A 12-year-old girl from Isfahan was admitted to the Mofid Children’s Hospital, Tehran, because of fever, pharyngitis, abdominal pain, and splenomegaly. She had a past history of splenomegaly since early childhood, the work-up for which was normal. Her parents were first cousin, and had a son who died of fever and organomegaly when he was three years old. The exact diagnosis, however, was not made.

Our patient came with progressive lymphadenopathy and splenomegaly, accompanied by pancytopenia and fever. Her first laboratory data revealed a WBC of 2000/mm³ with 32% PMN, and 68% lymphocytes; an RBC of 3,520,000/mm³ with 2% reticulocytes, an MCV of 75 fL and MCH of 24; Hb of 8.6 g/dL; Hct of 26%; and platelet count of 43,000/mm³. She had a sedimentation rate of 38 mm/hr and an LDH of 1150. The direct Coombs test was negative. The liver function test was normal. She had a serum uric acid of 2.9 mg/dL; a PT of 18 (MNPT: 13); and an aPTT of 46 sec (control: 35). Her plasma triglyceride was 687 mg/dL and her cholesterol was 328 mg/dL. Widal,
Wright, and 2ME tests; blood culture; urinalysis; and urine culture were all negative. She had a positive CMV IgG but her IgM against the virus was negative. Mono test was negative. She had also positive IgG against herpes virus type 1 but was negative for herpes virus type 1 and 2 IgM.

The hepatitis serologic tests, HIV antibody, and serologic test for leishmaniasis were all negative. The serum immunoglobulin level was within the normal range for age. She had a negative collagen vascular tests and a normal chest X-ray.

Abdominal and pelvic ultrasonography revealed paraaortic lymphadenopathy with splenomegaly. Abdominal and pelvic CT scans also showed paraaortic lymphadenopathy with hepatosplenomegaly. Chest CT scan revealed superior mediastinal lymphadenopathy. The brain CT scan, however, was normal. Bone marrow aspiration showed moderate hypocellularity with no evidence of malignant or abnormal hemophagocytic cells. CD flowcytometry of the bone marrow aspiration was also normal. Cervical lymph node biopsy report read reactive lymph node.

The patient developed respiratory distress three days after the biopsy, and was transferred to the pediatric ICU, where she stayed for five days. During the course of her disease, her pancytopenia continued, her liver function test became deteriorated, and she developed hyperbilirubinemia. Later on, she developed moderate pleural effusion with a mild pulmonary edema. Wide-spectrum antibiotic therapy was continued, which improved her respiratory distress. She underwent a second operation for a diagnostic laparotomy, splenectomy, and paraaortic lymph node biopsy. After the procedure, most of her problems were recovered. She became afebrile, her lymph nodes regressed, and her pancytopenia resolved. Her postoperative paraclinical findings showed a WBC of 8,600/mm³ with 60% PMN and 40% lymphocytes; a Hb of 12 g/dL; and a platelet count of 187,000/mm³.

Her LDH dropped to 292; her liver function test and PT and aPTT all became normal. She had a triglyceride of 755 and a cholesterol of 384 mg/dL; cerebrospinal fluid analysis was normal; tests for CMV, EBV, and M. tuberculosis PCR in CSF were negative. CMV, EBV, PCR analysis of blood were also negative. She had a normal bone survey, chest X-ray, and abdominal ultrasonography.

Bone marrow aspiration revealed mild hypocellularity. Bone marrow biopsy indicated a hypocellular bone marrow with proliferation of many histiocytes and degrees of hemophagocytosis.

Pathological reports of spleen and paraaortic lymph nodes showed the presence of hemophagocytosis with no malignant changes.

The patient was scheduled to receive 60 mg/m²/day prednisone for 6 weeks plus 100 mg/m²/day etoposide every 2 weeks for 4 doses, and 5 mg/kg/day cyclosporine, in addition to prophylactic oral penicillin.

Currently, after 6 months of treatment, she is doing well and in routine work-up, has no stigmata of disease recurrence.

What is Your Diagnosis?
See page 334 – 335 for the diagnosis.
Hemophagocytic lymphohistiocytosis (HLH) syndromes are heterogeneous groups of disorders, which mainly develop during childhood and manifest as fever, jaundice, pancytopenia, multiple organ dysfunction, coagulopathy, and hypertriglyceridemia. These disorders may begin after an episode of infectious or autoimmune process, malignancies, and drug reactions. The disease may sometimes have a genetic basis, which could be seen in familial erythrophagocytic lymphohistiocytosis (FEL). Hereditary form of HLH is an autosomal recessive (AR) process, which usually begins in the first two years of life. It may, however, develop later in older children or adolescents. It may also occur in sporadic forms.

