Hemophagocytic Syndrome in Children: An Important Diagnostic Consideration in Fever of Unknown Origin

Debra L. Palazzi,1 Kenneth L. McClain,2 and Sheldon L. Kaplan1

1Infectious Diseases Section and 2Section of Hematology and Oncology, Department of Pediatrics, Baylor College of Medicine and Texas Children's Hospital, Houston, Texas

To study the evolution of hemophagocytic syndrome (HPS) in children, we performed a retrospective review of 19 patients (median age, 17.4 months) in whom an infectious diseases consultation was requested at Texas Children’s Hospital during the period of September 1991 through September 2001. Clinical findings consistent with HPS most frequently presented during days 6–14 of illness, concomitant with laboratory abnormalities. Fever was present for a median of 19 days before the diagnosis of HPS. Elevated serum lactate dehydrogenase and ferritin levels were noted in all patients. An infectious agent was identified in 42% of patients; 16% were found to have immunologic or vasculitic disease. HPS is a rare but often fatal disease that can initially present as fever of unknown origin with varying clinical findings, and it can be recognized by physicians who are familiar with the evolution of HPS. It is likely that many of these cases remain undiagnosed because of the HPS’s rapidly fatal course.

Hemophagocytic lymphohistiocytosis (HLH), also called “hemophagocytic syndrome” (HPS), is a nonmalignant proliferative disorder that affects the antigen-processing macrophages and that results in uncontrolled hemophagocytosis and upregulation of inflammatory cytokines. Primary HLH is an autosomal recessive disease caused by defective immune regulation that can appear sporadically with no known familial association or as familial hemophagocytic (erythrophagocytic) lymphohistiocytosis (called FHL, FEH, and FHLH). The initial clinical presentation of FHL may be associated with infection and can appear identical to secondary HLH [1, 2]. A primary element of the defective immunity is markedly impaired natural killer (NK) cell function and other defects [3–6].

Secondary HLH is a reactive disorder causing strong immunologic activation often resulting from severe bacterial or parasitic infection (infection-associated HPS [IAHS]), viral infection (VAHS), malignancy (MAHS), use of drugs (phenytoin), or prolonged administration of parenteral nutrition involving soluble lipids (known as “fat overload syndrome”) [1, 5, 7–14]. HLH also has been reported after other conditions, such as Kawasaki disease and acute lupus erythematosus, have caused immunologic activation [15, 16]. These patients most often have defective NK cell function also.

Diagnostic criteria for HPS include fever; splenomegaly; cytopenia that affects ≥2 cell lines; hypertriglyceridemia and/or hypofibrinogenemia; and hemophagocytosis in bone marrow, spleen, or lymph nodes without evidence of malignancy [1]. There is increasing evidence that some patients do not meet all of these diagnostic criteria and that many patients do so only late in the course of their disease [1, 17]. Early diagnosis and treatment often are essential for survival [17, 18]. Therefore, in patients who are strongly suspected of...
having HPS and who do not meet the criteria for diagnosis, treatment should be initiated before severe disease progression occurs [19].

Infectious diseases specialists often are asked to evaluate patients with prolonged or otherwise unexplained fever. Prolonged fever is an important sign of HPS. To characterize the progression of clinical and laboratory abnormalities of HPS in pediatric patients, we conducted a retrospective review of cases at Texas Children’s Hospital in Houston in which an infectious diseases consultation was requested. We describe the progression of HPS in these pediatric patients and emphasize the high index of suspicion required for its identification in a timely manner.

MATERIALS AND METHODS

Definitions. A diagnosis of HPS was assigned by means of the HLH guidelines (HLH-94) [1, 19]. Pediatric patients with high likelihood of disease but for whom full laboratory confirmation was lacking were included in the study if supporting criteria, as described elsewhere [1, 17], were sufficient.

Study population. By use of the consultation records of the infectious diseases and the hematology-oncology services at Texas Children’s Hospital, we retrospectively identified pediatric patients (age, <18 years) who received a discharge diagnosis of HPS during the period of September 1991 through September 2001. Twenty-six subjects were initially identified. Two patients who had HPS diagnosed were not evaluated by the infectious diseases service and were excluded from the analysis. Another child met neither HLH-94 criteria nor supporting criteria for diagnosis of HPS. Because of the unavailability of medical records, 4 additional patients were excluded from the study. Demographic, clinical, and laboratory data were collected by a single investigator (D.L.P.) by means of a standardized data collection form. Laboratory values selected were those closest in time to when the diagnosis of HPS was established. This study was approved by the Institutional Review Board for Human Subject Research for Baylor College of Medicine and Affiliated Hospitals, Houston.

