hemophagocytic Syndrome in Adults: A Retrospective Analysis of 162 Patients

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ABSTRACT

OBJECTIVES: Current knowledge in reactive hemophagocytic syndrome mainly relies on single-center case series including a relatively small number of patients. We aimed to identify a multicenter large cohort of adult patients with reactive hemophagocytic syndrome and to describe relevant clinical and laboratory features, underlying conditions, and outcome.

METHODS: We conducted a multicenter study in 3 tertiary care centers in France over a 6-year period. The medical files of 312 patients with suspected hemophagocytic syndrome were retrospectively reviewed. Patients were classified with a positive, negative, or undetermined diagnosis of hemophagocytic syndrome by experts' consensus.

RESULTS: Among the 312 patients fulfilling our inclusion criteria, 162 were classified with positive hemophagocytic syndrome (male, 67%; median age, 48 [35-62] years). Compared with patients without hemophagocytic syndrome, patients with hemophagocytic syndrome more frequently had an underlying immunodepression (45% vs 33%, $P = .03$) and exhibited higher temperature, ferritin, triglycerides, aspartate transaminase, bilirubin, lactate dehydrogenase, and C-reactive protein, and lower hemoglobin, leukocytes, platelets, and sodium levels. Only 70% of them had hemophagocytosis features on bone marrow aspiration. Hematologic malignancies, especially non-Hodgkin lymphomas, were the main trigger of hemophagocytic syndrome, accounting for 56% of cases. The early mortality rate (ie, within 1 month after diagnosis) was 20%. Patients with hematologic malignancies-associated hemophagocytic syndrome had a poorer early outcome than those with underlying infection.

CONCLUSIONS: In this large, multicenter study, hematologic malignancies are the main disease associated with hemophagocytic syndrome in adults. Early mortality is high, and outcome is influenced by the underlying disease.

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KEYWORDS: Adult; Hemophagocytic lymphohistiocytosis; Hemophagocytic syndrome; Infection; Lymphoma; Outcome

Hemophagocytic syndrome is a rare but life-threatening disease caused by an uncontrolled immune response, resulting in a hyperinflammatory disease. The main clinical and biological features are prolonged high fever, hepatosplenomegaly, and cytopenias with histiocytic infiltration in bone marrow and other tissues. It was first described in 1939 by Scott and Robb-Smith[1] as "histiocytic medullary reticulosis." In 1952, a familial disorder termed "familial

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hemophagocytic reticulosis" was reported, and in the following decades,[2] hemophagocytic syndromes related to various disorders such as infections and rheumatic diseases were described.[3-5] Currently, the classification of hemophagocytic syndrome by the Histiocyte Society distinguishes the primary (genetic) and secondary (reactive) forms.[6] In the primary form, which comprises familial hemophagocytic syndrome and hemophagocytic syndrome associated with several inherited immune deficiencies,[7] symptoms usually occur in the first years of life. The secondary (ie, reactive) form can occur at any age and is more frequent than the primary form.[8] It can be triggered by various underlying conditions, mainly infections, malignancies, or autoimmune diseases.[9-12]

Diagnosis of reactive hemophagocytic syndrome is challenging. Clinical and biological features are nonspecific and can be encountered in severe sepsis or hematologic malignancies. On the other hand, hemophagocytosis patterns have been described in critically ill patients or after transfusion or cytotoxic therapies, out of a context of hemophagocytic syndrome.[13]

Because current knowledge in reactive hemophagocytic syndrome mainly relies on single-center case series including a relatively small number of patients, we conducted a retrospective, multicenter study over a 6-year period to identify all adult patients with suspected reactive hemophagocytic syndrome. From this large cohort of patients, we described relevant clinical and laboratory features, underlying conditions, and outcome.

CLINICAL SIGNIFICANCE

- Only 70% of patients with hemophagocytic syndrome had hemophagocytosis features on bone marrow aspiration.
- Approximately half of the patients have a known immunosuppression. All of the causes of immunosuppression identified led to defects in cellular immunity.
- Hematologic malignancies, particularly non-Hodgkin lymphomas, were the main diseases associated with hemophagocytic syndrome.
- Mortality rate within 1 month after diagnosis was 20%. Patients with hematologic malignancies—associated hemophagocytic syndrome have a poorer early outcome than those with underlying infection.

METHODS

Patients

Between June and November 2012, we retrospectively reviewed all the forms for and all the results of bone marrow aspirations performed between January 2006 and December 2011 in 3 French tertiary university hospitals. All forms requesting bone marrow aspiration for a suspicion of hemophagocytic syndrome and all bone marrow aspirations that were concluded to be hemophagocytosis were identified. We identified all patients coded in these centers during the study period as D76.1 (hemophagocytic lymphohistiocytosis), D76.2 (hemophagocytic syndrome, infection-associated), or D76.3 (other histiocytosis syndromes) following the International Classification of Diseases, 10th Revision. The 2 resulting lists of patients were crossed to ensure that no patient with a code for hemophagocytic syndrome who underwent a bone marrow aspirate was missed. We then retrospectively reviewed the medical records of all the corresponding patients, and medical information was extracted via a standardized questionnaire. The following clinical conditions were evaluated: age, gender, highest recorded temperature, duration of fever (if any), presence of hepatomegaly, splenomegaly, or adenomegaly, medical history and diseases known at the time of suspicion of hemophagocytic syndrome, known underlying immunodepression (ie, people known to have human immunodeficiency virus or to be chronically treated with an immunosuppressive therapy such as glucocorticoids, cyclosporine, or azathioprine), treatment prescribed, underlying disease, transfer in intensive care unit, and outcome. Laboratory data, such as leukocytes and platelets counts, hemoglobin, liver enzymes, ferritin, triglycerides, cholesterol, fibrinogen, C-reactive protein (CRP), lactate dehydrogenase, blood urea nitrogen, creatinine and sodium levels, and prothrombin time, were collected on the day of the bone marrow aspiration or in the 2 preceding or following days. The presence or absence of hemophagocytosis on bone marrow aspiration was recorded. Finally, the diagnosis retained by the medical team in charge of the patient was recorded. For patients with recurrent hemophagocytic syndrome, only the first episode was considered.

Classification Procedure

In a first step, 3 investigators involved in the diagnosis and treatment of adult patients with hemophagocytic syndrome (LG, PC, and LF) classified patients into 3 groups: hemophagocytic syndrome likely (positive cases), hemophagocytic syndrome possible (undetermined cases), and hemophagocytic syndrome unlikely (negative cases). Classification was based both on information available at the time of hemophagocytic syndrome diagnosis and on follow-up data regarding the hemophagocytic syndrome or the underlying disease. Each investigator classified patients blindly of the others' classification. Once the 3 investigators had classified all the patients, the results were compared. Positive/undetermined and undetermined/negative classifications were considered as minor discordances, whereas positive/negative classifications were considered as major discordances. All cases of minor discordances were

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