

**CASE RECORDS
OF THE
MASSACHUSETTS GENERAL HOSPITAL**



Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 37-1994

PRESENTATION OF CASE

A newborn boy was admitted to the hospital because of petechiae and massive splenomegaly.

The infant was born in the 39th week of the sixth pregnancy of a woman 35 years old. The pregnancy was complicated only by a febrile illness with vomiting, diarrhea, and dehydration during the third month. There was no evidence of fetal distress, and the baby was vigorous; the Apgar score was 8 at both one minute and five minutes. The birth weight was appropriate for the gestational age. In the nursery abdominal distention and petechiae were observed. Hematologic studies were performed (Table 1). The oxygen saturation declined gradually to 92 percent while the patient was breathing room air, and he was given oxygen by hood. The patient was transferred to this hospital while receiving glucose intravenously and supplemental oxygen. A specimen was obtained for blood culture, and ampicillin and gentamicin were administered intravenously.

The mother's blood group was A Rh positive, and her platelet count was 187,000 per cubic millimeter; an indirect Coombs' test and a serologic test for syphilis were negative; anti-rubella antibodies were present. Tests for hepatitis B antigen and alpha-fetoprotein were negative, and tests for cervical chlamydia and group B beta-hemolytic streptococci were positive. Rupture of the membranes occurred at the time of delivery. The mother did not have fever during delivery and received no antibiotics at the time. She used no tobacco, alcohol, or medications during the pregnancy and had no risk factors for human immunodeficiency virus (HIV) infection. A son had died of the sudden infant death syndrome six years earlier at the age of 2½ months; two of the patient's siblings were alive and well.

The temperature was 36.6°C, the pulse was 130, and the respirations were 60 to 90. The blood pressure was 65/35 mm Hg. The body length was 54 cm, the

weight 4.1 kg, and the head circumference 36.5 cm (all values in the 90th percentile).

On physical examination the baby appeared comfortable in an oxygen-enriched atmosphere. Petechiae were observed on the upper thighs, lower back, and abdomen, and there were ecchymoses in the inguinal areas; no eczematoid rash was present. Mobile lymph nodes, 5 mm, were palpated in each axilla, and inguinal lymph nodes, 8 to 10 mm, were palpable bilaterally. The head was normal, without dysmorphic features, and the neck was normal. The lungs were clear except for a few rhonchi, and the heart was normal. The abdomen was protuberant at 38 cm; the spleen descended 8 cm below the left costal margin, and the liver edge was palpated 5 or 6 cm below the right costal margin. The extremities had good pulses and were well perfused. The genitalia were normal. The anus was patent; no sacral dimple was seen. Neurologic examination was negative.

Hematologic and blood chemical studies were performed (Table 1 and Fig. 1). Values were normal for urea nitrogen, creatinine, electrolytes, uric acid, bilirubin, alkaline phosphatase, and aspartate and alanine aminotransferase; the glucose concentration was 56 mg per deciliter (3.1 mmol per liter), and the lactate dehydrogenase level 2002 U per liter. Radiographs of the chest and abdomen (Fig. 2) were normal except for evidence of hepatosplenomegaly. A computed tomographic (CT) scan of the cranium was negative. An ultrasonographic examination of the abdomen revealed a normal appearance of the inferior vena cava and hepatic and portal veins, with normal blood flow; there was marked hepatosplenomegaly, without ascites. X-ray films of the forearms and knees (Fig. 3) disclosed irregularity at the distal ulnar metaphyses

Table 1. Hematologic Laboratory Values.

