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ORIGINAL

# Critical care management of patients with hemophagocytic lymphohistiocytosis

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**Abstract** *Objective:* Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening condition associated with multiple organ dysfunction. We sought to describe ICU management and outcomes in HLH patients meeting HLH-2004 criteria and to identify determinants of mortality. *Design:* Retrospective study between January 1998 and January 2009. *Setting:* Medical ICU of a teaching hospital. *Patients:* Among the 72 patients fulfilling the HLH-2004 criteria, we report the 56 patients with complete follow-up and no missing data. *Interventions:* None. *Measurements and main results:* Clinical and laboratory data were abstracted from the medical records. Median SOFA score at admission was 6.5 (IQR, 4–8). At ICU admission, the number of HLH-2004 criteria was 6 (5–7). Sixty-six precipitating factors were found in 52 patients and consisted of 43 tumoral causes (8 Castleman's diseases, 18 B cell lymphoma and 17 various malignancies), 13 non-viral infections and 10 viral infections. Underlying immune deficiency was present in 38 (67.8%) patients. Etoposide was used in 45 patients, corticosteroids in 31 and intravenous immunoglobulins in 3. Mechanical ventilation was required in 32 patients, vasoactive agents in 30 and renal replacement therapy in 19. Hospital mortality was 29/56 patients. By multivariate analysis, factors associated with increased hospital death were shock at ICU admission [OR, 4.33; 95% confidence interval (95% CI), 1.11–16.90; $P = 0.03$] and platelet count <30 g/l (OR, 4.75; 95% CI, 1.20–18.81; $P = 0.02$). B cell lymphoma [odds ratio (OR), 0.17; 95% CI, 0.04–0.80; $P = 0.02$] and Castleman's disease (OR, 0.11; 95% CI, 0.02–0.90; $P = 0.04$) were associated with increased hospital survival. *Conclusions:* Aggressive supportive care combined with specific treatment of the precipitating factor can produce meaningful survival in patients with HLH responsible for multiple organ failures. Survival is highest in patients with HLH related to Castleman's disease or B cell lymphoma.

**Keywords** Macrophage activation · Histiocytosis · Outcomes assessment · Autoimmune diseases · Multiple organ failure

## Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening disorder in which dysregulation of natural killer (NK) cells and cytotoxic T cells can lead to multiple organ failure [1, 2]. Uncontrolled activation and proliferation of lymphocytes and/or histiocytes occurs, leading to cytokine overproduction and hemophagocytosis [3].

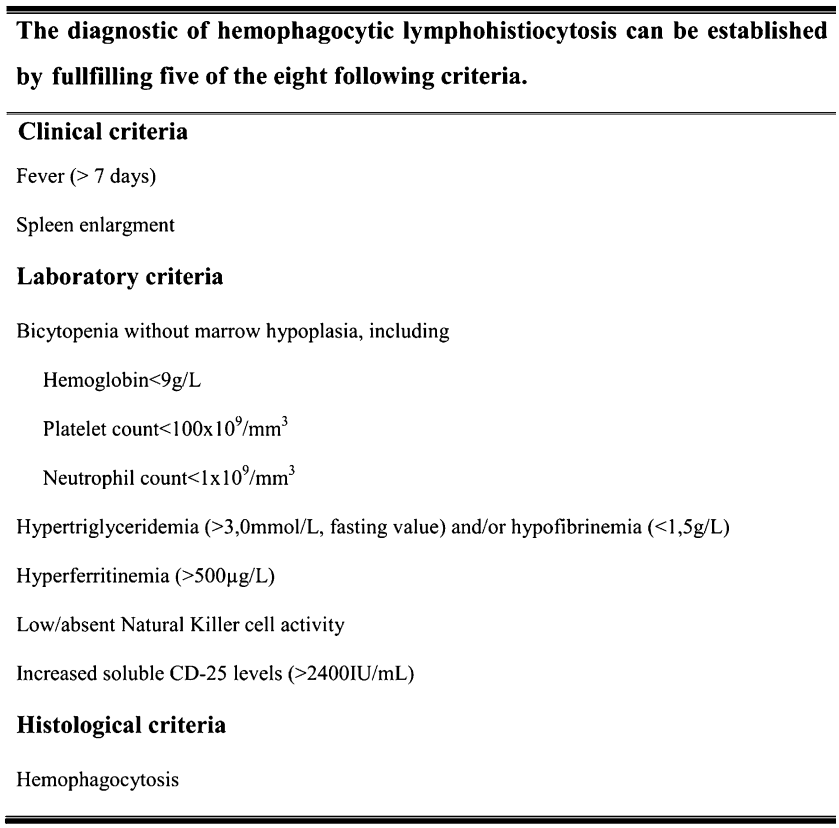


**Fig. 1** Diagnostic criteria for hemophagocytic lymphohistiocytosis (HLH) as established in the HLH-2004 protocol of the Histiocyte Society. HLH diagnosis can be established by fulfilling five of the eight proposed criteria

The main manifestations are a fever, enlargement of the liver and spleen, cytopenias (anemia, thrombocytopenia and leukopenia), liver dysfunction, high serum levels of triglycerides and ferritin, and histological evidence of hemophagocytosis [4, 5].

Beyond controversies about primary and secondary HLH [6], HLH in adults is a syndrome that can occur in all age groups in association with many diseases, including malignancies, connective tissue disease, infections and genetic abnormalities [7, 8]. Of the various criteria sets for the diagnosis of HLH [4, 9, 10], the most widely used was developed in 2004 by the Histiocyte Society [3, 4] and requires five of the eight criteria that are mentioned in Fig. 1. In addition to these criteria, a diagnosis of HLH is supported by the identification of a precipitating factor (e.g., infection, autoimmune disease or malignancy) and by the presence of immune deficiency.

HLH is associated with a broad spectrum of clinical manifestations and multiple organ dysfunctions that can require admission to the intensive care unit (ICU) [2, 11]. Autopsy studies suggest that HLH may be under-recognized in ICU patients [12]. On the other hand, HLH may be mistakenly diagnosed in patients with septic shock, a condition whose cause and symptoms overlap those of HLH [13]. Studies in critically ill patients with sepsis and cytopenia but no HLH found hemophagocytosis and macrophage activation in bone marrow smears in 0.8% and 4% of cases, respectively [10, 13]. However, these data are difficult to interpret as no cytological results from a relevant control population were available.

HLH was fatal in 22–59% of patients in previous studies [9, 14, 15]. Mortality rates were higher when the precipitating factor was a malignancy or Epstein-Barr virus (EBV) infection, as opposed to other infections (with viruses or intracellular bacteria) [14]. The most common causes of death were multiple organ failure, bleeding and sepsis [14]. Few studies assessed the factors associated with mortality in HLH patients, and none were conducted in ICU patients. Moreover, for HLH related to EBV infection, new therapy with etoposide initiation within 4 weeks of the diagnosis was associated with 90% long-term survival, compared to 56% when etoposide was started later [16]. However, none of these patients were described as having multiple organ dysfunction. To the best of our knowledge, there are no available data on outcomes of critically ill patients with HLH.

Here, our objective was to assess the features, ICU management and outcomes of critically ill patients with HLH, and to identify factors associated with mortality.

## Patients and methods

We conducted a retrospective study in all adults who were admitted to the medical ICU of the Saint Louis Teaching Hospital between January 1998 and January 2009 and who met the HLH-2004 criteria for HLH. Hemophagocytosis was defined as histological evidence of activated macrophages engulfing erythrocytes, leukocytes, platelets and their precursor cells in bone marrow smears or biopsies and/or in liver or spleen biopsies (Fig. 2). All patients were managed jointly by the ICU team and a hematologist-immunologist consultant. All survivors were discharged from the ICU to the department of clinical immunology in the same hospital. In patients admitted to the ICU more than once during the study period, only the first admission was included in the study. Our institutional review board approved the study and waived the need for informed consent.

The study data (Table 1) were abstracted from the medical records. Castleman's disease (or angiofollicular lymphoid hyperplasia) is a non-cancerous proliferation of lymph nodes associated with inflammatory symptoms and interleukin 6 (IL-6) dysregulation. In the context of human immunodeficiency virus (HIV) infection, multicenter Castleman's disease is associated with Kaposi sarcoma-associated herpesvirus type 8 (KSHV/HHV8). Performance status was measured as previously reported [17]. The diagnosis of HIV infection was based on positive ELISA and Western blot tests before or during the ICU stay. Organ dysfunction was assessed at admission then on days 1, 3 and 5 using the Sequential Organ Failure Assessment (SOFA) score [18]. All patients received full-code management. The use of etoposide and other anticancer agents was recorded. Vital status at ICU and hospital discharge was available for all patients.

