Fever, Hepatosplenomegaly, and Pancytopenia in a 5-Month-Old Infant

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Hepatosplenomegaly in a young child can be an ominous physical finding, potentially representing a metabolic, malignant, or infectious process. We present the case of a 5-month-old girl who had fever, hepatosplenomegaly, and hematologic abnormalities at the initial examination. This case demonstrates how a comprehensive understanding of the pathophysiologic characteristics of hepatosplenomegaly and a systematic and thorough workup can help ensure that important diagnoses are not overlooked.

Clinical Presentation (Kara Schmidt, MD): A previously healthy 5-month-old girl presented to James Whitcomb Riley Hospital for Children, Indianapolis, Ind, with a 1-week history of fever (temperature to 39.5°C), diarrhea, and irritability. The family denied that the infant had exhibited any respiratory symptoms or rash and reported only 1 episode of emesis. She had been evaluated at a local emergency department 4 days before presentation. The results of a chest radiograph and a urinalysis were normal; her parents had treated her symptomatically with acetaminophen and oral rehydration as instructed. When her fever continued and she became persistently irritable, she was brought to the Riley Hospital emergency department for further evaluation.

The infant’s birth history and medical history were unremarkable. Her development was normal, and she had no unusual dietary intake. The only medication she received was acetaminophen, and her immunizations were current. She lived with her parents and 3 sisters in a central Indiana farmhouse built in 1810, which was in the process of being remodeled. She did not attend day care consistently. Her physical examination revealed a well-developed, irritable female infant crying in her mother’s arms. Her temperature was 38.9°C; pulse, 186 beats/min; respirations, 32 breaths/min; oxygen saturation, 95% on room air; and weight, 6.35 kg (10th percentile for her age). Her anterior fontanelle was slightly depressed, and she had mild clear rhinorrhea. She was noted to have a distended abdomen and hepatosplenomegaly, with a liver edge palpable 5 cm below the right costal margin and a spleen tip palpable 3 to 4 cm below the left costal margin. The infant presented with fever, hepatosplenomegaly, and pancytopenia. My first step in creating a differential diagnosis is determining whether these findings are acute or chronic. If the history had suggested a more chronic process, I would be concerned about a slowly progressive disorder that infiltrates and replaces healthy reticuloendothelial and hematopoietic tissue, such as many storage diseases and some malignancies, although these rarely present with fever. However, in this particular set-

Laboratory Data (Kara Schmidt, MD): Initial laboratory findings included a complete blood count with a white blood cell count of 6180/µL (58% neutrophils, 3% bands, 33% lymphocytes, and 6% monocytes), a hemoglobin level of 8.6 g/dL, a mean corpuscular volume of 76 fl, and a platelet count of 96 × 10³/µL. Serum electrolytes and blood urea nitrogen and creatinine levels were within reference ranges, and results of cerebrospinal fluid analysis and urinalysis were normal. Bacterial cultures of blood, urine, and cerebrospinal fluid were obtained. Rapid antigen testing of nasal secretions was negative for 6 common respiratory viruses. A chest radiograph was normal (Figure 1). Treatment with ampicillin sodium and cefotaxime sodium was initiated in the emergency department on an empirical basis because of concern about an occult bacterial illness, and the patient was admitted.

Following admission, the infant was evaluated by a hematology/oncology consultant. Additional laboratory results included an additional white blood cell count of 4590/µL (41% neutrophils, 10% bands, 44% lymphocytes, and 7% monocytes); hemoglobin level, 6.9 g/dL; platelet count, 25 × 10³/µL; reticulocyte count, 2.5% of red blood cells; lactate dehydrogenase level, 1010 U/L; serum iron level, 8 µg/dL (1.4 µmol/L); total iron-binding capacity, 259 µg/dL (46.4 µmol/L); a negative direct Coombs test; and a normal lead level. All bacterial cultures and viral studies, including a parvovirus B19 antibody panel and serologic antibody testing for human immunodeficiency virus (HIV), Epstein-Barr virus, and cytomegalovirus, were negative. A bone marrow biopsy was ultimately performed; the pathological findings are shown in Figure 2 and Figure 3.

