

Idiopathic Hemophagocytic Syndrome With a Fulminant Clinical Course

Abha Khandelwal, MS, MD, Neel B. Shah, MD,
Peter Eichenseer, MD, Mike Welker, MD, Ira Miller, PhD, MD,
Julie Nangia, MD, Mohamed Farhat, MD, Alla Gimelfarb, MD,
Mohammad Kassar, MD, Marta Batus, MD, Sefer Gezer, MD,
Jamile Shammo, MD, Stephanie Gregory, MD, Henry Fung, MD,
Parameswaran Venugopal, MD

*Rush University Medical Center
Chicago, Ill.*

Hemophagocytic syndrome is an extremely rare condition in adults reported in only 116 cases in the literature since 1983. Most of these cases had an underlying etiology. It is observed mostly in children from birth to 2 years of age and is differentiated into primary or secondary, based on whether an underlying genetic disorder or other conditions, such as viral illness, are present. Hemophagocytic syndrome is diagnosed in an estimated 1.2 children per million per year in Sweden, but no data exist for its incidence in adults.¹ It has been associated with viral infections such as Epstein-Barr virus (EBV), cytomegalovirus (CMV), parvovirus, herpes simplex virus (HSV), varicella-zoster, measles, human herpes-8, and HIV.^{2,3} Some cases have also been linked to bacterial and parasitic infections.⁴ In adults, most cases are associated with an underlying autoimmune disorder such as lupus, rheumatoid arthritis, sarcoidosis, Sjögren syndrome, polyarteritis nodosa, or a mixed connective tissue disease.⁵⁻⁷ It has also been known to be associated with leukemias and lymphomas.⁸⁻¹² Of the 116 case reports found in the literature, all had speculated underlying or associated etiology. We report 2 patients with hemophagocytic syndrome in whom an underlying etiology could not be identified despite extensive work up.

Case Report

The first patient was an 83-year-old man who presented with a 4-month history of fever of unknown origin and progressive pancytopenia. His past medical history included diabetes, hypertension, hyperlipidemia,

and peripheral vascular disease. Prior to presentation, he was sporadically hospitalized at outside institutions with extensive evaluations, which were essentially negative, including a bone marrow biopsy that was reported as showing normocellular marrow with mild erythroid hyperplasia. He noted generalized fatigue, fever, and gradual weight loss. Physical examination was negative for lymphadenopathy and hepatosplenomegaly, with admission laboratory values notable for leukocyte count (1,800/mL), hemoglobin (8.9 g/dL), platelet count (15,000/mL), and serum ferritin (>10000 ng/mL). Workup included antinuclear antibody test (ANA), which was 1:160 with a nucleolar pattern, although the patient only had 2 of 11 criteria positive for lupus. EBV, immunoglobulin G, and immunoglobulin M were negative. Serum and protein electrophoresis was negative for a monoclonal protein. Further blood work for HIV, SSa, SSb, antineutrophilic cytoplasmic antibodies (ANCA), *Brucella*, acid-fast bacillus (AFB), and blood cultures were all negative. Initial bone marrow examination demonstrated a hypercellular marrow without evidence of leukemia and a normal male karyotype. Imaging included a computed tomography (CT) scan, bone scans, positron emission tomography scan, and ⁹⁹Tc liver spleen uptake scan, which demonstrated an accessory spleen but was otherwise insignificant. Further biopsies of bilateral temporal arteries, skin, muscle, and nerves did not reveal a diagnosis. No infectious, rheumatologic, or hematologic etiology was identified, but a repeat bone marrow biopsy revealed normocellular marrow with histiocytic infiltration with erythrocyte phagocytosis. The patient was started on treatment for hemophagocytic lymphohistiocytosis (HLH) with etoposide, dexamethasone, and cyclosporine, as used in the HLH-2004 treatment protocol. He expired 2 weeks after admission secondary to

Address correspondence to:

Neel B. Shah, MD, Division of Hematology and Oncology, Rush University Hospital, 1725 West Harrison Street Suite #809, Chicago, IL 60612-3824; Phone: 312-942-7015; Fax: 312-942-3192; E-mail: Neel_Shah@rush.edu.