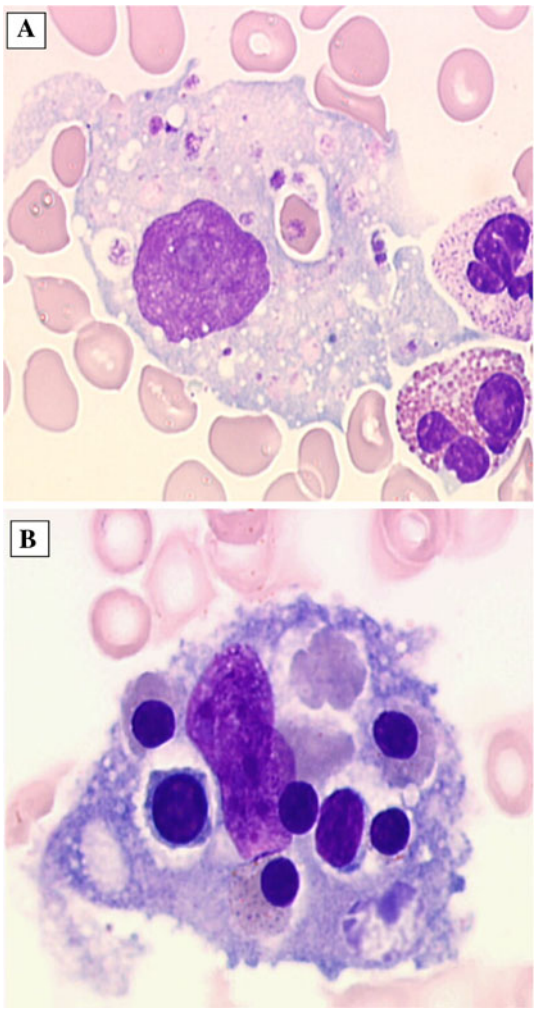


**Fig. 2** Histological evidence of hemophagocytosis. **a** Hematoxylin-eosin stain of bone marrow showing histiocytes phagocytizing erythroblasts and lymphocytes. **b** Hematoxylin-eosin stain of bone marrow showing phagocytic cells containing erythrocytes and platelets

### Statistical analysis

Results are reported as median (interquartile range) or number (%), unless stated otherwise. Patient characteristics were compared using the chi-square test or Fisher's exact test, as appropriate, for categorical variables and the Wilcoxon or Kruskal-Wallis test, as appropriate, for continuous variables. Associations linking patient characteristics (variables in Tables 1, 2) to hospital mortality were assessed using a logistic regression model. Multivariable analysis was performed using a forward stepwise selection procedure. In the first step, all variables associated with hospital mortality in the univariate analysis were entered into the model. Entered variables were dropped if they were no longer significant when other variables were added. Variables entered into the final model are listed in the Table 4 footnote. Odds ratios (ORs) and their 95% confidence intervals (95%CI) were computed. Kaplan-Meier survival curves were plotted over the follow-up period. All tests were two-sided, and $P$ values less than 0.05 were considered statistically significant. Analyses were done using the Statview 5.0 software package (SAS Institute, Cary, NC) on a personal computer.

## Results

During the study period, 5,027 patients were admitted to our medical ICU. Among them, 528 patients had bone marrow examinations that provided pictures of hemophagocytosis in 71 (13.5) cases. As shown in Fig. 3,

**Table 1** Patient characteristics at baseline, symptoms, precipitating factors and underlying immune deficiency in ICU patients with hemophagocytic lymphohistiocytosis (HLH)

| Variable | *n* (%) or medians [IQR] |
|---|---|
| Demographics | |
| Age, years | 49 [30–73] |
| Male gender | 43 (76.8) |
| Co-morbidities | |
| Viral hepatitis | 10 (17.9) |
| Hypertension | 11 (19.6) |
| Diabetes | 5 (8.9) |
| Chronic heart failure | 5 (8.9) |
| Autoimmune disease | 7 (12.5) |
| Immune deficiency | |
| Malignancies[a] | 26 (46.4) |
| HIV positive | 18 (32.1) |
| Immunosuppressive medications | 6 (10.7) |
| Prior history of HLH | 3 (5.3) |
| Time from hospital to ICU admission, days | 10 [4–21] |
| Reasons for ICU admission | |
| Acute respiratory failure | 17 (30.3) |
| Coma, confusion | 12 (21.4) |
| Shock | 10 (17.8) |
| Acute renal failure | 9 (16.1) |
| Fulminant liver failure | 5 (7.1) |
| Acute bleeding | 3 (5.3) |
| SOFA score at ICU admission | 6.5 [4–8] |
| HLH-related symptoms | |
| Clinical criteria | |
| Body temperature (°C) | 39.7 [38.5–40.0] |
| Spleen enlargement (physical exam and echography), *n* (%) | 43 (76.8) |
| Laboratory criteria | |
| Hemoglobin (g/dl) | 8.3 [7.4–9.5] |
| Platelet count ($\times 10^9$/mm$^3$) | 2.9 [1.9–5.0] |
| Neutrophil count ($\times 10^9$/mm$^3$) | 3.4 [1.8–8.4] |
| Triglycerides (mmol/l) | 2.65 [1.93–4.3] |
| Ferritin (μg/l) | 5,219 [2,752–10,000] |
| Fibrinogen (g/l) | 2.6 [1.7–4.5] |
| Histological evidence of hemophagocytosis, *n* of patients (%) | 44 (78.6) |
| Total number of diagnostic criteria | 6.0 [5–7] |
| Precipitating factors, *n* (%) (72 factors in 56 patients) | |
| Undetermined | 4 (7.1) |
| Tumoral diseases[b] | 43 (76.8) |
| Castleman's disease[c] | 8 |
| B cell lymphoma | 18 |
| Other malignant diseases | 17 |
| Non-viral infection | 13 (23.2) |
| Tuberculosis | 6 |
| Blood stream infections | 5 |
| Toxoplasmosis (1 case in B cell lymphoma patient) | 4 |
| Viral infections | 10 (17.9) |
| Herpes simplex reactivation associated with | 1 |
| B cell lymphoma | |
| Autoimmune disease (Kikuchi disease) | 1 |
| CMV reactivation associated with | |
| Castleman's disease | 1 |
| B cell lymphoma | 2 |
| Reactivation of both HSV and CMV infections | |
| Castleman's disease | 3 |
| B cell lymphoma | 1 |
| Hodgkin's disease | 1 |
| Underlying immune deficiency | |
| HIV infection | 18 (32.1) |
| Immunosuppressive agents | 20 (35.7) |
| Including corticosteroids | 14 (25.0) |

*HLH* hemophagocytic lymphohistiocytosis, *SOFA* Sequential Organ Failure Assessment, *ICU* intensive care unit, *HIV* human immunodeficiency virus

[a] Nineteen of the 26 malignancies had been previously diagnosed, and 7 were at the earliest phase (before any therapy) but diagnosed before ICU admission

[b] Sixteen patients had two precipitating conditions; five patients had blood stream infections associated with B cell lymphoma ($n = 3$) and T cell lymphoma ($n = 2$); three patients had tuberculosis with Hodgkin's disease, B cell lymphoma and Castleman's disease; eight viral infections occurred in patients with tumoral diseases

[c] Castleman's disease (or angiofollicular lymphoid hyperplasia) is a non-cancerous proliferation of lymph nodes associated with inflammatory symptoms and interleukin 6 (IL-6) dysregulation. In the context of human immunodeficiency virus (HIV) infection, multicenter Castleman' disease is associated with Kaposi sarcoma-associated herpesvirus type 8 (KSHV/HHV8)

among the 102 patients who met the HLH criteria, 27 had pictures of hemophagocytosis but did not meet the HLH-2004 criteria. Reasons for not meeting the criteria are reported in Fig. 3. Complete follow-up data were available for 56 of the remaining 75 patients. These 56 patients form the basis for this study.

The main patient characteristics at baseline are reported in Table 1. The median SOFA score was 6.5 (4–8), indicating that most patients had severe failure of at least two organs. HLH was diagnosed before ICU admission in 32 patients and during the ICU stay in 24 (43%) patients. The time from diagnosis to ICU admission was 10 days (4–20) in the 32 diagnosed before the ICU. Reasons for ICU admission were acute respiratory failure in 17 (30.3%) patients, coma or confusion in 12 (21.4%), shock in 10 (17.8%), acute renal failure in 9 (16.1%), fulminant liver failure in 5 (7.1%) and acute bleeding in 3 (5.3%). At ICU admission, 7 (12.5%) patients had a known history of connective tissue disease and 26 (46.4%) of malignancy. Furthermore, three (5.3%) patients had a prior history of HLH. Performance status indicated no or mild limitation in 37 (66%) patients.

Table 2 lists the manifestations of HLH in the study patients. At ICU admission, the number of HLH-2004 criteria was 6 (5–7). A fever (>37.8°C) was present in 37 (66.1%) patients, cytopenia of at least one line in 54 (96.4%), alanine aminotransferase elevation to more than twice the upper limit of normal in 23 (41.2%), and serum

**Table 2** Life-supporting treatments, investigations and adjuvant treatments for hemophagocytic lymphohistiocytosis during the intensive care unit stay and outcome

| Characteristic | *n* (%) or median [IQR] |
|---|---|
| Mechanical ventilation | 32 (58.2) |
| Vasoactive drugs | 30 (53.6) |
| Renal replacement therapy | 19 (33.9) |
| Bone marrow examination | 49 (87.5) |
| Nosocomial infection | 13 (23.2) |
| Antibacterial treatment | 46 (82.8) |
| Antifungal therapy | 17 (30.3) |
| Antituberculous treatment | 9 (16.1) |
| Antiviral therapy | 10 (17.8) |
| Corticosteroids | 31 (55.4) |
| Intravenous immunoglobulins | 3 (5.3) |
| Etoposide | 45 (80.3) |
| Anticancer chemotherapy | 32 (57.1) |
| Splenectomy | 4 (7.4) |
| Time to etoposide initiation (hours) | 5 [2–14] |
| ICU length of stay (days) | 8.5 [3.7–12.5] |
| Hospital length of stay (days) | 23.5 [11.2–41.7] |
| Death in the ICU | 22 (39.2) |
| Death in the hospital | 29 (51.8) |

sodium lower than 135 mmol/l in 40 (71.4%). As reported in Table 2, the main precipitating factors were tumoral causes ($n = 43$, 76.8%), including 17 that were newly diagnosed, non-viral infections ($n = 13$, 23.2%) and viral infections in 10 (17.9%) patients. In four (7.1%) patients, no precipitating factor was found. Among the 43 patients with tumoral diseases, 18 patients were diagnosed with B cell lymphoma, 8 with Castleman's disease and 17 with various types of malignancies. The search for a cause of immune deficiency identified HIV infection in 18 patients, and 20 were taking immunosuppressive medications. Table 3 reports the main abnormalities at ICU admission. For diagnostic purpose, bone marrow smears were performed in 49 of the 56 patients, bone marrow biopsies in 2, liver biopsies in 12 and diagnostic splenectomy in 4. Etoposide was used in 45 patients, corticosteroids in 31 (55.4%) and intravenous immune globulins in 3. The time from ICU admission to the first etoposide dose was 5 (2–14) h. Cancer chemotherapy was given to 32 patients. Life-sustaining treatments included mechanical ventilation in 32 patients, vasoactive agents in 30 and renal replacement therapy in 19 (Table 4). Antimicrobial agents were used in 46 patients and blood transfusions in 41 (73.2%).

