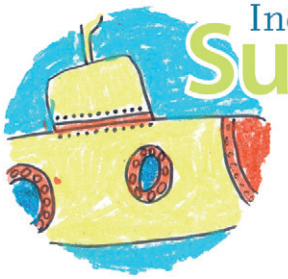

3 Hepatosplenomegaly in a 2-year-old Boy

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CASE PRESENTATION

A 2-year-old boy is admitted for evaluation of massive hepatosplenomegaly. He has had a fever for the past 2 days. He was previously healthy, with no history of jaundice, loss of appetite, or weight loss. He is the only child of nonconsanguineous parents and was born at term after an uncomplicated pregnancy, with birthweight at the 50th percentile. He had regular health supervision visits for vaccinations until 1 year of age, at which his growth, development, and physical examination findings were normal. He has been healthy and has not seen a doctor for almost 1 year. Family history is noncontributory.

Physical examination reveals a febrile child who looks well. Other vital signs are normal for his age. His weight is above the 97th percentile and his height and head circumference are at the 75th percentile. He is scratching his skin and sweating excessively but has no rashes. He has a protuberant abdomen with distended veins and massive hepatosplenomegaly. The rest of the examination findings are normal.

Laboratory evaluation reveals a normal basic metabolic panel, liver function test shows elevated aspartate aminotransferase of 82 U/L (1.37 μkat/L) (normal, 20–60 U/L [0.33–1.00 μkat/L), alanine aminotransferase of 52 U/L (0.87 μkat/L) (normal, 10–35 U/L [0.17–0.58 μkat/L), and alkaline phosphatase of 401 U/L (6.70 μkat/L) (normal, 130–350 U/L [2.17–5.85 μkat/L]). In addition, the bilirubin measurement is normal and lactate dehydrogenase is elevated at 1089 U/L (18.19 μkat/L) (normal, 250–580 U/L [4.18–9.69 μkat/L]). Hemoglobin is 10.4 g/dL (104 g/L), hematocrit is 30.5% (0.35), mean corpuscular volume is 74.4 μm^3 (74.4 fL), and red cell distribution width is 17.9. Reticulocyte count is normal. Platelet count is low at $66\times10^3/\mu$L (66×10^9/L). White blood cell count is 3900/μL (3.9×10^9/L), with an absolute neutrophil count of 570/μL (0.57×10^9/L) and mild monocytosis at 144/μL (1.44×10^9/L). Computed tomography (CT) scan of the abdomen demonstrates nodular, hypodense, nonenhancing lesions in the liver, spleen, and kidneys (Figure). Further procedures help in confirming the diagnosis.

CASE 3 DISCUSSION

The differential diagnoses considered for this 2-year-old boy with massive hepatosplenomegaly were: 1) storage disorders, including glycogen storage disease, Gaucher disease, and Niemann-Pick type A disease; 2) myeloproliferative diseases; 3) malignancies, including leukemia, lymphoma, and hepatoblastoma; and 4) granulomatous diseases such as sarcoidosis. Ultrasonography and CT scan

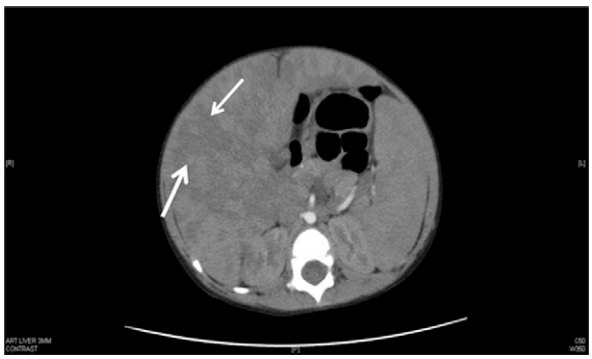

Figure. Computed tomography scan of the abdomen showing nonenhancing hypodense lesions scattered throughout the liver and spleen, which are grossly enlarged.

of the abdomen showed nodular lesions in the liver, spleen, and kidneys suggestive of malignancies such as leukemia, lymphoma, or hepatoblastoma. Juvenile myelomonocytic leukemia was a possibility due to the presence of peripheral monocytosis. The peripheral blood smear did not show any blast cells, and bone marrow aspiration and trephine biopsy results were normal, making leukemia an unlikely diagnosis. The alpha-fetoprotein value was normal, making hepatoblastoma unlikely, and the angiotensin-converting enzyme value was high, indicating sarcoidosis. The differential diagnoses at this point were lymphoma, secondary malignancies, and sarcoidosis.