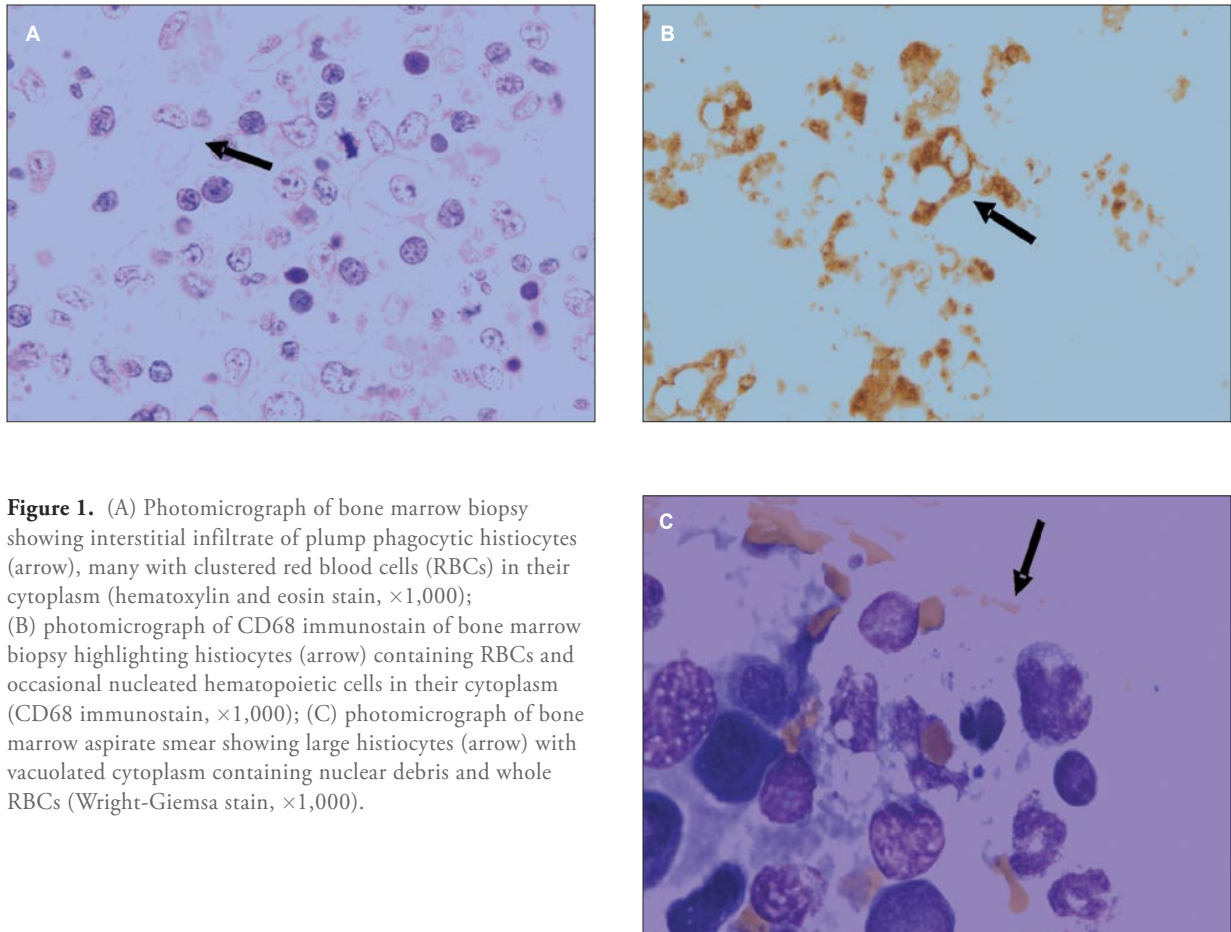


Figure 1. (A) Photomicrograph of bone marrow biopsy showing interstitial infiltrate of plump phagocytic histiocytes (arrow), many with clustered red blood cells (RBCs) in their cytoplasm (hematoxylin and eosin stain, $\times 1,000$); (B) photomicrograph of CD68 immunostain of bone marrow biopsy highlighting histiocytes (arrow) containing RBCs and occasional nucleated hematopoietic cells in their cytoplasm (CD68 immunostain, $\times 1,000$); (C) photomicrograph of bone marrow aspirate smear showing large histiocytes (arrow) with vacuolated cytoplasm containing nuclear debris and whole RBCs (Wright-Giemsa stain, $\times 1,000$).

worsening pancytopenia and newly acquired colitis with subsequent sepsis.