Differential Diagnosis (James H. Conway, MD): We describe an infant with a history, physical examination results, and laboratory findings that would raise significant concern for any pediatrician. Because there are multiple problems detailed in the case presentation, my approach to the evaluation and diagnosis of this patient focuses on the most immediately troublesome aspects of the history and physical examination, namely, that a young infant presented with fever, hepatosplenomegaly, and pancytopenia. My first step in creating a differential diagnosis is determining whether these findings are acute or chronic. If the history had suggested a more chronic presentation, we would be concerned about a slowly progressive disorder that infiltrates and replaces healthy reticuloendothelial and hematopoietic tissue, such as many storage diseases and some malignancies, although these rarely present with fever. However, in this particular set-

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ting, with such a young infant and with a more acute clinical course, my initial reaction is to formulate a differential diagnosis addressing 2 pathological categories: oncologic disease and infectious disease.

I choose to initially focus on either infection or oncologic disease for 2 reasons. First, there are a limited number of disease processes in which the presentation includes fever, hepatosplenomegaly, and pancytopenia. Although many diseases can present with some combination of these symptoms, only a few diseases have simultaneous manifestations of all 3. Certainly, infections and hematologic malignancies are more common than most of the other entities that can cause this triad of findings. Second, oncologic or infectious diseases in a symptomatic infant of this age can be life threatening and require a rapid diagnosis to ensure prompt and appropriate treatment. Especially pertinent in infants, proper and timely therapy for treatment of identified infections is critical.

I should also mention that, in contrast to the tenet of Occam’s razor, “Pluralitas non est ponenda sine necessitate” (“the simpler the explanation, the better” or “don’t multiply hypotheses unnecessarily”), it is entirely possible that this infant has a primary hematologic malignancy affecting immune function and subsequently has developed an infection. I have seen many children present with unusual or overwhelming infections that proved...
out to be a marker of another underlying immunologic or oncologic disorder. Of course, we must always consider the inconvenient phenomena of small children with an underlying disease who develop an unrelated acute viral illness that complicates the evaluation at the time of their initial presentation. Therefore, fever by itself cannot sway me from considering other entities. In practice, the diagnostic evaluation of a patient with this presentation must be multidisciplinary, and simultaneous tests are required for an accurate and rapid diagnosis. For the sake of this discussion, however, I will address the evaluation of each entity separately.

In the presence of fever and hepatosplenomegaly with leukopenia, thrombocytopenia, and/or anemia, regardless of whether blasts are noted on the peripheral blood smears, malignancy is an immediate concern. In this age group, the most common malignant disorders include acute and chronic lymphoblastic leukemias and lymphomas, Langerhans cell histiocytosis, neuroblastomas, and Wilms tumors. Although rare, primary malignancies of the liver, including hepatoblastoma and hepatocellular carcinomas, do occur in children and can present as hepatosplenomegaly. The presence of pancytopenia or other focal hematologic abnormalities, such as leukopenia, thrombocytopenia, or anemia, makes an infiltrative process even more likely because the bone marrow can be similarly infiltrated and impeded from ongoing hematopoietic activity. Fever is often reported as a symptom in the initial presentation of such patients.

The diagnostic studies recommended by the hematology/oncology consultant did not offer a definitive answer as to whether a malignant process was present. Specifically, there were no blast cells seen in the peripheral smear, and the lactate dehydrogenase/uric acid levels were not dramatically elevated to the level expected of a child with massive cell turnover from a malignant process. Personally, however, I have often found these markers to be unreliable, and, subsequently, I agree that evaluation of the bone marrow is usually indicated, as was the case here.

Incidentally, bone marrow aspiration and biopsy are often underappreciated as diagnostic tests for nonhematologic or nononcologic disorders. Many metabolic and infectious diseases can be identified from stains or cultures of bone marrow material. In addition, although sometimes an uncomfortable procedure, bone marrow sampling is far safer and simpler than liver biopsy and often more timely than awaiting blood tests, such as serologic titers. In this case, the bone marrow biopsy specimen did not show signs of a hematologic malignancy.

Although initially reassuring, the peripheral blood smears and bone marrow studies do not definitively rule out malignancy. However, I must now broaden my differential diagnosis and consider other etiologies. A somewhat reassuring caveat is that if this infant does have cancer, delaying the initiation of oncologic therapy for a short period of time while additional studies are performed will not likely affect the overall prognosis. Furthermore, as mentioned earlier, I still am compelled to try and identify any simultaneous infectious disorders that might complicate initiation of therapy, for that underlying illness anyway.