VARIABLE	AT OTHER HOSPITAL	ON ADMISSION	1 TO 2 WEEKS AFTER ADMISSION	3 TO 4 WEEKS AFTER ADMISSION
Hematocrit (%)	54	48.1	37.5–47.2	27.4–33
White-cell count (per mm ³)	40,000	48,200	25,000	Up to 56,800
Differential count (%)				
Neutrophils	16	22	28	31
Band forms	18	5	5	17
Metamyelocytes		3	2	5
Myelocytes		2		4
Promyelocytes		1		2
Eosinophils	1	2	1	
Basophils	1	1	3	
Monocytes*	19	24	25	16
Lymphocytes	45†	40	36‡	25‡
Blast forms		Rare		
Nucleated red cells/100 white cells*	98	55	0–3	1–10
Platelet count (per mm ³)	317,000	15,000	30,000–73,000	20,000–71,000
Prothrombin time (sec)§		11.3		
Partial-thromboplastin time (sec)		38.9		
Fibrinogen (mg/dl)		194		
Blood group	O, Rh+			

*Representative cells are shown in Figure 1.

†These lymphocytes included many hematogones (normal B-cell precursors) and atypical forms with irregular, normochromatic nuclei.

‡Hematogones and atypical lymphocytes were present.

§Control value, 10.2.

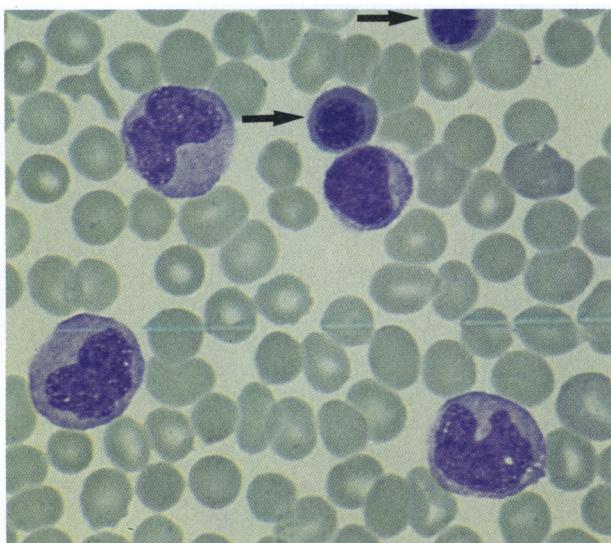


Figure 1. Peripheral-Blood Smear, Showing Three Monocytes and Two Normoblasts (Arrows) (Wright's Stain, $\times 550$).
The sixth cell is a lymphocyte.

and irregularity and widening of the distal femoral metaphyses, findings consistent with rickets.

Supplemental oxygen, ampicillin, and gentamicin were continued, and allopurinol was begun. One unit of platelets was transfused, and the platelet count rose to 48,000 per cubic millimeter. The boy remained afebrile, and repeated physical examinations showed no change in the lymphadenopathy or hepatosplenomegaly. He was weaned from oxygen to room air, and

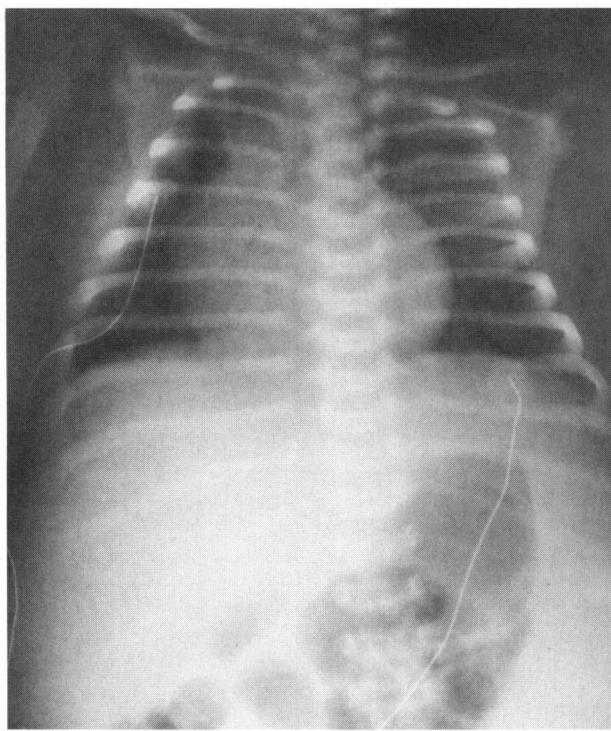


Figure 2. Radiograph of the Chest and Abdomen.
The radiograph is normal except for the evidence of hepatosplenomegaly.

the ampicillin and gentamicin were discontinued after seven days. Repeated platelet transfusions were required to maintain the platelet count above 30,000 per cubic millimeter.