The second patient was a 64-year-old woman who presented with several months of pancytopenia, intermittent fever, and worsening jaundice. Her past medical history included osteoarthritis, hyperlipidemia, coronary artery disease, and reflux disease. Prior to presentation, she had several hospitalizations at outside institutions with no diagnosis established. A bone marrow biopsy was performed at an outside institution that revealed nonspecific nonnecrotizing granulomas. On admission, she noted generalized fatigue, fever, and gradual weight loss. Physical exam revealed worsening jaundice and splenomegaly. Laboratory evaluation was notable for leukocyte count (830/mL), hemoglobin (6.6 g/dL), platelet count (17,000/mL), serum ferritin ($>10,000$ ng/mL), total bilirubin (21.8 mg/dL), alkaline phosphatase (696 IU/L), aspartate aminotransferase 233 IU/L, and alanine transaminase 188 IU/L. Further evaluation included ANA titer, which was less than 1:40. EBV, CMV, HSV, HIV, rapid plasma reagin (RPR), AFB, *Rubella*, *Bartonella*, *Legionella*, *Klebsiella pneumoniae*, *Leptospira*,

Tropheryma whippelii, ANCA, hepatitis serologies, histoplasmosis, respiratory syncytial virus, and blood cultures were all negative. Liver biopsy showed nonspecific lobular cholestasis. Imaging with CT of chest, abdomen, and pelvis noted small pleural effusions and cholelithiasis. No infectious, rheumatologic, or hematologic etiology was identified, but a repeat bone marrow biopsy revealed mildly hypocellular marrow with significant interstitial infiltrate of plump phagocytic histiocytes containing clustered erythrocytes in their cytoplasm (Figures 1A–1C). The patient began HLH treatment with etoposide, dexamethasone, and cyclosporin as used in the HLH-2004 treatment protocol (although she was not enrolled in a study). She expired 3 weeks after admission secondary to worsening liver failure.

Discussion

The diagnosis of hemophagocytic syndrome must be included in the fever of unknown origin (FUO) workup, especially in those patients with pancytopenia and organ failure. In both cases, diagnosis was delayed despite the

multiple bone marrow biopsies that were performed to determine the etiology of these patients' symptoms. In 20% of reported cases there is no evidence of hemophagocytosis on the first bone marrow examination, and in both of our cases multiple bone marrow biopsies were performed before the diagnosis was made.¹³ Treatment can and should be initiated immediately if the diagnosis of hemophagocytosis is suspected and the criteria are fulfilled.

The essential abnormality in hemophagocytic syndrome seems to be cytokine dysfunction resulting in accumulation of activated histiocytes in multiple organs, including the bone marrow. In these patients, the immunoglobulin levels are normal, but inflammatory markers such as tumor necrosis factor alpha and interleukin (IL)-6, -10, -12, and -16 may be elevated.¹⁴ Some studies have indicated that elevated IL-16 recruits macrophages.¹⁵ IL-18, if elevated, may also stimulate macrophages and natural killer (NK) cells.¹⁶ Furthermore, a reduction in NK cells and cytotoxic T-cell activity has also been seen in these types of patients.^{17,18} A murine model demonstrates that lack of intracellular perforin expression across all cytotoxic cell types is critical in causing HLH. The mice in this study developed HLH only after exposure to a viral illness.¹⁹ Other abnormalities seen in hemophagocytosis include *MUNC13-4* mutations, which result in abnormal packaging of cytolytic granzymes.²⁰ Defective apoptosis and less spontaneous activation of caspase-3-like enzyme in activated lymphocytes could explain the accumulation of these lymphocytes in the lymph nodes, spleen, liver, or bone marrow.²¹

Diagnosis

The diagnosis of hemophagocytosis is based on five major and three minor criteria and usually requires all five major criteria. The five major criteria include fever, splenomegaly, cytopenia in a minimum of two cell lines, hypertriglyceridemia or hypofibrinogenemia, and tissue demonstration of hemophagocytosis. The additional minor criteria include low or absent NK cell activity, serum ferritin concentration of greater than 500 ng/L, and soluble CD25 (IL-2 receptor) greater than 2,400 U/mL. Elevated serum ferritin and soluble CD25 may substitute for a major criterion. Diagnosis is difficult, and often multiple bone marrow samples are required for the analysis.²² Our first patient fulfilled these criteria with fever, cytopenia, hypertriglyceridemia, bone marrow involvement, and elevated ferritin. Our second patient had fever, cytopenias, bone marrow involvement, hepatosplenomegaly, hypertriglyceridemia, and elevated ferritin. Presentation is often late in the illness and the prognosis is poor if treatment is not initiated early in the course of the disease. In both the

cases diagnosis was established after symptoms were present for months, which led to organ failure and resulted in death during treatment.