Initial tests for oncologic disease failed to yield a definitive diagnosis, so I next consider an infectious process. Because both the liver and spleen are integral parts of the reticuloendothelial system, the most likely cause of organomegaly in children is an inflammatory response to a systemic infection. Hepatosplenomegaly is commonly associated with many systemic viral infections, including acute Epstein-Barr virus or cytomegalovirus infections, viral hepatitis (hepatitis A, B, C, etc) and HIV. Although lymphocytosis is often seen with acute viral illnesses, many viral illnesses can cause some transient suppression of bone marrow activity, particularly with transient leukopenias. Statistically, viral infections are the most likely cause of infections in children. Bacterial infections can also cause hepatosplenomegaly, both by activation of the reticuloendothelial system and via phagocytosis of organisms and macrophage engagement. Both processes may be involved to varying degrees by entities such as septicemia, tuberculosis, endocarditis, cholangitis, bartonellosis, and brucellosis. Bacterial sepsis can present with leukopenia or leukocytosis, although I find that leukopenia is both more common and a graver prognostic sign in infants than in older children. Less common infectious causes of hepatosplenomegaly in North America are parasitic (eg, toxoplasmosis or malaria) and fungal (eg, histoplasmosis or disseminated candidiasis) infections, which can present with acute, chronic, or subacute symptoms.

Evaluation for an infectious disease should focus on a detailed history of the tempo of developing symptoms to determine the acuity of the illness. Potential exposures should be carefully examined, including contacts with persons who may have tuberculosis, viral hepatitis, or mononucleosis. Other pertinent exposures may include cats and raw meat ingestion, which can result in toxoplasmosis or bartonellosis (cat scratch disease). A history of blood transfusions or intravenous drug use in the mother raises the possibilities of HIV or hepatitis B or C. Travel or residence in an area with endemic diseases, such as histoplasmosis or malaria, should be discussed. In this case, the patient has a unique risk factor that may be overlooked by physicians who do not practice in the midwestern United States. The infant lives in Indiana in a very old house that has recently undergone renovations, which puts her at high risk for exposure to histoplasmosis.

Serologic testing for specific organisms may be indicated depending on the exposure history and clinical findings. Monospot examinations for Epstein-Barr virus (testing for heterophile antibodies) may be unreliable in very young children, and, therefore, specific Epstein-Barr virus and cytomegalovirus serologic testing may be more accurate and useful. IgM and IgG antibody testing is available in most laboratories for both viruses. Serum transaminase levels and fractionated bilirubin levels assess the degree of hepatobiliary disease. Markedly elevated serum transaminase levels indicate the need for acute hepatitis serologic testing, including hepatitis A IgM, hepatitis B surface antigen, hepatitis B core IgM, and hepatitis C antibody, or RNA polymerase chain reaction. Placement of intradermal purified protein derivative for tuberculin screening and intradermal controls to assess for anergy should be considered. Serial large volume blood cultures are critical in detecting low-grade or intermit-
tent bacteremia that can be seen with endocarditis. Bone marrow aspiration for hematopathologic examination may be necessary, and additional bacterial cultures and special stains for acid-fast bacilli (mycobacterial infections) and fungi should be included. Specific testing for histoplasmosis will be discussed later in the article.

If I were to ignore the fact that this patient had a prolonged history of fever and only focus on the hepatosplenomegaly with or without the hematologic abnormalities, I would have to address a broader differential diagnosis. Clearly, hepatosplenomegaly can occur as a result of noninfectious inflammatory conditions. These include autoimmune disorders such as sarcoidosis and systemic lupus erythematosus, although most of these entities are apparent in a patient’s history through a careful review of systemic symptoms and have additional findings on physical examination. Hepatosplenomegaly can also result from vascular congestion. Suprahepatic or posthepatic venous outflow obstruction may lead to backup into the liver and spleen. Examples include congestive heart failure, pericardial disease, and hepatic vein obstruction (Budd-Chiari syndrome). Intrahepatic obstructive diseases that can similarly cause hepatomegaly with biliary stasis and secondary congestive splenomegaly include cirrhosis, hemangiomas, focal nodular hyperplasias, and congenital fibrosis.