Of the 56 patients, 22 (39.2%) died in the ICU, and 7 others died before hospital discharge (29/56, 51.8%). Differences between hospital survivors and nonsurvivors are reported in Table 3. By univariate analysis, SOFA scores on days 0 and 3 were significantly higher in nonsurvivors than in survivors ($P < 0.001$ and $P = 0.05$, respectively; Fig. 4). Of the four factors that independently predicted hospital mortality in the multivariate analysis (Table 4), two were associated with increased mortality: shock at ICU admission (OR, 4.33; 95% CI, 1.11–16.90; $P = 0.03$) and platelet count <30 g/l (OR, 4.75; 95% CI, 1.20–18.81; $P = 0.02$). The two factors that had protective effects were Castleman's disease (OR, 0.11; 95% CI, 0.02–0.90; $P = 0.04$) and diagnosis of B cell lymphoma (OR, 0.17; 95% CI, 0.04–0.80; $P = 0.02$).

## Discussion

We describe the characteristics of adults with early stage HLH who met the HLH-2004 diagnostic criteria and who required ICU admission for the diagnosis and management of multiple acute organ failures. A precipitating factor was identified in 93% of patients, and about half the patients had a readily identifiable cause of

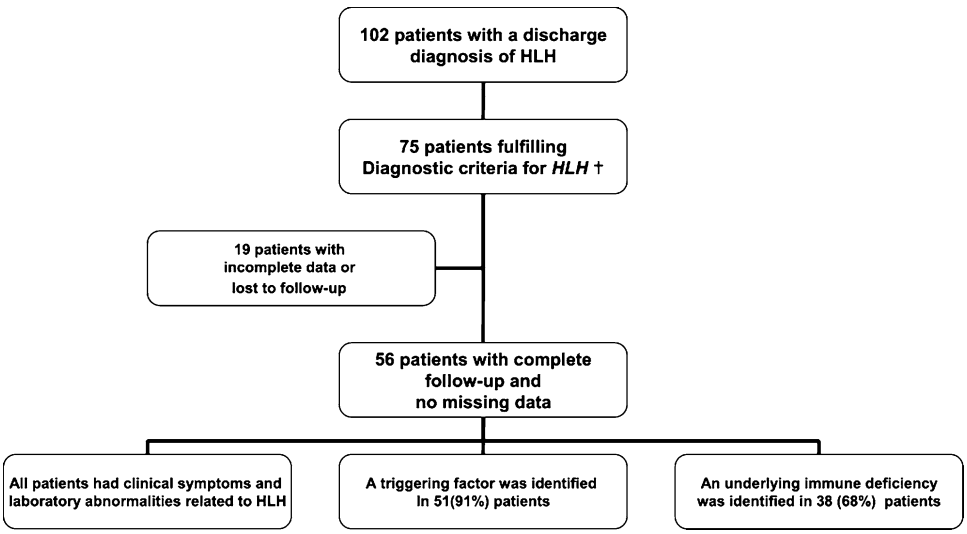


**Fig. 3** Patient flow chart. †Twenty-seven patients had pictures of macrophage activation and were coded as HLH patients but did not fulfill the HLH 2004 criteria. Indeed, none of them had cytopenia, elevated triglycerides or ferritinemia

**Table 3** Comparison of survivors and nonsurvivors

| Patients characteristics, $n = 56$ patients | Non-survivors, $n = 29$ (%) | Survivors $n = 27$ (%) | $P$ value |
|---|---|---|---|
| Age, years | 50 [36–60] | 48 [35–60] | 0.91 |
| Male gender | 22 (75.8) | 21 (77.8) | 0.86 |
| Number of comorbid conditions[a] | 0 [0–1] | 0 [0–1] | 0.63 |
| Previous history of malignant disease | 21 (72.4) | 22 (81.5) | 0.42 |
| Time from hospital to ICU admission, days | 12 [4–17] | 10 [2–23] | 0.94 |
| SOFA | | | |
| Day 0 | 8 [5–10] | 5 [2–7] | 0.001 |
| Day 3 | 12 [9–17] | 7 [3–12] | 0.05 |
| Day 7 | 4 [2–7.5] | 9.5 [8–13] | 0.02 |
| Temperature | 39.5 [38.5–40] | 39.8 [38.6–40.0] | 0.70 |
| Spleen enlargement | 22 (75.8) | 21 (77.7) | 0.86 |
| Platelet count ($\times 10^{12}$/mm$^3$) | 27 [13–34] | 38 [26–71] | 0.05 |
| Hemoglobin (g/dl) | 8.4 [7.5–9.5] | 8.3 [7.4–9.7] | 0.80 |
| Leucocytes ($10^9$/mm$^3$) | 3,500 [1,700–11,000] | 3,300 [1,200–8,200] | 0.33 |
| Ferritin (μg/l) | 6,300 [2,700–10,000] | 4,500 [2,700–7,700] | 0.66 |
| Triglycerides (mmol/l) | 2.9 [2.2–4.3] | 2.6 [1.8–4.3] | 0.43 |
| Hemophagocytosis (histology or cytology) | 26 (89.6) | 18 (66.6) | 0.04 |
| Reasons for ICU admission | | | |
| Shock[b] | 21 (72.4) | 13 (48.1) | 0.04 |
| Acute respiratory failure | 10 (34.5) | 7 (25.9) | 0.80 |
| Acute kidney injury | 4 (13.8) | 5 (18.5) | 0.90 |
| Confusion/coma | 7 (24.1) | 5 (18.5) | 0.90 |
| Fulminant hepatitis | 4 (13.8) | 1 (3.1) | 0.30 |
| Life-sustaining therapies | | | |
| Mechanical ventilation | 21 (72.4) | 11 (40.7) | 0.01 |
| Vasopressors | 21 (72.4) | 9 (33.3) | 0.004 |
| Renal replacement therapy | 14 (48.2) | 5 (18.5) | 0.02 |
| HLH etiologies | | | |
| Undetermined | 3 (10.3) | 1 (3.7) | 0.32 |
| Castleman's disease[c] | 2 (6.9) | 6 (22.2) | 0.09 |
| B cell lymphoma[c] | 6 (20.7) | 12 (44.5) | 0.05 |
| Other malignancy[c] | 11 (37.9) | 6 (22.2) | 0.27 |
| HLH-related to non-viral infections | 8 (27.6) | 5 (18.5) | 0.53 |
| HLH related to viral infections | 6 (20.7) | 4 (14.8) | 0.73 |
| Specific HLH therapies | | | |
| Steroids | 14 (48.2) | 17 (62.9) | 0.41 |
| Intravenous immunoglobulins | 2 (6.9) | 1 (3.7) | 0.90 |
| Time from admission to etoposide, hours | 6 [2–24] | 4 [2–15] | 0.19 |
| Splenectomy | 2 (6.9) | 2 (7.4) | 0.90 |
| Chemotherapy | 17 (58.6) | 15 (55.6) | 0.90 |

*SOFA* Sequential Organ Failure Assessment

[a] Comorbid conditions included hypertension, COPD, chronic cardiac or renal insufficiency, diabetes, chronic B or C hepatitis and cirrhosis. The score that is mentioned is the sum of all comorbidities

[b] Hypotension was defined as a systolic blood pressure below 85 mmHg

[c] Among the 45 malignant diseases (Castleman's disease, B cell lymphoma and other malignancies), 26 were diagnosed prior to ICU admission

immunosuppression. With etoposide-based therapy, treatment of precipitating factors and full-code life-supporting treatment, hospital mortality was 51.8%. Factors that independently influenced hospital mortality were admission to the ICU for shock and thrombocytopenia <30 g/l. Castleman's disease and B cell lymphoma were precipitating factors associated with decreased hospital mortality. Etoposide (VP-16) is a cytotoxic drug that selectively targets the monocyte line through the enzyme topoisomerase-2. Etoposide and steroids comprise an immunochemotherapy that benefits patients with HLH [16, 29]. It acts rapidly, within 24–48 h. Its efficacy far outweighs the risk of secondary leukemia and transient worsening of the neutropenia.