The hallmark pathologic finding in the bone marrow is histiocytic hyperplasia with prominent phagocytosis of mature and immature hematopoietic elements. The histiocytes show abundant cytoplasm containing the phagocytized cells; cytoplasmic vacuoles and granules are also frequently seen. The remainder of the marrow usually shows hypoplasia of granulocytic and erythroid lines with megakaryocytic hyperplasia.

The main differential diagnosis is a histiocytic sarcoma, which, in contrast to hemophagocytic syndrome, presents as large atypical histiocyte nuclei and usually a minimal degree of hemophagocytosis. There is also an entity known as macrophage activation syndrome (MAS), which occurs in patients with juvenile rheumatoid arthritis and lupus, has most of the clinical features of HLH, and has been considered by some authors as an acquired form of HLH.

Treatment of HLH is not well defined in the adult population. A consensus statement for children was published in 2004. Initial treatment with etoposide and dexamethasone followed by pulse therapy and cyclosporin demonstrates a 55% survival for a median follow-up of 3.1 years in children.²³ Hematopoietic stem cell transplantation can also be used following drug therapy and offers the best hope for a curative effect; however, mortality even in this subset can be as high as 46%. Patients with HLH and concurrent EBV infection did better than those treated only with monotherapy of steroids, intravenous immunoglobulin, or cyclosporin.^{1,24-26} A protocol for chemotherapy in adults has not yet been established due to the lack of a sufficient number of cases in this age category. Ultimately, more studies are needed to investigate other therapeutic options that may yield an improved morbidity and mortality.

Conclusions

In summary, clinicians must have a high suspicion of idiopathic hemophagocytic syndrome when evaluating patients presenting with signs and symptoms as described above. Hemophagocytic syndrome should always be considered in patients who present with FUO and cytopenias. The proliferation of histiocytes can be highlighted on a bone marrow biopsy with CD68 immunostain. An underlying etiology may not be evident. The longer the delay in diagnosis and treatment, the more likely the patient is to have a poor outcome. Lymph node and bone marrow biopsies may be negative but if the patient has no alternative diagnosis and meets the criteria listed above, we would recommend starting treatment immediately. Once

more data on adults with hemophagocytic syndrome have been accumulated, a consensus should be established to develop guidelines for an optimal therapeutic approach to treating this patient population.

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(Clinical Case Study, continued from page 590)

Review

Healing Hemophagocytic Syndrome in Adults: the Challenge Continues

Arnaud Hot, MD,^{1,2} Jacques Ninet, MD¹

¹Department of Internal Medicine, Edouard Herriot Hospital Lyon, Claude Bernard Lyon I University

²Joint Unit Hospices Civils de Lyon, Biomerieux, Inflammation and Genomic, Edouard Herriot Hospital Lyon Lyon, France

Khandelwal and colleagues report two cases of hemophagocytic syndrome without clear etiology.¹ The first patient was an 83-year-old man, who initially had a fever of unknown origin (FUO), which eventually led to the diagnosis of hemophagocytic syndrome, as the underlying cause could not be identified. This patient was treated with etoposide, dexamethasone, and cyclosporin. Despite this treatment, the patient died during the course of pancytopenia. The second patient was a 64-year-old woman who for several months had pancytopenia, episodic fever, and jaundice. She was diagnosed with aplasia and liver involvement. These clinical and biologic features were related to hemophagocytic syndrome, also without etiology, and she began hemophagocytic syndrome treatment with etoposide, dexamethasone, and cyclosporin. She died 3 weeks after her admission.

Physicians facing FUO systematically look for infections, cancer, or chronic inflammatory disorders; each disorder can be accompanied by hemophagocytic syndrome.² Hemophagocytosis by macrophages as an isolated phenomenon can be found in many disease states, such as hemolytic anemia, metabolic diseases, or malignancies. In hemophagocytic syndrome, hemophagocytosis is part of a sepsis-like clinical syndrome caused by severe hypercytokinemia as the consequence of a highly stimulated, but ineffective, immune response. The spectrum of hemophagocytic lymphohistiocytosis (HLH) in adults has not been well characterized.³ Hemophagocytic syndrome is either primary (inherited) or secondary, in which case it is due to infections, malignancies, or metabolic or autoimmune diseases.² All of these causes had been considered in the 2 presented patients. As the authors reported in their case study, few cases of hemophagocytic syndrome

in adults remain idiopathic, and infections, specifically herpes virus infections, are the leading cause.⁴ However, some autoimmune diseases, such as adult-onset Still disease (AOSD), which is a disease classically associated with hemophagocytic syndrome, should also be considered in these clinical settings.⁵

