Clinical Pediatrics
Volume 47 Number 1
January 2008 89-90

10.1177/0009922807305265
http://clp.sagepub.com
hosted at
http://online.sagepub.com

A Toddler With Fever, Pancytopenia, and Elevated Liver Enzymes

Saúl Oswaldo Lugo Reyes, MD

Keywords: pancytopenia; hepatosplenomegaly; hemophagocytic lymphohistiocytosis

A 15-month-old girl was brought to the emergency department with a 7-day history of diarrhea, vomiting, pancytopenia, and bleeding. The patient was born in Mexico City, Mexico, where she lived with her parents and two elder preschool-aged siblings, all in good health. All the members of the family were poorly fed and slept in the same room under unhygienic conditions. Her vaccination scheme was up-to-date, and her previous medical history was unremarkable.

Seven days prior to admission, she started passing greenish watery stools with mucus (3 times a day) and had intermittent fever (38°C to 38.5°C). She was seen in a private office and managed as an outpatient with trimethoprim/sulfamethoxazole and acetaminophen but showed no improvement. Three days prior to referral, she was admitted to another hospital for dehydration and treated with intravenous fluids, penicillin, and amikacin. After 3 days, she was referred to our hospital for irritability, pallor, pharyngeal hyperemia, bilateral cervical adenomegaly, hepatomegaly, petechiae in the inguinal region, and upper gastrointestinal bleeding. Mild hyponatremia and pancytopenia were detected. A triple-antibiotic intravenous regime (ceftriaxone, amikacin, and metronidazole) was started for suspected sepsis, along with ranitidine, vitamin K, and transfusions with fresh frozen plasma, packed red blood cells, and platelets.

From Pediatrics Emergency Department, "La Raza" National Medical Center's General Hospital, Mexico City, Mexico.

Address correspondence to: Saúl O. Lugo Reyes, MD, Biomedical Research Unit on Immunology and Infectology, La Raza National Medical Center, Av. Jacarandas s/N, esq. Av. Vallejo, Delg Azcapotzalco, 06920, Mexico City, Mexico; e-mail: saul_oswaldo@hotmail.com.

On arrival in the emergency department, with coffee-ground material draining through her nasogastric tube, cervical and inguinal adenomegaly was corroborated. A complete blood count and blood chemistry analysis provided the following values: hemoglobin, 11.8 g/dL; leukocytes, 860; platelets, 38 900; creatinine, 0.4 mg/dL; aspartate aminotransferase, 2045 IU/L; alanine aminotransferase, 295 IU/L; lactic acid dehydrogenase, 21 100; Na, 145 mEq/L; K, 4.6; and Cl, 115 mEq/L. Prolonged coagulation times were observed (reported as noncoagulating), with fibrinogen 88 mg.

The condition of the patient deteriorated quickly with pallor, tachycardia, somnolence, intercostal retractions, abdominal pain, and compensated metabolic acidosis. An albumin load and a dopamine drip were started. She was intubated electively and transferred to the pediatric intensive care unit.

In the pediatric intensive care unit, the patient developed epistaxis, bilateral rales, anuria, ascites, pleural effusion, and generalized edema with delayed capillary refill. The laboratory results and bedside monitoring showed liver, heart, and kidney failure and early signs of brain death. She was treated with furosemide, albumin, dopamine, dobutamine, intravenous immunoglobulin, endovenous antibiotics (vancomycin, meropenem, metronidazole, trimethoprim/sulfamethoxazole), filgrastim, and heparin. A thoracic drainage was started for a severe bilateral hemothorax, and an abdominal paracentesis revealed peritoneal bleeding.

An emergency laparotomy showed several clots from previous bleedings (approximately 500 mL), with an intact bowel, a pale liver, and a congestive enlarged spleen. In the operating room, she developed cardiopulmonary arrest refractory to advanced

cardiopulmonary resuscitation maneuvers and was pronounced dead on her third day in hospital.