An ophthalmologic consultant found no abnormality. Both the mother and the baby had IgG antibodies to cytomegalovirus and to rubella. The titer for Epstein-Barr viral capsid IgG antibody was positive, at 1:160; that for early-antigen diffuse IgG antibody was less than 1:10; that for restricted IgG antibody was 1:10; and that for the Epstein-Barr nuclear antibody was 1:40. The findings were consistent with the presence of maternal antibodies. No serologic evidence of toxoplasma, syphilis or HIV, herpes simplex, or *Borrelia burgdorferi* infection was detected, and a test for urinary group B streptococcal antigen was negative. The results of hematologic studies during the



Figure 3. Anteroposterior View of the Knees, Showing Irregularity of the Femoral Metaphyses, a Finding Consistent with Rickets.

next two weeks are presented in Table 1. Microscopical examination of two bone marrow aspirates and a bone marrow-biopsy specimen (Fig. 4 and 5) yielded similar results; the aspirate smear disclosed complete erythroid and granulocytic maturation; a 500-cell differential count showed 0.6 percent blast forms, 0.6 percent promyelocytes, 15.4 percent maturing neutrophil precursors, 2 percent eosinophils, 0.4 percent basophils, 7 percent monocytes, 51 percent erythroid precursors, and 23 percent lymphocytes; the lymphocytes included many hematogones; the monocytes appeared normal. Megakaryocytes were not seen in the smears but were present in the biopsy specimen; the marrow cellularity was normal, and no evidence of storage disease was found. Immunophenotyping of the blood and bone marrow confirmed the presence of a subset of B-cell precursors and an increase in monocytes that had a normal immunophenotype. Microscopical examination of stained specimens of the bone marrow disclosed no acid-fast bacilli or fungi, and all bacteriologic, fungal, and viral cultures remained negative. Tests for Gaucher's disease and other storage

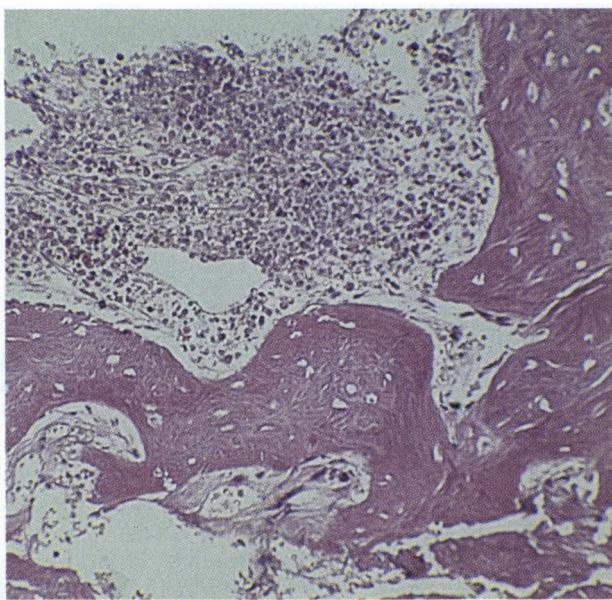


Figure 4. Bone Marrow—Biopsy Specimen ($\times 25$).
Erythroid and granulocytic maturation is complete. The thickened bone trabeculae are of the woven type.