It is of major importance for critical care physicians to be aware that pictures of hemophagocytosis can be encountered during sepsis [6, 13] or multiple organ failure [19], and that HLH and sepsis-associated hemophagocytosis may overlap, share common features and may not be reliably discriminated by the diagnostic criteria of HLH. Usually, sepsis-induced thrombocytopenia is mostly related to peripheral consumption such as DIC or pulmonary

**Table 4** Predictors of hospital mortality by multivariable analysis

| Variable | Odds ratio | 95% CI | *P* value |
|---|---|---|---|
| ICU admission for shock | 4.33 | 1.11–16.90 | 0.03 |
| Platelet count <30 g/l | 4.75 | 1.20–18.81 | 0.02 |
| Diagnosis of B cell lymphoma | 0.17 | 0.04–0.80 | 0.02 |
| Castleman's disease | 0.11 | 0.02–0.90 | 0.04 |

The following variables were entered in the multivariate model: First hemophagocytosis, thrombocytopenia and ICU admission for shock were introduced in the model. Since hemophagocytosis was dropped by the model, we then entered Castleman's disease and B cell lymphoma. Last, etoposide administration was forced in the model to be consistent with the literature

Goodness of fit (Hossmer Lemeshow chi-square *P* value) = 0.22

*95% CI* 95% confidence interval

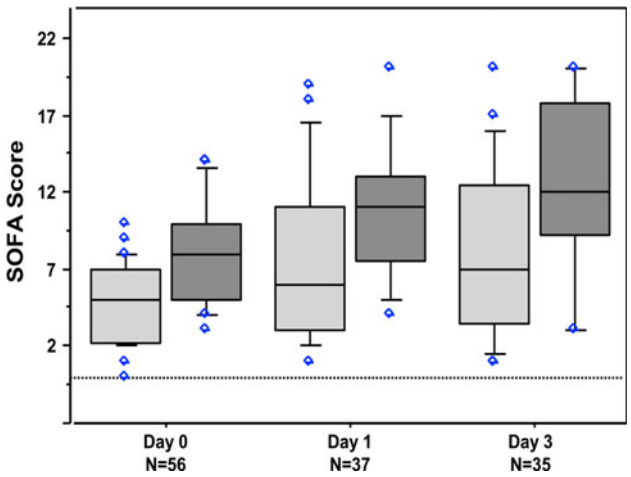


**Fig. 4** Sequential SOFA score assessment according to vital status at hospital discharge. Survivors are in *light gray* and nonsurvivors in *dark gray*. *Box plots* indicate the median and the 5th and 95th percentiles. *P* values < 0.01 for all comparisons between survivors and nonsurvivors using the Mann-Whitney test

sequestration. Nonetheless, in septic patients, impaired platelet production by medullar hemophagocytosis may contribute to thrombocytopenia [20–23]. However, the potential link with macrophage dysregulation and cytokine imbalance still seems to be unclear in the setting of sepsis-induced immunosuppressive response. In HLH, the primary abnormality is cytokine-driven macrophage activation against a background of preexisting immune deficiency leading to hemophagocytosis and organ dysfunction [7].

We identified two factors that were associated with increased short time survival, Castleman's disease and B cell lymphoma. Castleman's disease related to human herpesvirus 8 infection and Kaposi's sarcoma is known to be associated with HLH [24]. In patients with Castleman's disease, etoposide has been reported to ensure the prompt resolution of HLH [25, 26]. Conceivably, anticancer chemotherapy may be effective in resolving HLH associated with malignancies. Therefore, we suppose that HLH associated with lymphoma may be more responsive to chemotherapy with quickly resolving organ dysfunctions. Shock at ICU admission was associated with a higher rate of hospital mortality in our study. This finding is consistent with data from patients with sepsis showing that a greater number of organ failures is associated with a higher mortality rate [27].

Our study has several limitations. First, the cohort was recruited at a single center. Nevertheless, our ICU has extensive experience in the management of patients with hematological malignancies, and we work in close collaboration with the hematologists at our hospital [17, 28]. HLH is an uncommon syndrome that is best managed at centers caring for large numbers of hematology patients. Thus, our ICU is representative of the appropriate setting for managing HLH patients. Second, we used a retrospective design. However, over the 11-year study period the senior physicians at our ICU and hematology departments remained the same and used the same standardized approach to the management of HLH. Furthermore, the medical records contained reliable information on all the pre-defined study variables. Third, throughout the study period patient's management may have changed. However, we did not identify any changes over time in ICU management and/or treatments for precipitating factors such as hematological malignancies. Finally, two-thirds of our patients had hematological malignancies, compared to only 41% with infections and one patient with autoimmune disease. These data are difficult to compare to the literature since no case series of non-selected ICU patients with HLH are available. Whether our findings can be generalized to cohorts characterized by different distributions of precipitating factors is unclear.

In summary, even when HLH is responsible for multiple organ failures requiring ICU admission, aggressive supportive care combined with treatment of the precipitating factor ensures the survival of nearly half the patients. The chances of short-term survival are particularly high in patients with Castleman's disease or B cell lymphoma, possibly related to sensitivity to cancer chemotherapy.

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CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL



# Case 10-2011: A Woman with Fever, Confusion, Liver Failure, Anemia, and Thrombocytopenia

Lawrence M. Tierney, Jr., M.D., Ashraf Thabet, M.D., and. Ha Nishino, M.D.

## PRESENTATION OF CASE

*Dr. Andrea L. Russo* (Medicine): A 60-year-old woman was admitted to this hospital because of fever, confusion, liver failure, anemia, and thrombocytopenia.

The patient had been in her usual state of health, with a history of hepatitis C virus infection and cirrhosis, until 2 to 3 weeks before admission, when low-grade fevers developed and relatives noted she was acting strangely, with slurred speech and urinary incontinence. Approximately 3 days before admission, increasing confusion and diarrhea developed. The day before admission, emergency medical services were called, and she was taken to another hospital. On examination, she was restless and oriented to person and place; her speech was slurred and her verbal responses to questions were confused. The temperature was 38.2°C, the blood pressure 127/63 mm Hg, the pulse 125 beats per minute, the respiratory rate 25 breaths per minute, and the oxygen saturation 97% while she was breathing ambient air. The sclera were icteric; the abdomen was tender without rigidity, and bowel sounds were present; there were ecchymoses on her abdomen and legs, with trace edema of the legs. Asterixis was present; the remainder of the examination was reportedly normal.

The level of D-dimer was 19.18 μg per milliliter (reference range, 0.0 to 0.49), and plasma levels of glucose, globulin, magnesium, and ammonia and tests of renal function were normal; other results are shown in Table 1. Urinalysis showed cloudy urine with 2+ blood and 1+ protein; results were otherwise normal. Screening tests revealed immunity to hepatitis A and B viruses, the presence of cannabinoids in the urine, and occult blood in the stool. An electrocardiogram revealed sinus tachycardia (121 beats per minute). Chest radiography showed elevation of the right hemidiaphragm and minimal atelectasis at the base of the right lung. Computed tomography (CT) of the head without the administration of contrast material showed postoperative changes in the left frontal lobe, which were consistent with the surgical evacuation of an intracranial hemorrhage in the past and were unchanged from the findings on a CT examination performed 2 years earlier, after a fall. An abdominal ultrasonographic examination showed sludge in the gallbladder and pericholecystic fluid, with no clear evidence of Murphy's sign or hepatic or portal-vein thrombosis. Cultures of the blood were sterile. Ceftriaxone, vancomycin, rifaximin, vitamin K,

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**Table 1. Laboratory Data.***

| Variable | Reference Range, Adults† | Other Hospital | This Hospital | Other Hospital | This Hospital | | | |
|---|---|---|---|---|---|---|---|---|
| | | 7–10 Mo before Admission | 7 Wk before Admission | On Admission | On Admission | Day 2 | Day 3 | Day 4 |
| Hematocrit (%) | 36.0–46.0 (in women) | 38.5 | 29.8 | 18.5 | 22.6 | 20.4 | 26.2 | 24.5 |
| Hemoglobin (g/dl) | 12.0–16.0 (in women) | 13.2 | 9.7 | 6.6 | 7.7 | 7.6 | 9.5 | |
| White-cell count (per mm$^3$) | 4500–11,000 | 5200 | 2400 | 5100 | 6000 | 6200 | 3000 | 2700 |
| Differential count (%) | | | | | | | | |
| Neutrophils | 40–70 | 55 | 55 | 80 | 82 | 91 | 88 | 76 |
| Band forms | 0–10 | | | 0 | 0 | | 7 | 8 |
| Lymphocytes | 22–44 | 33 | 35 | 17 | 14 | 6 | 4 | 8 |
| Monocytes | 4–11 | 8 | 9 | 3 | 2 | 2 | 1 | 4 |
| Eosinophils | 0–8 | 3 | 1 | 0 | 1 | 1 | | 2 |
| Basophils | 0–3 | 1 | 0 | 0 | 1 | 0 | | 0 |
| Metamyelocytes | 0 | | | | | | | 2 |
| Platelet count (per mm$^3$) | 150,000–400,000 | 108,000 | 82,000 | 42,000 | 47,000 | 60,000 | 36,000 | 32,000 |
| Smear | | | | 1+ schistocytosis, burr cells, anisocytosis, few ovalocytes | 2+ anisocytosis | 1+ anisocytosis | 2+ anisocytosis | Smudge cells, 1+ anisocytosis |
| Erythrocyte sedimentation rate (mm/hr) | 1–17 (in women) | | | | | 53 | | |
| Reticulocytes (%) | 0.5–2.5 | | | | | | 1.1 | |
| Haptoglobin (mg/dl) | 16–199 | 40 | | | | | <6 | |
| Activated partial-thromboplastin time (sec) | 21.0–33.0 | | | 47 | 39.7 | 42.8 | | 38.9 |
| Prothrombin time (sec) | 10.8–13.4 | 13.8 | | 20.8 | 17.4, icteric | 15.9 | | 16.0 |
| International normalized ratio for prothrombin time | | 1.1 | | 1.8 | 1.5, icteric | 1.4 | | 1.4 |
| Fibrinogen (mg/dl) | 150–400 | | | 94 (ref, 200–470) | 170 | | 89 | 142 |
| Bilirubin (mg/dl) | | | | | | | | |
| Total | 0.0–1.0 | 0.9 | 1.2 | 2.3, slightly hemolyzed specimen | 3.4 | 3.1 | 4.1 | 5.0 |
| Direct | 0.0–0.4 | 0.3 (ref 0.0–0.2) | 0.6 | 1.3 | 2.2 | 1.8 | 2.8 | 3.4 |
| Protein (g/dl) | | | | | | | | |
| Total | 6.0–8.3 | 7.4 | 7.5 | 6.2 | 6.4 | 6.4 | 6.6 | 6.4 |
| Albumin | 3.3–5.0 | 3.4 | 3.8 | 2.0 | 2.4 | 2.7 | 2.2 | 1.8 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Alkaline phosphatase (U/liter) | 30–100 | 88 | 96 | 123 | 127 | 109 | 127 | 128 |
| Aspartate aminotransferase (U/liter) | 9–32 | 99 (ref 0–46) | 87 | 773 | 1312 | 1032 | 1047 | 976 |
| Alanine aminotransferase (U/liter) | 7–30 | 106 | 81 | 294 | 399 | 335 | 381 | 363 |
| $\alpha_2$-Macroglobulins (mg/dl) | 110–276 | 275 | | | | | | |
| Apolipoprotein A-1 (mg/dl) | 110–205 | 156 | | | | | | |
| HCV fibrosis score | 0.00–0.21 | 0.76 | | | | | | |
| Necroinflammation activity score | 0.00–0.17 | 0.75 | | | | | | |
| Alpha-fetoprotein (ng/ml) | <6.0 | 25.9 | | | | | | |
| HCV RNA on PCR assay (IU/ml) | <43, not quantifiable | | 46,500 | | 3380 | | | |
| Sodium (mmol/liter) | 135–145 | | | 120 | 125 | 128 | 128 | 132 |
| Potassium (mmol/liter) | 3.4–4.8 | | | 5.4 | 4.3 | 3.6 | 3.9 | 4.2 |
| Chloride (mmol/liter) | 100–108 | | | 86 | 95 | 94 | 97 | 102 |
| Carbon dioxide (mmol/liter) | 23.0–31.9 | | | 22 | 21.5 | 24.9 | 23.3 | 22.4 |
| Phosphorus (mg/dl) | 2.6–4.5 | | | 2.9 | 2.0 | 2.3 | 2.3 | 2.6 |
| Calcium (mg/dl) | 8.5–10.5 | | | 6.5 | 6.7 | 6.6 | 7.1 | 6.9 |
| Lipase (U/liter) | 13–60 | | | 90 | 105 | | | |
| Amylase (units/liter) | 3–100 | | | 175 | 126 | | | |
| Lactate (mmol/ liter) | 0.5–2.2 | | | 4.9 | 2.0 | | | |
| Creatine kinase (U/ liter) | 40–150 | | | | 1333 | | 644 | |
| C-reactive protein (mg/liter) | <8.0 | | | | | 61.6 | | |
| Lactate dehydrogenase (U/liter ) | 110–210 | | | | | | 2265 | |
| Ferritin (ng/ml) | 10–200 | | | | | | 68,741 | 48,986 |
| Iron ($\mu$g/dl) | 30–160 | | | | | | 175 | |
| Iron-binding capacity ($\mu$g/dl) | 230–404 | | | | | | 184 | |
| Lipid levels (mg/dl) | | | | | | | | |
| Total cholesterol | <200, desirable | | | | | | | 120 |
| Triglycerides | 40–150 | | | | | | | 1221 |
| HDL | 35–100 | | | | | | | 10 |