A bone marrow aspirate, taken the day before, showed scarce cells and macrophages containing engulfed erythrocytes and leukocytes. Her parents declined an autopsy.

Commentary

Ernesto Zarco Martínez
Pediatrics Emergency Department, "La Raza" National Medical Center's General Hospital, Mexico City, Mexico

Hemophagocytic Lymphohistiocytosis

Hemophagocytic lymphohistiocytosis (HLH) is a disorder of immune regulation that can be hereditary, as an autosomal recessive disorder, or acquired as a result of infection, malignancy, or arthritis. It is characterized by fever, splenomegaly, cytopenia, hypertriglyceridemia, and hipofibrinogenemia. Hepatomegaly, elevated blood levels of lactate dehydrogenase, neurologic findings, liver and coagulation abnormalities, and hyperferritinemia are also common and have been considered signs of the syndrome.

The primary or familial form is usually apparent in children younger than 2 months. Although there is a genetic heterogeneity, about half these cases are caused by a defect in the perforin gene and thus in the NK cells' ability to induce cell death. The acquired form is considered a reactive disorder of the mononuclear phagocytic system, characterized by a benign proliferation of hystiocytes, with marked hemophagocytosis. Approximately 85% of all patients are younger than 2 years, and 49% of them have a positive family history. Clinically, the primary and reactive forms can be indistinguishable; assignment to the genetically determined form usually requires a positive family history, parental consanguinity, or both. Familial HLH occurs in approximately 1 in every 50 000 live births, with an equal gender distribution. Many times, even in this familial presentation, the hemophagocytosis is triggered or unmasked by a viral infection.

Secondary HLH is usually associated with an infection, more often of the herpes virus group, but it can also occur in autoimmune or rheumatologic patients being treated with immunosuppressive drugs. It is usually seen in older infants and toddlers.

The clinical presentation is that of a prolonged fever (91%), hepatomegaly (90% to 94%), and splenomegaly (97% to 100%). Neurologic symptoms (20% to 45%), rash (6% to 65%), and lymphadenopathy (17% to 52%) are seen less frequently.

A hallmark of this disorder is the pathologic finding of activated macrophages with engulfed erythrocytes, leukocytes, platelets, and their precursors in bone marrow aspirates or in lymph nodes and liver sections. The Histiocyte Society diagnostic criteria are as follows: fever and splenomegaly (clinical criteria); cytopenias affecting at least two lineages (hemoglobin <9 g/dL, platelets <100 000, and neutrophils <1000); hypertriglyceridemia or hipofibrinogenemia (laboratory criteria); hemophagocytosis in bone marrow, lymph nodes, or spleen; and no evidence of malignancy (histopathologic criteria).

In some of these patients, the reactive disease shows up as a self-limited complication. In infants infected with Epstein-Barr virus, however, it frequently has a catastrophic course. The average interval from diagnosis to death has been reported to be less than 2 weeks. Even with aggressive treatment consisting of immunosuppressive chemotherapy and anti-inflammatory drugs, prognosis is uncertain. Unfortunately, this is still an unrecognized, unsuspected cause of systemic inflammation and multiorgan failure.

In our hospital, HLH has been confused with fulminant viral hepatitis, severe sepsis with disseminated intravascular coagulation, and/or acute leukemia on presentation, and the low level of suspicion has delayed appropriate referral and treatment. Raising awareness of the occurrence and refining the treatment of this traumatic disease is an urgent task for hematologists, immunologists, and everyone involved in the care of pediatric patients.

References

1. Filipovich AH. Hemophagocytic lymphohistiocytosis. *Immunol Allergy Clin North Am.* 2002;22:281-300.
2. Fisman D. Hemophagocytic syndromes and infection. *Emerg Infect Dis.* 2000;6:601-618.
3. Lim ME, Kim KS. Hemophagocytic lymphohistiocytosis. *Pediatr Infect Dis.* 1999;18:154-155.