Outcome measures. Particular emphasis was placed on evaluating the progression of disease. Clinical and laboratory findings were analyzed according to frequency of occurrence and day of illness during which they appeared. Fever was defined as a temperature of \( \geq 38.3 ^{\circ}C \) (\( \geq 101^{\circ}F \)). Hepatosplenomegaly was determined with use of physical examination records, with no true measurements of organomegaly required for inclusion. Determination of lymphadenopathy similarly was subjective. Hypotension was defined as systolic blood pressure less than the fifth percentile for age or a 20-point decrease in either systolic or diastolic pressures. Respiratory distress was determined by use of subjective physical examination reports as well as age-matched normal values for respiratory rate, need for supplemental oxygen, and progression to the need for mechanical ventilation. Infectious agents were identified by serum antibody studies or by rapid antigen assay, PCR, or culture of body fluid specimens. Relevant laboratory data were extracted as described above and analyzed.

Statistical analysis. Descriptive statistical data analysis was performed with Microsoft Access and the worksheet Excel on Microsoft Windows NT. Median values were reported for non-normally distributed data. For dichotomous outcomes, 2-tailed Fisher’s exact test was performed by use of True Epistat (Epistat Σ Service).

RESULTS

We reviewed the charts for 19 pediatric patients who had HPS during the 10-year period of this study and who were evaluated by the infectious diseases service at Texas Children’s Hospital. There were 6 boys and 13 girls with associated case fatality rates of 33.3% and 61.5%, respectively (\( P = .14 \)). Patients ranged in age from 7 days to 16 years, with a median age at diagnosis of 17.4 months (figure 1). Children aged <12 months accounted for 42.1% patients and had a case fatality rate of 75%. The case fatality rate for pediatric patients aged \( \geq 12 \) months was 36.4% (\( P = .17 \)). The overall fatality rate was 52.6%. The ethnic origins of the patients were as follows: Hispanic, 42.1%; white, 31.6%; Asian, 15.8%; and African American, 10.5%. All patients had previously been healthy, without serious underlying illness or immunosuppression.

The most common reason for hospital admission was fever with or without additional symptoms or signs. The primary reason for consulting the infectious diseases service was fever (94.7% of patients) with additional clinical or laboratory findings, such as arthralgias, pancytopenia, hepatosplenomegaly, rash, and liver dysfunction noted in many patients (table 1).

Clinical features. The clinical features observed in 19 patients with HPS are shown in figure 2. The most common findings were fever (100% of patients), hepatosplenomegaly (94.7% of patients), lymphadenopathy (68.4% of patients), and rash (57.9% of patients). The rashes observed were polymorphous and varied from diffuse erythematous maculopapular rashes to scattered petechial rashes. The median duration of fever before diagnosis of HPS was 19 days (range, 4–41 days). Many patients had respiratory distress and hypotension (89.5% had both). The severity of these findings was such that 15 patients (78.9%) required endotracheal intubation and 14 patients (73.7%) required vasopressor support.

The chronology of clinical findings from onset of illness and before diagnosis of HPS is shown in figure 3. Considerable variation existed among patients. However, hepatosplenomegaly, respiratory distress, and hypotension frequently appeared...
Figure 1. Age of patients at the time of diagnosis of hemophagocytic syndrome

during days 6–10 of illness, with an appearance by day 15 being common. Lymphadenopathy and rash more frequently had onset during days 16–21 of illness.

Laboratory findings. The laboratory results for 19 patients with HPS are shown in table 2. Anemia (hemoglobin level, <9 g/dL) was observed in 84.2% of patients, thrombocytopenia (platelet count, <100 × 10³ platelets/L) was observed in 78.9%, and neutropenia (neutrophil count, <1 × 10³ cells/L) was observed in 42.1%. Coagulopathy, which was defined as a prolonged prothrombin time, partial thromboplastin time, or positive D-dimers, was present in 94.7% of pediatric patients; each of these 18 patients required blood product transfusions. Direct hyperbilirubinemia (conjugated bilirubin level, >1.0 mg/dL) occurred in 80% of patients, hyponatremia (serum sodium level, <135 mM) occurred in 78.9%, and infiltrates on chest radiograph were noted in 100%. Increased aspartate aminotransferase (AST) levels (i.e., >40 IU/L) and alanine aminotransferase (ALT) levels (i.e., >55 IU/L) occurred in 89.5% patients; 52.9% had AST levels that were 3-fold greater than normal. An equivalent elevation in both ALT and AST levels occurred in 47.1% of patients.