* To convert the values for calcium to millimoles per liter, multiply by 0.250. To convert the values for phosphorus to millimoles per liter, multiply by 0.3229. HCV denotes hepatitis C virus, HDL high-density lipoprotein, PCR polymerase chain reaction, and ref reference range.

† Reference values are affected by many variables, including the patient population and the laboratory methods used. The ranges used at Massachusetts General Hospital are for adults who are not pregnant and do not have medical conditions that could affect the results. They may therefore not be appropriate for all patients.

lactulose, and pantoprazole were administered, and normal saline, platelets, packed red cells, and fresh frozen plasma were infused, with improvement in tests of coagulation. The patient became increasingly confused and agitated and was transferred to this hospital in the early hours of the next morning.

A diagnosis of hepatitis C virus (HCV) (genotype 1a) infection had been made several years earlier; the level of RNA copies was 1,080,000 U per milliliter 17 months before admission. During the year before admission, imaging studies had revealed splenomegaly, normal liver echotexture with two hepatic hemangiomas, and no evidence of esophageal varices or hepatic or colonic cancer. The plasma level of γ-glutamyl transpeptidase was 95 IU per liter (reference range, 0 to 60) and, with the results of tests of other serum biochemical markers ($\alpha_2$-macroglobulin, haptoglobin, apolipoprotein A-1, bilirubin, and alanine aminotransferase) (Table 1), was consistent with stage F4 cirrhosis and stage A3 severe necroinflammation (according to the results of analysis by means of HCV FibroSURE[1]). Treatment with peginterferon alfa-2b and ribavirin was begun 3 months before admission. One month later, the patient reported fatigue; laboratory-test results are shown in Table 1. Epoetin alfa (administered parenterally) was added.

The patient had a history of depression and anxiety, intravenous drug abuse 30 years earlier, cocaine use, and alcohol abuse (until 9 years earlier). Other medications included fluoxetine, bupropion, omeprazole, and antacids. She had no allergies. She was born in the United States and traveled to Europe and Central America more than 5 years earlier. She lived with her boyfriend and many dogs, birds, and cats, including strays; one cat had recently scratched her. Her mother had died at 88 years of age, with an unspecified blood disorder and stomach cancer; her father had died at 51 years of age from emphysema. Her son was healthy.

On examination, the patient was agitated, disoriented, and incontinent of maroon stool; she followed commands minimally. The temperature was 39.8°C, the blood pressure 149/64 mm Hg, the pulse 126 beats per minute, the respiratory rate 26 breaths per minute, and the oxygen saturation 98% while she was breathing ambient air. The right pupil was approximately 4 mm in diameter and the left approximately 1 to 2 mm; both were minimally reactive to light and there was evidence of light sensitivity. There were petechiae on the tongue, active bowel sounds, voluntary abdominal guarding and tenderness with no palpable organomegaly, multiple ecchymoses (3 to 6 cm in diameter), and an ulceration on the right buttock. The remainder of the examination was normal. The level of factor V was 58% (reference range, 60 to 140), and the level of factor VIII 124% (reference range, 50 to 200). Hematologic indexes; levels of magnesium, total protein, globulin, and ammonia; and renal function were normal (other results are shown in Table 1). Urinalysis revealed amber, cloudy urine with a pH of 6.0; a specific gravity of 1.017; 3+ occult blood; 1+ bilirubin, urobilinogen, and albumin; trace ketones; and 50 to 100 white cells, more than 100 red cells, and a few squamous cells per high-power field.

The patient's agitation increased, and haloperidol was administered, without benefit. Four hours after her arrival, the trachea was intubated and the patient was sedated to protect the airway and so that the diagnostic evaluation could be completed. CT of the chest showed dependent opacities in both lower lobes, nodules in the posterior left upper lobe (6 to 7 mm in diameter) and right upper lobe (2 to 3 mm), enlarged mediastinal and right peridiaphragmatic lymph nodes, and a small left pleural effusion. CT of the abdomen and pelvis revealed morphologic characteristics of the liver that were compatible with cirrhosis, without any focal lesions; splenomegaly (16.8-cm span; upper limit of the normal range, 13 cm); perigastric varices; mild pelvic ascites; prominent periportal lymph nodes; and a 5.2-cm hematoma within the sheath of the right rectus muscle. Six hours after arrival, the temperature rose to 40.9°C. External cooling was begun, and amoxicillin and acyclovir were added. Repeat chest radiography showed evidence of mild pulmonary edema and persistent air-space opacities in the left lower lung. Additional units of fresh frozen plasma, platelets, and red cells were transfused, and interferon and ribavirin were discontinued.

On the second day, magnetic resonance imaging (MRI) of the brain showed postsurgical changes and no acute process. Ultrasonography of the abdomen showed morphologic characteristics of the liver that were compatible with cirrhosis, patent hepatic vasculature, and splenomegaly (19.5 cm in the craniocaudal dimension), with no evidence of cholelithiasis or cholecystitis. A lumbar punc-

ture was performed; analysis of the cerebrospinal fluid revealed clear, colorless fluid with a glucose concentration of 37 mg per deciliter (2.1 mmol per liter) (reference range, 50 to 75 mg per deciliter [2.8 to 4.2 mmol per liter]), protein 33 mg per deciliter (reference range, 5 to 55), 3 white cells per cubic millimeter (reference range, 0 to 5) in both tube 1 (100% monocytes) and tube 4 (40% lymphocytes, 40% neutrophils, and 20% monocytes) and 76 red cells and 313 red cells per cubic millimeter (reference value, 0) in tubes 1 and 4, respectively. Cytologic examination of the cerebrospinal fluid showed no malignant cells.

During the first 3 days of hospitalization, extensive testing of the blood, urine, sputum, nares, stool, and cerebrospinal fluid was performed. Evidence of past exposure to the Epstein–Barr and varicella–zoster viruses was detected, and test results were negative for syphilis, bartonella species, mycobacteria, legionella, *Borrelia burgdorferi*, babesia, toxoplasma, cryptococcus, pneumocystis, herpes simplex virus, the human immunodeficiency virus (HIV), parvovirus, respiratory viruses, cytomegalovirus, other bacteria, stool pathogens, and urinary histoplasma antigen. The serum level of complement C3 was 46 mg per deciliter (reference range, 86 to 184) and the level of complement C4 was 11 mg per deciliter (reference range, 16 to 38). A test for antinuclear antibodies was positive, at 1:40 and 1:160 in a speckled pattern, and a test for antibodies to smooth muscle was positive, at 1:40 (reference value, negative at 1:20). Test results were negative for rheumatoid factor; antibodies to double-stranded DNA; the SSA (Ro), SSB (La), Sm, RNP, and Scl-70 antigens; anti–cyclic citrullinated peptide IgG antibodies; and antineutrophil cytoplasmic antibodies. Other results are shown in Table 1.