The two cases presented by Khandelwal and colleagues question the possibility of reactive hemophagocytic syndrome being associated with AOSD even though it remains a syndrome rather than a clearly defined disease. In fact, data show that criteria for AOSD has been met in 40% of patients with hemophagocytic syndrome.⁶ Furthermore, AOSD and hemophagocytic syndrome share not only clinical and biologic features but pathogenesis as well; in both a decrease in natural killer (NK) cells and perforin activity have been observed.⁷ This disease should be considered in the presence of hemophagocytic syndrome without etiology. Even if a diagnosis of AOSD is made, it should not delay the start of treatment of hemophagocytic syndrome. Additionally, it should be kept in mind that lymphoma could also masquerade as FUO or hemophagocytic syndrome.

The sequence of events leading to acquired hemophagocytic syndrome remains only partially understood. Hypotheses are mainly derived from observations of primary HLH. In patients with hemophagocytic syndrome, splenic macrophages appear to be activated, as evidenced by increased expression of MHC-I and MHC-II molecules, as well as the macrophage colony-stimulating factor receptor.⁸ In addition, many studies have shown that patients with macrophage activation syndrome (MAS) had substantially raised serum levels of pro-inflammatory cytokines, such as interferon gamma, interleukin (IL)-12, IL-18, tumor necrosis factor α , IL-1 β , and IL-6, compared with control. IL-18 is a cytokine mainly produced by activated macrophage lineage cells, such as Kupffer cells.⁹ This cytokine seems to play a key role in the pathogenesis of hemophagocytic syndrome. Macrophage activation may also be due in part to the secretion of stimulatory cytokines by lymphocytes. Inadequate cellular cytotoxicity due to improper intracellular trafficking, impaired apoptosis, and defect in effector molecules such as perforin have also been implicated.¹⁰ Recent studies have shown that dysfunction of NK cells due to mutations of the perforin and *MUNC13-4* genes leads to familial lymphohistiocytosis.

Patients with secondary hemophagocytic syndrome may develop severe quantitative and functional deficiencies of NK cells during the course of their illness.¹¹ The inability of NK and CD8 T cells to efficiently terminate an immune response leads to sustained activation of T-lymphocytes and macrophages. Furthermore, NK cells,

Address correspondence to:

Arnaud Hot, MD, Department of Internal Medicine, Edouard Herriot Hospital Lyon; Claude Bernard Lyon I University, 5 Place d' Arsonval, 69003 Lyon, France; Phone: 33 4 72 11 75 65; Fax: 33 4 72 11 74 98; E-mail: arnaud.hot@wanadoo.fr.

which normally regulate immune response by destroying proliferating immune cells, may be unable to perform this function in the presence of MAS. The end result is an impaired and destructive immunologic response that escapes the usual mechanisms of autoregulation. This deficient toxicity also impairs the contraction of the immune response and creates very deficient negative feedback mechanisms.

Prolonged fever, hepatosplenomegaly, and pancytopenia are the prominent features of hemophagocytic syndrome. Lymphadenopathy, rash, jaundice, and neurologic symptoms such as seizures or cranial nerve palsies are less frequent. Characteristic laboratory values include a high level of triglycerides and a high level of ferritin and low percentage of its glycosylated fraction.¹² Transaminases and coagulopathy with a low fibrinogen are also frequently observed. The alpha chain of the soluble IL-2 receptor (sCD25) is a good disease marker because its level always remains high during the course of hemophagocytic syndrome.¹³

The creation of criteria guidelines by the Histiocyte Society has contributed significantly to the improvement of diagnosis in children. These criteria include clinical features such as fever; splenomegaly; cytopenia; biologic parameters such as hypertriglyceridemia and/or hypofibrinogenemia; hemophagocytosis in bone marrow, liver, or cerebral spinal fluid; low or absent NK cell activity; ferritin higher than 500 µg/L; and sCD25 higher than 2,400 U/mL. Although hemophagocytosis has given the disease its name, it should be kept in mind that this condition is not an obligatory feature, and treatment should not be delayed if hemophagocytosis is absent on bone marrow examination.¹³ Despite these criteria, diagnosis in adults remains unclear and new tools are needed to define this disease in the adult population.