Although neither is a component of the diagnostic criteria for HPS, the most consistent laboratory abnormalities noted in our patients were elevated levels of serum lactate dehydrogenase (LDH) and ferritin [1]. In all patients, LDH and ferritin levels were abnormal, with LDH levels of >1000 IU/L observed in 84.6% of patients and ferritin levels of >4000 μg/L observed in 94.7%. Ferritin levels were >10,000 μg/L in 11 of 19 patients. The mean ferritin level was 25,212 μg/L (median, 13,768 μg/L; range, 703–85,167 μg/L). Two of the components of the diagnostic criteria for HPS—hypertriglyceridemia (triglyceride level, >2 mM) and hypofibrinogenemia (fibrinogen level, <1.5 g/L)—were observed only in 43.8% and 61.5% of our patients, respectively [1].

The time from the onset of illness to the appearance of abnormal test values is depicted in figure 4. Similar to what was observed for clinical findings, there was variation among patients. Nonetheless, laboratory abnormalities consistent with HPS appeared in the majority of pediatric patients during days

Table 1. Reasons for infectious diseases consultation for 19 pediatric patients with hemophagocytic syndrome.

<table>
<thead>
<tr>
<th>Symptom class, description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infectious</td>
</tr>
<tr>
<td>Hepatitis (2)</td>
</tr>
<tr>
<td>Hepatitis, lymphadenopathy, rash</td>
</tr>
<tr>
<td>Hepatitis, pancytopenia</td>
</tr>
<tr>
<td>Neonatal meningitis, pneumonitis</td>
</tr>
<tr>
<td>Pneumonia, myalgias</td>
</tr>
<tr>
<td>Sepsis, neutropenia</td>
</tr>
<tr>
<td>Immunologic</td>
</tr>
<tr>
<td>Rash, arthralgias</td>
</tr>
<tr>
<td>Stevens-Johnson syndrome, neutropenia</td>
</tr>
<tr>
<td>Hematologic</td>
</tr>
<tr>
<td>Pancytopenia, HSM</td>
</tr>
<tr>
<td>Pancytopenia, HSM, jaundice</td>
</tr>
<tr>
<td>Pancytopenia, HSM, jaundice, rash, BC</td>
</tr>
<tr>
<td>Pancytopenia, splenomegaly</td>
</tr>
<tr>
<td>Thrombocytopenia, HSM</td>
</tr>
<tr>
<td>Miscellaneous</td>
</tr>
<tr>
<td>Arthralgias, vomiting</td>
</tr>
<tr>
<td>HSM</td>
</tr>
<tr>
<td>Recurrent Kawasaki disease</td>
</tr>
</tbody>
</table>

NOTE. All patients had fever. Two consultations were for persistent or recurrent fever alone. BC, conjugated hyperbilirubinemia; HSM, hepatosplenomegaly.
6–10 of illness. Although neutropenia, anemia, thrombocytopenia, conjugated hyperbilirubinemia, and a 3-fold increase in baseline transaminase levels most often occurred during days 6–10 of illness, appearance of an abnormal coagulation profile was distributed throughout the illness.

Associated illnesses. Infectious agents were identified in 8 (42.1%) of 19 patients. Five of these children were <12 months old. All of the infections were associated with viruses and, in some cases, >1 agent: Epstein-Barr virus (EBV) and adenovirus (4 patients each), respiratory syncytial virus (RSV) (2 patients), and parainfluenza 3 virus (1 patient). Two of the 4 pediatric patients with EBV infection died. In 1 child, RSV antigen was detected in nasopharyngeal washings and adenovirus was isolated from a stool culture. Another patient had EBV detected by PCR of a liver biopsy specimen and on the basis of serologic findings consistent with acute EBV infection, RSV antigen detected by rapid screen, and adenovirus detected by means of stool electron microscopy. In each of these patients, additional viral cultures and serial physical examinations did not define which viral agent was most proximate to the onset of HPS.

Noninfectious causes of HPS were identified in 3 (15.8%) of 19 patients. A 5-year-old girl was thought to have an acute presentation of systemic lupus erythematosus accompanying the onset of HPS, and Kawasaki disease preceded HPS in a 10-
year-old girl. Acute systemic juvenile rheumatoid arthritis was diagnosed subsequently in another 10-year-old girl. Despite extensive diagnostic investigations into the possible agents or diseases associated with HPS in our patients, 42.1% of cases occurred without associated illnesses.

**Biopsy findings.** Hemophagocytosis was detected in 18 (94.7%) of 19 patients. Fourteen had some evidence of hemophagocytosis only in the bone marrow. One child had positive findings for bone marrow and lymph node samples assessed via biopsy, and another had hemophagocytosis seen in bone marrow and liver. Lymph node biopsy alone provided the diagnosis for 1 patient. Two patients had no evidence of hemophagocytosis noted during antemortem bone marrow examinations, but each had strong supporting evidence for HPS, and one of these pediatric patients had hemophagocytosis found in multiple autopsy specimens.