During the second and third days, the patient's temperature rose to 38.0°C or higher. On the third day, acyclovir was continued and doxycycline begun; other antimicrobial agents were discontinued. Testing of the buttock lesion showed no evidence of herpes simplex virus or varicella–zoster virus. Other test results are shown in Table 1.

A diagnostic procedure was performed.

## DIFFERENTIAL DIAGNOSIS

*Dr. Lawrence M. Tierney, Jr.:* May we review the imaging studies?

*Dr. Ashraf Thabet:* The CT study of the abdomen and pelvis was performed with the administration of intravenous and oral contrast material. There is a nodular hepatic contour that is compatible with cirrhosis, as well as a small amount of perihepatic ascites (Fig. 1A). Splenomegaly is present (Fig. 1B), with the spleen measuring 16.8 cm in the craniocaudal dimension. Periportal lymph nodes are mildly enlarged, a common finding in hepatitis C infection; perigastric varices and a hematoma within the sheath of the right rectus muscle are evident.

Ultrasonographic examination of the abdomen shows cirrhosis, as well as gallbladder sludge and pericholecystic fluid (Fig. 1C), without cholelithiasis or clear evidence of Murphy's sign. There is splenomegaly (Fig. 1D), with the craniocaudal dimension of the spleen measuring 19.5 cm. Doppler examination of the hepatic vasculature shows normal directional flow in the hepatic veins, portal veins, and hepatic artery.

*Dr. Tierney:* Fever, abnormal mental status, and abdominal discomfort developed in this woman with hepatitis C and cirrhosis. Splenomegaly was present, and the results of numerous blood and urine studies were abnormal. Are these problems interrelated?[2,3]

### COMPLICATIONS OF CHRONIC HEPATITIS C

Chronic liver disease, with active inflammation and cirrhosis, must be accounted for in any synthesis of this patient's problem. The neurologic abnormalities did not improve on treatment with lactulose and rifaximin,[4] as would have been expected had they been caused by hepatic encephalopathy. The elevated level of D-dimer suggests intravascular coagulation, but levels may also be elevated in patients with liver failure. This patient had hypocomplementemia and an active urinary sediment, suggesting glomerulonephritis; glomerulonephritis may occur in patients with hepatitis C infection,[5] but numerous other causes of hematuria are possible. Cannabinoids cause a temporary change in mental status, but not the dramatic change in this patient, and they would not explain the other findings. The patient's splenomegaly could be attributed to portal hypertension, with hypersplenism causing cytopenias. Associations between hepatitis C and a wide variety of conditions have been noted.[2,5-7] Idiopathic thrombocytopenic purpura and autoimmune hemolytic anemia associated with hepatitis C infection could well be contributing factors, and non-

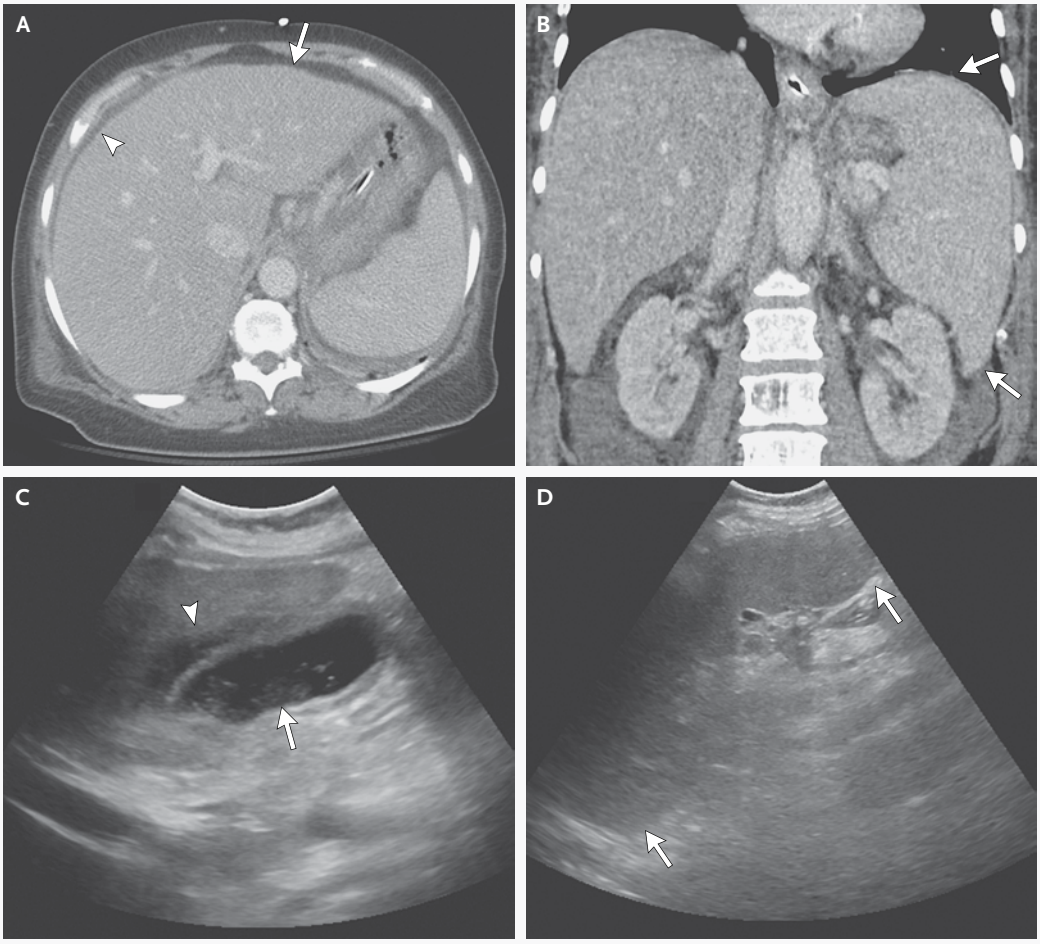


**Figure 1. CT Scan of the Abdomen and Pelvis, with Administration of Oral and Intravenous Contrast Material.**
An axial image of the abdomen (Panel A) shows nodularity along the contour of the liver (arrow), which is consistent with cirrhosis. There is also a small amount of perihepatic ascites (arrowhead). The coronal reformatted image of the abdomen shows splenomegaly (Panel B, arrows), with the craniocaudal dimension of the spleen measuring 16.8 cm (upper limit of normal, 13 cm). A sagittal image of the gallbladder is shown in an ultrasonogram of the abdomen (Panel C), revealing gallbladder sludge (arrow) and pericholecystic fluid (arrowhead); no sonographic Murphy's sign could be elicited. Splenomegaly was also identified (Panel D), with the craniocaudal dimension of the spleen measuring 19.5 cm (arrows).

specific abnormalities of the central nervous system other than hepatic encephalopathy have been well described. Essential mixed cryoglobulinemia, which is closely associated with hepatitis C infection, explains certain aspects of this case but is more likely to be an epiphenomenon than a cause.

The lumbar puncture showed hypoglycorrhachia without white cells, a finding in carcinomatous or lymphomatous meningitis. Indeed, a rapidly progressive lymphoma, such as Burkitt's or intravascular lymphoma, might account for the fever, splenomegaly, and elevated level of lactate dehydrogenase, but the remainder of the clinical picture does not support this diagnosis. Indolent lymphomas have been associated with chronic hepatitis C,[6] but the clinical process in this patient seems too aggressive to be explained by an indolent lymphoma. The autoantibody testing was not sufficiently comprehensive to diagnose concomitant rheumatologic disorders such as systemic lupus erythematosus, since low levels of complement may be nonspecific in patients with hepatitis C infection.[7]

### COMPLICATIONS OF TREATMENT OF HEPATITIS C

This patient's hepatitis C has the least favorable genotype prognostically; it may have been acquired through the remote use of parenteral nonprescription drugs.[8,9] The staff at the referring hospital probably concluded that the number of RNA copies was high enough to warrant treatment. Treatment with peginterferon alfa-2B and ribavirin was begun 3 months before admission, and the deterioration in her condition appeared to start thereafter, especially the hematologic abnormalities. Interferon predictably causes influenza-like symptoms as well as cytopenias; ribavirin administration often results in autoimmune hemolytic anemia but not neurologic abnormalities.[8,9] There is a high risk of side effects of these agents, but in view of the severity of the patient's liver disease, they are more effective than other drugs in securing a virologic response.[9] The use of erythropoietin derivatives is often necessary, since anemia is often pronounced when liver disease is advanced.

The fact that the patient had received psychotropic therapies for depression, together with the striking elevation of body temperature, suggests the possibility of the serotonin syndrome or the neuroleptic malignant syndrome. However, other features of these conditions, such as serotonergic effects and seizures, muscle rigidity, and hyperreflexia, are absent, making them unlikely considerations. Interferon, with its forceful stimulation of interleukin production, may have contributed to her fever.

### INFECTIONS

In a critically ill patient with fever, infectious diseases rank high among the diagnostic possibilities. One organism to consider, particularly in light of the dramatic elevation in the ferritin level and the hyperferremia, is *Vibrio vulnificus*. This is a gram-negative, curved bacillus that is most likely to be detected in late summer months in places close to brackish water. It causes a syndrome that is not dissimilar to the one we are observing in this patient and is especially severe in patients with cirrhosis, although skin lesions are typically bullous. One must consider widespread tuberculosis; this disease may cause pancytopenia, which was detected in a well-known case reported in the *Journal* in 1963.[10] Although the patient has photophobia, there is no mention of conjunctival injection; a disorder such as leptospirosis could simulate this patient's clinical picture, but severe conjunctivitis is expected in the most aggressive form of that disease. Ehrlichiosis merits mention, although the severity of this patient's illness is not characteristic of ehrlichiosis. Many viral infections are possible; systemic fungal infections are epidemiologically unlikely. The same is true for rickettsial diseases, all of which are accompanied by rash, with the exception of Q fever; encephalopathy, systemic toxicity, and hematologic abnormalities such as those seen in this patient are typical. We have recently observed cutaneous leishmaniasis in U.S. soldiers returning from the Middle East, but it is not otherwise endemic in this country; its visceral form has been associated with a clinical picture that is similar to the findings in this patient. Her physicians ordered numerous serologic studies, which ruled out HIV infection and the acquired immunodeficiency syndrome (AIDS), cytomegalovirus infection, and acute infection with Epstein–Barr virus.