Some authors have proposed other markers for hemophagocytic syndrome, such as CD163, which is exclusively expressed on cells of the monocyte-macrophage lineage. The extracellular fragment of this receptor can be detected in the serum by enzyme-linked immunosorbent assay.¹⁴

During the last decade, we have witnessed the improved survival of patients with hemophagocytic syndrome for several reasons. First, the proposal of the criteria guidelines by the Histiocyte Society has significantly contributed to better diagnosis of hemophagocytic syndrome.¹⁵ Second, much progress has been made in the treatment of this disease. Although the guidelines are a successful diagnostic tool, they were established to treat children and, therefore, few data are available for adults.

The treatment regimen currently used is designed to control T-cell activation (steroids, cyclosporine, and etoposide) and macrophage activation (intravenous immunoglobulin [IVIG], etoposide).

In Epstein-Barr virus (EBV)-associated hemophagocytic syndrome, etoposide, rather than IVIG, is the widely used treatment, although both have proven efficacious. The use of etoposide is supported by previously published Japanese articles, although mostly as case reports. In addition, some authors found that therapeutic results were better for patients who received etoposide instead of IVIG early (<4 weeks from diagnosis) in their treatment course.¹⁶ The clinical benefit of IVIG in patients with hemophagocytic syndrome has also been reported. Researchers have reported on the efficacy of IVIG in virus-associated hemophagocytic syndrome. Larroche and colleagues presented IVIG effectiveness in 17 cases that were non-EBV-associated hemophagocytic syndrome or were triggered by other causes.¹⁷ It is possible that IVIG modulates hemophagocytosis due to hypercytokinemia, but it may not suppress the growth of the underlying, clonally proliferating cells like the ones existent in EBV-associated hemophagocytic syndrome. Further studies are necessary to determine the optimal treatment for hemophagocytic syndrome, which is often a fatal disease.

Cyclosporin has often been described as a beneficial treatment for hemophagocytic syndrome. In fact, cyclosporin affects not only the early stages of T-cell activation but also macrophage and dendritic cell function. Cyclosporin thus remains a good choice for targeting the various inflammatory cells implicated in the pathogenesis of hemophagocytic syndrome and for reducing hypercytokinemia.¹⁸ Although there may not be a consensus on the use of this drug in the setting of hemophagocytic syndrome, in our opinion, this drug should be administered intravenously early in the course of severe hemophagocytic syndrome.

Despite the available therapeutic options, the 2 reported patients died during the course of their disease. The poor prognosis is probably linked to a delay in diagnosis and an absence of etiology. Also of note, an underdiagnosed lymphoma may also be the cause of hemophagocytic syndrome. New therapeutic options are now available in the treatment of hemophagocytic syndrome. A B-cell-directed regimen with the anti-CD20 monoclonal antibody rituximab (Rituxan, Genentech) seems to be a promising therapy in EBV-associated hemophagocytic syndrome.¹⁹ Even though the efficacy of rituximab seems to be related to the exhaustion of the EBV reservoir, it may play a role in the cytokine storm. Three mechanisms can be used to explain the effects of anti-CD20 monoclonal antibody in this syndrome. In the first mechanism, rituximab acts as a nonspecific IVIG and inhibits C3a and C5a activity. In the second, a mechanism of Fc receptor saturation by the opsonized CD20-positive cells are involved to explain the initial phase of response. In the third mechanism, rituximab acts by eliminating

B cells. These cells are very efficient antigen-presenting cells, particularly after they have been activated. This loss of antigen presentation could result in less stimulation of T cells, which is an important part of hemophagocytic syndrome, particularly because T cells regulate macrophage activation. These three mechanisms can also be used to explain the effect of rituximab on lymphoma-associated hemophagocytic syndrome.²⁰ Prospective clinical trials evaluating B-cell depletion as salvage therapy in hemophagocytic therapy are now clearly warranted.

Although knowledge of hemophagocytic syndrome in childhood forms has increased, much needs to be learned about this disease in adults, as the mortality rate of hemophagocytic syndrome remains high (50%). Further studies are needed to advance the diagnosis of hemophagocytic syndrome in adults, and therapeutic guidelines need to be established. It would be of interest to see whether polymorphisms in genes of cytotoxic effector pathways contribute to the pathogenesis of hemophagocytic syndrome in adults, as was recently described in patients with tuberculosis-associated hemophagocytic syndrome.²¹

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