Also, because the liver is responsible for biosynthesis and storage of nutritional materials, metabolic disorders can cause hepatomegaly. The liver stores carbohydrates as glycogen and buffers serum glucose levels through gluconeogenesis. Circulatory proteins, including albumin, complement components, and secretory and transport proteins as well as lipoproteins and lipids, are also synthesized and stored. Because of the metabolic functions of the liver, inborn errors of metabolism and other congenital enzymatic deficiencies can result in increased accumulation of both intracellular and extracellular metabolic by-products. Typically, such derangements present in the first years of life. Examples include storage disorders of lipids, such as Gaucher disease and Niemann-Pick disease, and a variety of glycogen storage diseases, including Hurler disease. These are often associated with other physical findings, such as abnormal craniofacial features. Any of these disorders can gradually result in displacement or replacement of the normal function of the bone marrow compartment. Other disorders resulting primarily in hepatomegaly include Wilson disease, hypervitaminosis A, and hemochromatosis. Symptoms of all such disorders generally present subacutely and are rarely associated with fever.

Returning to the details of this case, the bone marrow biopsy specimen revealed several histiocytes containing intracellular yeastlike forms (Figure 2 and Figure 3). For reasons mentioned above, this infant is at high risk for exposure to *Histoplasma capsulatum* and, as such, this organism is the most likely culprit.

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**COMMENT**

**Disseminated Histoplasmosis of Infancy (Jason M. Kane, MD):** This case demonstrates the classic presentation of progressive disseminated histoplasmosis of infancy. Histoplasmosis, caused by the thermally dimorphic fungus *H capsulatum*, is the most common primary systemic mycosis in the United States. The organism is endemic in certain areas of Latin America and the United States, where most cases originate in the Ohio, Missouri, and Mississippi River valleys. Bird and bat excrement enhance the growth of the organism, and aerosolization of the microconidia occurs when the contaminated soil is disturbed, such as with areas of new construction or with renovation of old buildings or houses.

The severity of illness after inhalation of *H capsulatum* varies depending on the intensity of exposure and the immunity of the host. Low-intensity exposure in healthy individuals usually leads to asymptomatic infection or mild pulmonary disease, whereas a large inoculum may cause severe, diffuse pulmonary infection. However, despite potentially heavy exposures to *H capsulatum*, as many as 50% of pulmonary infections in healthy people are subclinical. Of the infected individuals who become symptomatic with acute pulmonary histoplasmosis, most display flu-like symptoms such as chills, fever, headache, myalgia, and nonproductive cough. The fungus can spread from the lungs to other tissues by both hematogenous and lymphatic dissemination. Although the illness is usually nonprogressive, when a previously uninfected child is exposed to a large amount of inoculum, it may overwhelm the host’s immunity and cause significant complications, including fibrosing or granulomatous mediastinitis, pericarditis, or progressive disseminated histoplasmosis.

Disseminated histoplasmosis of infancy often manifests initially as persistent, unexplained fever and weight loss or failure to thrive. Hepatosplenomegaly is present in almost every case, and hematologic abnormalities, including pancytopenia, are often severe. Hepatosplenomegaly and lymphadenopathy occur largely from hyper trophy owing to both local infiltration and phagocytosis of organisms, and this dissemination similarly affects other sites, including the bone marrow, which can be heavily infiltrated. Pulmonary symptoms are less common than in older children with self-limited disease, but respiratory symptoms are sometimes present. Chest radiographic findings range from normal to focal or diffuse infiltrates. In this case, there were no significant abnormalities on the chest radiographs, which may mislead people more accustomed to older patients with acute pulmonary histoplasmosis (Figure 1).

Infants with disseminated histoplasmosis are frequently referred to hematologists or oncologists to rule out lymphoma or leukemia as the underlying cause of their symptoms, and, often, the diagnosis is only suspected after a bone marrow biopsy specimen or peripheral blood smear reveals the presence of fungal elements. In a recent study, the characteristic triad of fever, hepatosplenomegaly, and hematologic abnormalities has been shown to be present in 100% of patients suspected of having disseminated histoplasmosis. Risk factors for dissemination include exposure to large quantities of the pathogen, young age of the infant (usually younger than 1 year), interstrain virulence, and host immunity. Patients with a prolonged history of fever, failure to thrive, and signs of disseminated intravascular coagulation are at a higher risk of mortality.
Making the diagnosis of disseminated histoplasmosis requires a high index of suspicion. That our patient’s family lived in a rural central Indiana farmhouse undergoing heavy renovation represented a high-risk exposure situation. Coupled with the history of fever, hepatosplenomegaly, and pancytopenia, the patient’s housing situation should have placed disseminated histoplasmosis high in the differential diagnosis.