The first reported case of HLH was called histiocytic medullary reticulosis and published in 1939. In that case, presentation with histiocyte proliferation was presumed to be a malignant process. After several reports of the familial form of the disease and submission of infections as pathogenetic factors of HLH by Risdall et al, the disease was called infection associated hemophagocytic syndrome (virus associated hemophagocytic syndrome) (IAHS [VAHS]). In 1979, the genetic or infectious basis of the disease was identified.

Currently, we use reactive HLH to differentiate infectious from hereditary or noninfectious form of the disease.

In HLH, hemophagocytosis in all cell lines (white blood cells, erythrocytes, and platelets) could be seen in bone marrow, liver, spleen, and other organs. Therefore, diagnosis of HLH can be made on clinical, laboratory, and histopathologic features of the disease.

**Clinical features**

Fever and splenomegaly are the most common clinical findings. Hepatomegaly, lymphadenopathy, maculopapular or nodular skin rashes, and signs and symptoms of central nervous system involvement such as seizure, encephalopathy, and meningismus are also notable in HLH.

**Laboratory findings**

Some of the most important paraclinical findings in these patients are listed below:

1. Cytopenia includes anemia, leucopenia, and thrombocytopenia.
2. Hyperbilirubinemia and increased LDH.
3. Hypertriglyceridemia and hypofibrinogenemia.
4. DIC findings such as increased FDP.
5. Increased serum ferritin level.

Some of these findings are considered as poor prognostic factors.

**Histopathology**

In this syndrome, hemophagocytosis caused by activated macrophages may be seen in spleen, liver, lymph nodes, bone marrow, and sometimes in CNS and skin.

Presence of five out of eight criteria of the American Society of Histiocytosis can establish the diagnosis of HLH. The first five criteria are: fever, cytopenia (2 out of 3 cell lines), splenomegaly, hypertriglyceridemia or hypofibrinogenemia, and detection of hemophagocytosis in the pathologic samples. Now, three other criteria have been added to the previous ones, which include decreased or absence of activated natural killer cells, increased serum ferritin level, and an increase in the plasma level of CD25/SIL 2 receptor. In addition, a positive family history is of special concern.

**Pathophysiology**

The characteristic pathophysiologic finding of HLH is the phagocytic activity by monocytes and activated macrophages. An increased macrophage and monocyte activation in HLH is caused by the production of T lymphocyte-induced activating cytokines. These cytokines include IL1, IL6, TNF\(\gamma\), and SIL2 receptor. Some of these cytokines worsen the prognosis of patients with HLH. An increase in IL18 production by monocytes in HLH, augments TNF\(\gamma\) and IFN\(\alpha\) excretion by natural killer cells and T lymphocytes, which can increase Fas ligand expression on lymphocytes that increases the cytotoxic effects of T lymphocytes. The exact mechanism of cytokine production by lymphocytes is not fully understood. In the setting of nonviral infections, it may be caused by inappropriate T helper cell response to the intracellular pathogens such as salmonella, leishmania, and M. tuberculosis.
chromosomes 9 or 10 that are coding genes for perforin (T lymphocytes and natural killer cells regulatory protein) and mutations of MUNC 13 – 14 gene are responsible for the disease.\textsuperscript{1, 2}

**Prognosis and treatment**

Supportive care and treatment of the underlying infections are associated with recovery in 60% – 70% of the reactive HLH-associated pathogens other than EBV. Reactive HLH, however, is usually lethal in the presence of EBV infection, because of bleeding, superimposed infections, and multiorgan involvement.\textsuperscript{1, 2, 5}

In the familial form of disease, immunotherapy and chemotherapy with corticosteroid, etoposide, and stem cell transplantation may be beneficial. In the presence of CNS involvement, intrathecal injection of methotrexate is recommended.

If the process starts after an EBV infection, immunotherapy and chemotherapy with etoposide and corticosteroid is recommended. Cyclosporine A and antithymocyte globulin (ATG) are also useful treatments for HLH.

Stem cell transplantation is the treatment of choice for nonfamilial form of the disease, if they do not respond to eight weeks of chemotherapy. Acyclovir and other antiviral agents are not recommended for EBV-associated disease, but in other viral infections, such as adenovirus or herpes virus type 8, vidarabin and foscarnet are effective, respectively. The role of IVIG in treating HLH has not been proven.

**References**