Following liver biopsy, histology showed diffuse infiltrates of large lymphocytes positive for CD20, CD79A, CD10, and BCL6. They were negative for CD30, ALK1, TDT, CD56, TIA1, BCL2, and MUM1. MYC was positive in fewer than 40% of cells. Ki67 proliferation was approximately 60%. The patient was diagnosed with diffuse large B-cell lymphoma (DLBCL) with B symptoms (fever, sweating, and pruritus). The phenotype supported a germinal center B cell origin. Whole-body positron emission tomography/CT scan revealed extensive fludeoxyglucose-avid lymphadenopathy above and below the diaphragm; multiple lesions within the liver, spleen, and both kidneys; bony lesions involving the spine; and a right retroperitoneal deposit adjacent to the right psoas muscle (stage IV disease). Cytologic and chemical analysis of cerebrospinal fluid obtained by lumbar puncture yielded normal findings.

The Condition

Non-Hodgkin lymphoma (NHL) represents approximately 60% of all lymphomas in the pediatric population. DLBCL is a form of NHL that is seen predominantly in adults. DLBCL can arise in lymph nodes or outside of the lymphatic system in the gastrointestinal tract, testes, thyroid, skin, breast, bone, or brain. DLBCL can be divided into three clinically relevant groups using gene-expression profiling: germinal center type, activated B-cell type, and mediastinal large B-cell lymphoma.

DLBCL is an aggressive tumor with a tendency to metastasize; the majority of cases eventually show some extranodal component. The bone marrow is involved in only about 10% of cases. DLBCLs are positive for B-cell markers such as CD19 and CD20, and most express BCL-6 protein, with some demonstrating a rearrangement of the BCL-6 gene. DLBCLs that express germinal center markers CD10 or BCL-6 tend to have a better prognosis than those that express activated B-cell markers MUM1/IRF4 or CD138. In the nongerminal center group, expression of BCL-2 and cyclin D2 are considered adverse predictors.

Management

Because DLBCL is an aggressive tumor, treatment should begin immediately. A combination of chemotherapy and the monoclonal antibody rituximab with or without radiation therapy has led to cure in a large number of patients. The current standard treatment for DLBCL is R-CHOP, which is a combination of rituximab and chemotherapy drugs (cyclophosphamide, doxorubicin, vincristine, and prednisone). DLBCL is fatal if left untreated and can now be cured in more than 50% of patients. A "cure" is generally defined as 5-year disease-free survival.

Autologous hematopoietic stem cell transplantation is the treatment of choice for patients who relapse. High-dose chemotherapy coupled with a stem cell transplant can be used to treat patients with DLBCL who fail initial chemotherapy but are responsive to a second-line chemotherapy regimen.

Patient's Clinical Course

This patient was offered chemotherapy with R-CHOP, but the parents requested more time to take a decision. He is clinically stable at this time.

Lessons for the Clinician

- Massive hepatosplenomegaly has a short differential diagnosis list for children that includes storage disorders such as glycogen storage disease, Gaucher disease, and Niemann-Pick disease; malignancies such as leukemia and lymphoma; parasitic infections such as malaria and leishmaniasis; and hematologic conditions that include myelofibrosis with myeloid metaplasia and thalassemia major.
- A stepwise approach toward diagnostic evaluation helps to minimize trauma and cost.

- Constitutional B symptoms (fever, night sweats, pruritus, fatigue, and weight loss) may be features of lymphoma in children and their presence indicates a poorer prognosis.
- The presence of nodular lesions in the liver and spleen and B symptoms even in the absence of significant peripheral lymphadenopathy should prompt consideration of a malignant tumor such as lymphoma.
- DLBCL is rare in children. Patients with extranodal tumors should undergo a thorough evaluation, including computed tomography scan of the chest and abdomen, bone marrow analysis, cerebrospinal fluid studies, and positron emission tomography scan to screen for other organ involvement.

Case 3: Hepatosplenomegaly in a 2-year-old Boy

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