Children who are immunosuppressed, particularly those with cellular immune dysfunction, are at increased risk for disseminated histoplasmosis. In children not immunocompromised by HIV, histoplasmosis usually manifests initially with prolonged fevers, weight loss, and interstitial lung disease. Once the fungus disseminates, extrapulmonary complications include oral ulcers, destructive bone changes, and, rarely, meningitis or endocarditis. In an individual with HIV, the diagnosis of disseminated histoplasmosis is an acquired immunodeficiency syndrome–defining illness. Pulmonary infections develop in the majority of individuals, as do hepatosplenomegaly and lymphadenopathy. A small number of HIV-infected patients develop a sepsislike syndrome characterized by multiple organ system failure and disseminated intravascular coagulation.

A number of laboratory tests for histoplasmosis are available that, when used appropriately, can provide for the accurate diagnosis and effective treatment of disease. Specific laboratory tests include complement fixation antibody assay, immunodiffusion antibody assay, and radioimmunoassay for histoplasma antigen in urine. The latter is a rapid, semiquantitative test with high sensitivity that is also useful for monitoring treatment of patients with progressive disseminated disease. The antigen test is also valuable in making a rapid diagnosis of histoplasmosis in immunocompromised patients who are unable to produce adequate detectable antibodies. The histoplasmin skin test had been the only diagnostic test for sensitization to \textit{H} \textit{capsulatum}, but it is of little use today and is difficult to obtain. An overwhelming number of people living in an endemic area will have a positive skin test even without any clinical disease. Also, the skin test may be falsely negative in children with disseminated disease. Yeast forms may be demonstrated histologically in tissue from patients with severe forms of the disease. As seen in Figure 2 and Figure 3, the patient’s bone marrow was overwhelmed with yeastlike forms of \textit{H} \textit{capsulatum} phagocytopically engulfed by marrow macrophages.

Progressive disseminated histoplasmosis can be fatal without appropriate antifungal therapy; however, outcome is excellent when the disease is adequately treated. Acute pulmonary histoplasmosis in an asymptomatic individual requires no treatment, and the clinical course after low-level exposure is usually benign. Fever persisting for longer than 3 weeks in acute pulmonary infection may indicate that the patient is developing progressive disseminated disease and requires treatment. Patients with disseminated histoplasmosis of infancy as well as any immunocompetent host sufficiently ill enough to require hospitalization should be treated with parenteral antifungal therapy. The treatment of choice is amphotericin B dosed at 0.7 to 1 mg/kg per day with a total dosage of 30 to 35 mg/kg given during 4 to 6 weeks. Antigen testing may be useful for monitoring therapy because antigen concentrations decrease with therapy and increase with relapse. Treatment should continue until antigen concentrations revert to negative levels or at least reach low levels of less than 4 U. Follow-up antigen levels should be monitored every 3 to 6 months until they become negative. In some circumstances in which antifungal therapy is indicated, itraconazole may be justified as an alternative agent. In addition, oral itraconazole is used for long-term suppression after completing induction therapy with amphotericin B in some immunocompromised patients.

Hepatosplenomegaly in a young child can be an ominous physical finding, potentially representing a metabolic, malignant, or infectious process. As such, any child presenting with hepatosplenomegaly mandates a comprehensive evaluation. The workup is best guided by a meticulous history, with particular attention paid to the presence and duration of associated symptoms and possible environmental or infectious exposures. In the case of this infant, the diagnosis of disseminated histoplasmosis was made after direct examination of the bone marrow.

Although previously described as a rare entity, disseminated histoplasmosis of infancy should be included in the differential diagnosis in a young child who presents with fever, hepatosplenomegaly, and hematologic abnormalities, particularly when that child resides in or has recently visited an endemic area.

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REFERENCES


The aim of “Clinical Problem Solving” is to demonstrate how master clinicians approach complex problems. Contributions for the section are encouraged; informal inquiries via e-mail to the editorial office are advised prior to preparing and submitting a manuscript.