**DISCUSSION**

HPS is a rare, often fatal clinical disorder in which upregulation of tissue macrophage activity results in uncontrolled hemophagocytosis and release of inflammatory cytokines. Typically, affected patients have fever, splenomegaly, cytopenia in 2 cell lines, and hypertriglyceridemia and/or hypofibrinogenemia. Our results support prior evidence that not all patients present with all or even most of these features; thus, diagnosis in a timely fashion often is difficult [1, 17]. Similar to what has been reported by others, the most frequent missing criteria were hypertriglyceridemia and hypofibrinogenemia [1, 4, 20]. In our experience, such laboratory studies often were not obtained before the child died of the disease. The overall case fatality rate for our patients was 52.6%, a rate similar to that reported by other investigators [21]. Although not significantly different, pediatric patients aged <12 months had a higher rate than pediatric patients who were ≥12 months (75% vs. 36.4%; \( P = .17 \)), which is possibly indicative of unrecognized familial disease or a delay in diagnosis and in subsequent initiation of immunosuppressive and cytotoxic therapy. The girls had a mortality rate twice that of boys (\( P = .14 \)), a finding for which we have no clear explanation. Interestingly, during 1999–2001, 50% of pediatric patients in our series were Hispanic. However, review of hospital demographic records revealed that Hispanic pediatric patients were responsible for only 28% of all hospital admissions to Texas Children’s Hospital during the same time period.

Although the median age at diagnosis of HPS in our patients was 17.4 months, a bimodal distribution of ages was observed. Children aged <2 years constituted the majority of cases, again reflecting the possibility that some of these patients had undiagnosed familial disease. A second peak occurred in pediatric patients aged ≥6 years, a finding previously noted by McClain et al. [5]. In contrast to other case series that mention pediatric patients of older ages, all of the patients in our study had previously been healthy and did not have underlying immunosuppression [17].

The pathogenesis of HPS is unknown, but many associated triggers have been suggested, including bacteria, viruses, fungi, use of drugs (phenytoin), and underlying immunosuppression [1, 2, 5, 7–16]. Despite extensive laboratory investigations attempting to identify agents or disease processes associated with HPS in our patients, 42% of cases had no known associated triggers.
illnesses. This percentage is higher than the rate of 5%–31% reported in most other series [5, 7, 17].

Common clinical findings in HPS include fever, hepatosplenomegaly, lymphadenopathy, and rash. Although not frequently cited by others, our patients had a high incidence of respiratory distress and hypotension as presenting findings in the development of HPS [1, 7, 17, 22, 23]. In fact, the appearance of these clinical findings during days 6–14 of illness was characteristic, and in combination with fever and hepatosplenomegaly, it often prompted an infectious diseases specialist to consider HPS (figure 3). CNS symptoms, such as lethargy and irritability, have been reported frequently in patients with HPS, but these findings were not common in our patients, possibly because the majority of pediatric patients had rapid progression, necessitating intubation and sedation, thereby rendering accurate neurological evaluation impossible [24].

There are many laboratory abnormalities that can assist in
the diagnosis of HPS but that are not specifically required as criteria [1, 25]. The majority of laboratory findings consistent with HPS manifested during days 6–10 of illness, paralleling the timing of the clinical findings in all patients (figure 4). Although they were not frequently noted by others, we found that direct hyperbilirubinemia, hypotension, and pulmonary infiltrates were common findings that provided helpful supporting evidence for the diagnosis (figure 5) [1, 4, 20, 21].

Although the number of pediatric patients in our series is small, and although considerable variation in their HPS presentations was noted, the concomitant appearance of clinical and laboratory abnormalities during days 6–14 of illness is an important observation. To our knowledge, no other investigators have attempted to describe the evolution of disease by timing the clinical manifestations and supporting laboratory data. This information may be extremely helpful in prompting clinicians to consider the diagnosis of HPS in patients who lack full diagnostic criteria.

Because patients with HPS have an evolving disease process suggestive of infection or sepsis and often present with fever of unknown origin, infectious disease specialists frequently are consulted to assist with their evaluation and management. With such a severe and life-threatening clinical syndrome, prompt recognition of disease is essential for initiation of appropriate therapy [19]. The diagnosis of HPS can be difficult to make, because the symptoms of many patients do not fully fit the criteria at presentation. However, this review provides the spectrum of supporting clinical and laboratory findings that may accompany the disease, and we hope it will assist infectious diseases specialists and other clinicians in early recognition of HPS. Prompt recognition of HPS leading to the initiation of appropriate therapy may be critical. The diagnosis and treatment of HPS are most appropriately determined under the guidance of a hematology-oncology specialist.

Acknowledgments

We thank Carol J. Baker for her critical review of the article in manuscript and for her suggestions and support, and we thank Edward O. Mason, Jr., for his assistance with database development.

References