Tantalizing pieces of the patient's history make a strong case for infection. She had traveled to Europe and Central America, and more recently, she was exposed to dogs, birds, and stray cats, and one cat actually scratched her. This is the typical epidemiologic setting for infection with *Bartonella henselae*, and the decision to test for it was reasonable. Capnocytophaga bacteremia that is the result of an animal bite may cause a severe septic syndrome in persons with cirrhosis, such as this woman, and also in asplenic persons. Fleas, assuming they were correctly identified entomologically, are vectors of scrub typhus, which is very unlikely in this country.

The physical examination and imaging studies do not provide specific clues to the diagnosis. Interpretation of the reported pupillary asymmetry is not possible without a more detailed neurologic examination, but it may be a result of the patient's previous head injury and neurosurgery. The bleeding diathesis, with maroon stools, persistent hematuria, and cutaneous ecchymoses, indicates a coagulopathy. However, the factor V level is inconsistent with fulminant hepatic failure, and the normal level of factor VIII makes disseminated intravascular coagulation improbable. The pulmonary nodules are tiny and probably insignificant. Abdominal lymphadenopathy is often observed with hepatitis.[7,11]

Surely this patient has an uncommon condition, which might be obscured in the diagnostic assessment because of certain biases in clinical analysis.[12] The tendency is to mold what is ob-

**Table 2. Diagnostic Criteria for Hemophagocytic Lymphohistiocytosis.***

| |
|---|
| Fever |
| Splenomegaly |
| Cytopenia affecting two or more blood-cell lineages |
| Hypertriglyceridemia, hypofibrinogenemia, or both |
| Hemophagocytosis in bone marrow, spleen, or lymph nodes |
| Natural killer cell activity low or absent |
| Ferritin ≥500 μg/liter |
| Soluble interleukin-2 receptor (CD25) ≥2400 U/ml |

* Five of eight criteria must be met to establish a diagnosis. Adapted from Henter et al.[16]

served to fit more familiar conditions, which was a common inclination early in the HIV–AIDS epidemic, before it was recognized as a discrete entity. Excessive testing is invited in such situations.

### HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

Any hypothesis must explain this patient's abnormal mental status, fever, splenomegaly, cytopenias, active urine sediment, and finally, the extreme elevation of ferritin and triglyceride levels. Thrombotic thrombocytopenia purpura must be considered, and many of its features are present. Diagnosis of this condition, which is caused by the enzymatic inhibition of a metalloprotease needed for the proper functioning of von Willebrand factor, is tempting. I was able to review the blood smears, however, and the absence of microangiopathy is inconsistent with thrombotic thrombocytopenia purpura. I therefore believe that this patient has a syndrome known as hemophagocytic lymphohistiocytosis. This disorder, which is characterized by excessive macrophage function,[13,14] has been linked to specific genetic abnormalities in children, notably mutations in the perforin gene[15]; it occurs sporadically in adults. This patient had fever, splenomegaly, cytopenias, hypofibrinogenemia, hypertriglyceridemia, and hyperferritinemia — six of the eight diagnostic criteria for hemophagocytic lymphohistiocytosis (Table 2).[16]

The challenge is to identify the trigger for the abnormal hyperfunctionality of macrophages in this patient. Epstein–Barr virus in particular has been linked to this syndrome in childhood, as have autoimmune conditions.[17] It is tempting to speculate whether interferon and ribavirin may have played a role.

In summary, my diagnosis is hemophagocytic lymphohistiocytosis. I believe the diagnostic procedure was bone marrow aspiration, and I would expect examination of the aspirate to show phagocytosis of hematopoietic cells by histiocytes. All common precipitants appear to have been ruled out; in the absence of these agents, I wonder whether the culprit was the therapy for hepatitis C.

*Dr. Nancy Lee Harris* (Pathology): Dr. Amy Sievers, who saw the patient, will summarize the clinical thinking and tell us what the procedure was.

*Dr. Amy C. Sievers* (Oncology): I was called on the third hospital day for the Hematology Service. For the reasons summarized by Dr. Tierney, my colleagues and I also strongly suspected that the patient had hemophagocytic lymphohistiocytosis. The diagnostic procedure was a bone marrow biopsy.

## CLINICAL DIAGNOSIS

Hemophagocytic lymphohistiocytosis.

## DR. LAWRENCE M. TIERNEY'S DIAGNOSIS

Hemophagocytic lymphohistiocytosis.

## PATHOLOGICAL DISCUSSION

*Dr. Ha Nishino:* The bone marrow–biopsy specimen showed hypercellular marrow with maturing trilineage hematopoiesis and increased histiocytes with abundant, occasionally vacuolated cytoplasm (Fig. 2A). Immunohistochemical stains revealed numerous histiocytes that were positive for CD68 and CD163 (Fig. 2B and 2C), many of which contained erythroid elements. The aspirate smear was hemodilute but showed frequent hemophagocytic histiocytes containing intact and degenerated erythroid precursors and mature erythrocytes within their cytoplasm (Fig. 2D). Concurrent flow cytometry and cytogenetic studies showed no abnormalities.

The constellation of clinical and laboratory findings described in this patient fulfill the minimal diagnostic criteria for acquired hemophagocytic lymphohistiocytosis (Table 2). In the context of these findings, the presence of hemophago-

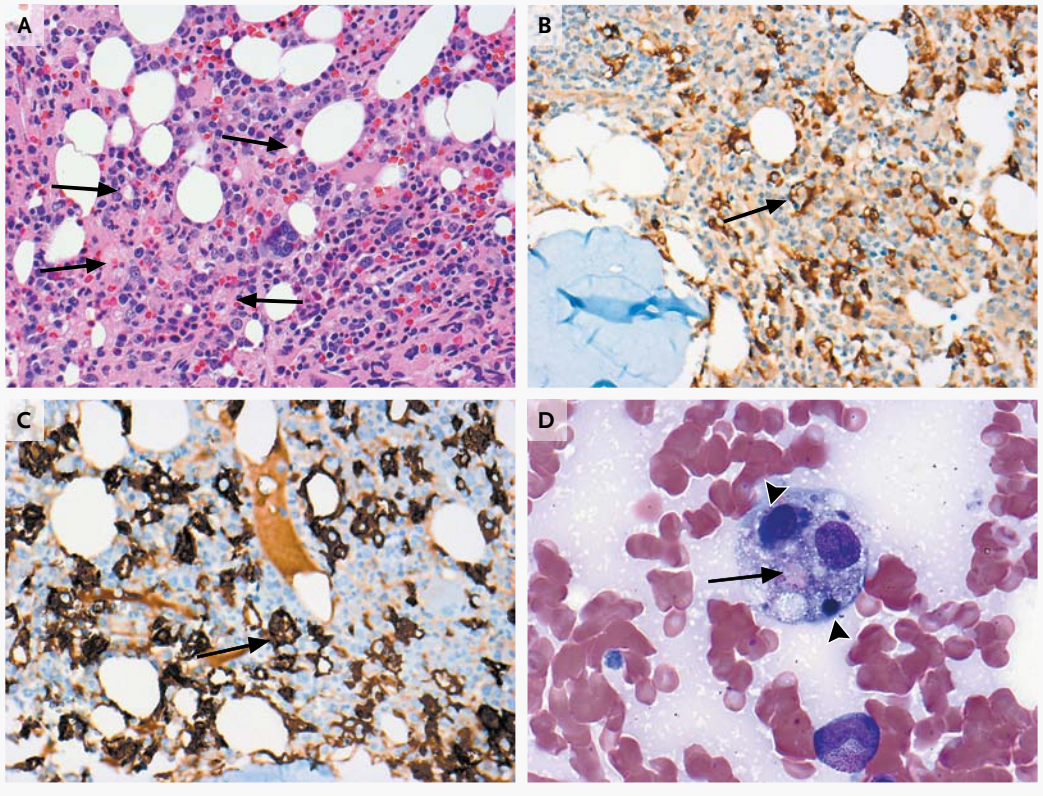


**Figure 2. Results of Bone Marrow Biopsy and Aspirate.**

A bone marrow–biopsy specimen (Panel A, hematoxylin and eosin) contains hypercellular marrow, with numerous histiocytes with abundant flocculent cytoplasm (arrows) and occasional intracytoplasmic vacuoles. Immunohistochemical staining of a biopsy specimen for CD68 (Panel B) and CD163 (Panel C) reveals numerous histiocytes, with cytoplasm often containing erythroid elements (arrows). The bone marrow–aspirate smear (Panel D, Wright–Giesma), although hemodilute, shows frequent hemophagocytic histiocytes, with both degenerated erythrocytes (arrow) and nucleated cells (arrowheads) within their cytoplasm.

cytosis in the patient's marrow provided support for a diagnosis of hemophagocytic lymphohistiocytosis. As seen in this patient, this condition is a hyperinflammatory syndrome characterized by prolonged high fever, splenomegaly, cytopenias, and characteristic laboratory abnormalities.[18] Despite the disease's name, hemophagocytosis may be an uncommon finding in the early disease process but is characteristically seen with disease progression.[19,20] Combined with the other findings, the presence of hemophagocytosis in bone marrow provides support for the diagnosis of hemophagocytic lymphohistiocytosis.

*Dr. Harris:* Dr. Sievers, would you tell us how you treated this patient?

*Dr. Sievers:* Hemophagocytic lymphohistiocytosis is a highly lethal disease, with up to 95% mortality, depending on the underlying cause. The principle of treatment is immune suppression to try to reduce the cytokine storm that is triggered in this condition. In this case, we were faced with a patient whose baseline liver function was abnormal and who was very ill. Immediately after the bone marrow biopsy, we initiated treatment with glucocorticoids and intravenous immune globulin in an attempt to stabilize her condition. Her condition improved rapidly, and since etoposide works very well but not very quickly, we began treatment with it after her initial improvement.

*Dr. Harris:* Dr. Soverow, would you tell us what happened to the patient?

*Dr. Jonathan Soverow* (Medicine): The dose of

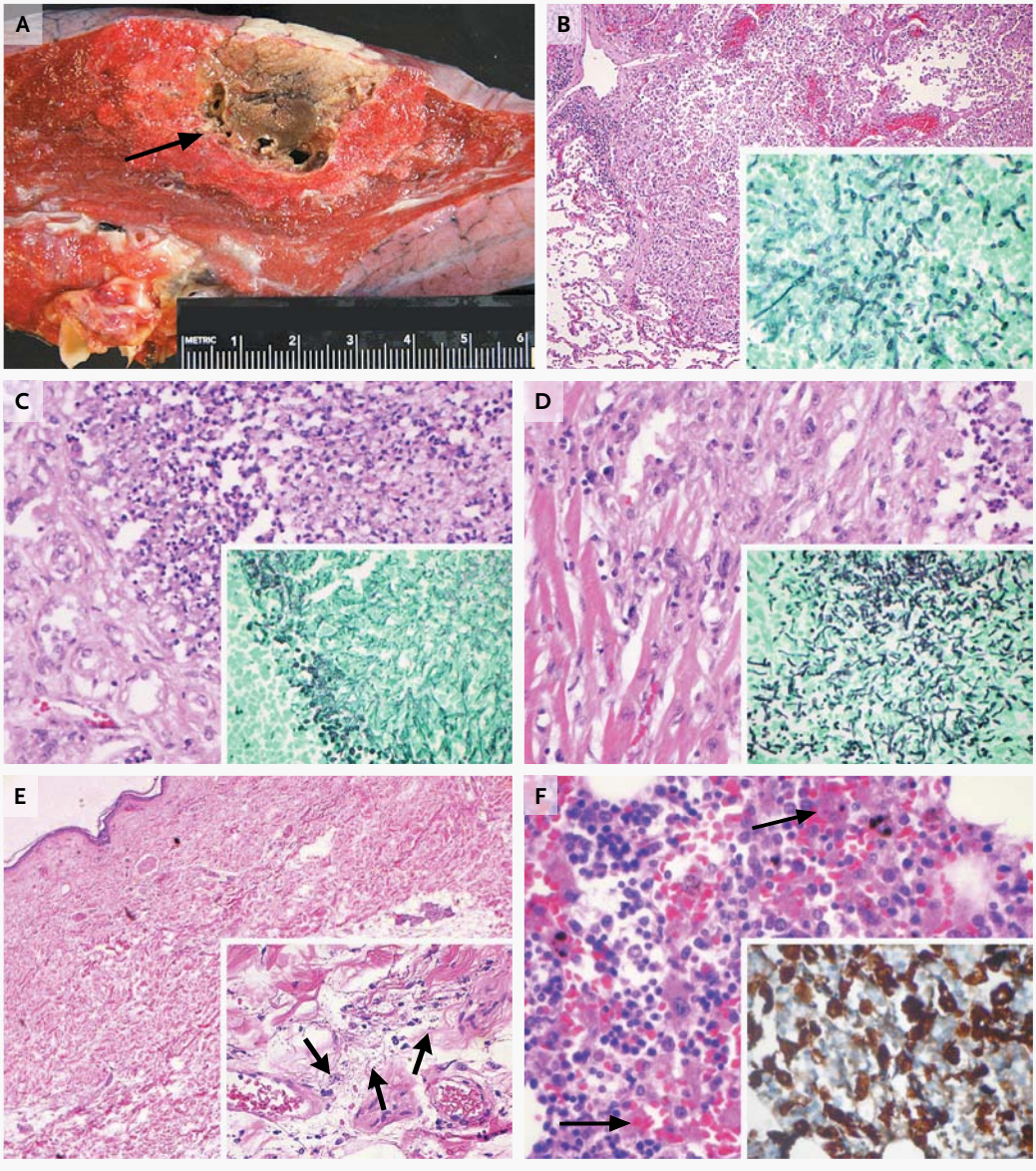


**Figure 3. Pathological Findings at Autopsy.**

A photograph of the left lung (Panel A) shows a 4-cm necrotic, cavitated mass (arrow) in the left upper lobe with surrounding erythema. Microscopical assessment (Panel B, hematoxylin and eosin) reveals an inflammatory infiltrate with extensive necrosis; Grocott's methenamine silver staining shows filamentous fungal overgrowth consisting of septate hyphae branching at an angle of 45 degrees (inset, Gomori's methenamine silver), consistent with the presence of aspergillus species. Specimens from the kidney (Panel C, hematoxylin and eosin) and heart (Panel D, hematoxylin and eosin) show fungal infection, with numerous budding yeasts and pseudohyphae highlighted on Grocott's methenamine silver staining (insets, Gomori's methenamine silver), a finding consistent with the presence of candida species. A specimen of deep skin lesion of the left leg (Panel E, hematoxylin and eosin) shows bacterial infection; acinetobacter species were isolated from an antemortem wound culture. The inset shows bacteria (arrows) at higher magnification. A bone marrow sample (Panel F, hematoxylin and eosin) shows increased numbers of histiocytes and the presence of hemophagocytosis (arrows); immunohistochemical staining for CD163 highlights the histiocytes (brown-stained cells in inset, immunoperoxidase staining for CD163).

dexamethasone was tapered, and intravenous immune globulin was administered for 4 days at a dose of 500 mg per kilogram of body weight per day; treatment with etoposide, at a dose of 75 mg per square meter of body-surface area, was started on hospital day 6. Afebrile and with improving mental status, the patient was extubated on hospital day 8 and transferred out of the intensive care unit (ICU). The serum level of ferritin decreased to 3000 ng per milliliter, and acyclovir was discontinued when the result of a polymerase-chain-reaction assay for herpes simplex virus in cerebrospinal fluid was negative. The level of soluble interleukin-2 receptor (CD25) was elevated, at 11,223 U per milliliter (reference range, 45 to 1105), and the level of soluble CD163 was 17,345 ng per milliliter (reference range, 369 to 1377). After 2 weeks of hospitalization, the patient became febrile and neutropenic, prompting the use of broad-spectrum antimicrobial agents, including vancomycin, cefepime, levofloxacin, and micafungin. Blood cultures grew *Escherichia coli* and *Candida albicans*. Chest CT performed without the administration of contrast material showed consolidation in the left upper lobe. The fever resolved but recurred 1 week later; a repeat chest CT study showed progression of the mass in the left upper lobe, with central necrosis. Voriconazole was started but replaced with liposomal amphotericin 1 week later, when blood cultures grew *C. albicans*. Within 2 days, the patient became hypotensive, febrile, and unresponsive. She was transferred to the ICU, where an expanding erythematous lesion on her left leg was débrided. Her clinical status deteriorated, and she died on the 37th hospital day. Permission for an autopsy was granted.

*Dr. Nishino:* At autopsy, the major findings were related to complications of immunosuppression. Gross examination of the left lung (Fig. 3A) revealed an ill-defined, necrotic mass with cavitation and overlying pleural plaque formation. On microscopical examination (Fig. 3B), there was an inflammatory infiltrate with extensive necrosis and focal angioinvasion; a silver stain showed numerous branching septate hyphae, and microbiologic cultures isolated *Aspergillus terreus*. These findings were consistent with invasive pulmonary aspergillosis.

In addition, there was disseminated candida infection of multiple organs, including the kidneys, spleen, and heart (Fig. 3C and 3D). A deep skin lesion of the left leg showed bacterial infection (Fig. 3E); the specimen that had been sent for culture the day before the patient died grew acinetobacter species that were resistant to multiple antibiotics, as did a blood culture from the same day. This organism was also isolated from the lung at autopsy. Postmortem analysis of bone marrow revealed hemophagocytosis (Fig. 3F).

The cause of death was sepsis due to drug-resistant acinetobacter species; pulmonary aspergillosis and disseminated candida infection were also present, presumably complications of immunosuppression. The bone marrow showed hemophagocytosis that was consistent with the clinicopathological syndrome of hemophagocytic lymphohistiocytosis.

*Dr. Harris:* Are there any questions for the discussants?

*A Physician:* Is it true that the differential diagnosis for very high levels of ferritin is remarkably limited?

*Dr. Tierney:* Yes. Still's disease, systemic histoplasmosis, and hemophagocytosis are associated with such a remarkably high level of ferritin. Other chronic inflammatory disorders elevate ferritin levels appreciably, but not to this degree. The numbers we saw in this patient suggest that macrophages had relentlessly ingested all the iron in the red-cell mass. It is interesting that the ferritin level did decrease with treatment.

*Dr. Harris:* At the time this patient was in the ICU, there was another patient in the ICU with a hemophagocytic syndrome, a young man who lived in the same town as our patient, about a mile away. He also died. He had Epstein–Barr virus infection, with a markedly elevated viral load and serologic indicators of past infection. This remarkable coincidence might suggest some common exposure that triggered the syndrome.

## ANATOMICAL DIAGNOSIS

Hemophagocytic lymphohistiocytosis.

This case was presented at a Medicine Case Conference.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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