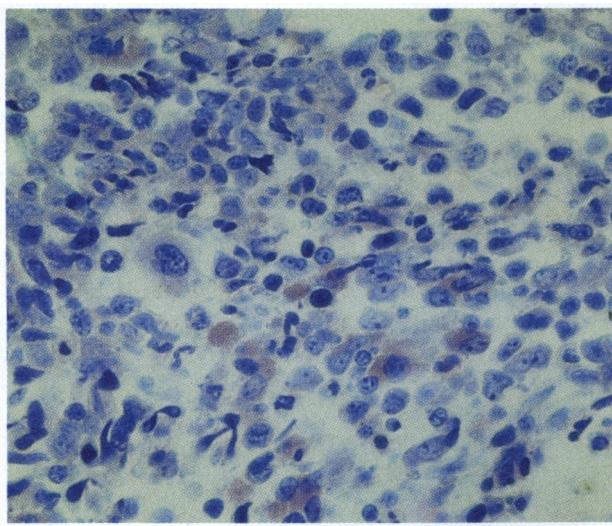


Figure 5. Bone Marrow—Biopsy Specimen (Giemsa Stain, $\times 350$).
A normal-appearing megakaryocyte is present.

diseases were negative. During the ensuing two weeks additional hematologic studies were done (Table 1).

A diagnostic procedure was performed.

DIFFERENTIAL DIAGNOSIS

DR. ROBERT I. PARKER*: May we review the radiologic studies?

DR. ROBERT T. BRAMSON: The radiographs of the knees and wrists reveal a slight widening of the metaphyseal region of the ulna, with frayed edges. Similar changes about the distal femoral metaphysis (Fig. 3)

are consistent with rickets. A radiograph of the chest and abdomen (Fig. 2) is normal except for densities in the upper portion of the abdomen that are consistent with hepatosplenomegaly.

DR. PARKER: Will you comment on the bone mineralization and density and cortical thickness? Do you have any observations on the orbits and the optic foramina as shown on the bone windows of the CT scan?

DR. BRAMSON: The overall bony mineralization was normal. There was no abnormality in the corticomedullary junction of the long bones that were visualized. The CT-scan bone windows showed no abnormality.

DR. PARKER: The differential diagnosis in this case includes disorders that produce marked neonatal hepatosplenomegaly, lymphadenopathy, a leukoerythroblastic blood picture, and a hypocellular marrow with an abnormal architecture of the bony trabeculae. I reviewed the slides of the bone marrow specimen and concluded that the bony trabeculae were somewhat thickened. I shall begin by discussing disorders that are less likely, before turning to the disease that I believe to be the correct diagnosis in this case (Table 2).

Although intrauterine infection can result in organomegaly, lymphadenopathy, and thrombocytopenia, that diagnosis does not explain well the leukocytosis. Furthermore, the overall clinical presentation does not strongly suggest intrauterine infection. Although neonatal sepsis can produce thrombocytopenia and a leukoerythroblastic peripheral-blood picture,¹ there is no other evidence to suggest that diagnosis.

Storage diseases are unlikely to be manifested to this extent at birth, and the bone marrow studies appear to exclude them. Severe anemia, as is seen with abnormalities of red-cell production or survival, such as Rh incompatibility, dyserythropoietic syndromes, and alpha-thalassemia syndromes, may result in hepatosplenomegaly and a leukoerythroblastic picture in newborns due to congestive heart failure or extramedullary hematopoiesis, or both.¹ However, this infant was born with a normal hematocrit, and the bone marrow studies demonstrated normal erythropoiesis. Although a reticulocyte count and the result of a Coombs' test are not available, intrauterine hemolysis is highly unlikely in view of the normal hematocrit at birth.

Mechanical obstruction of splenic and hepatic ve-

Table 2. Differential Diagnosis.

Less likely disorders
Intrauterine infection
Sepsis
Mechanical obstruction of splenic or hepatic venous drainage
Intrauterine anemia or hydrops
More likely disorders
Letterer-Siwe disease
Hemophagocytic syndromes
Juvenile chronic myelogenous leukemia (or related disorder)
Systemic mast-cell disease
Osteopetrosis

*Associate professor of pediatrics, State University of New York at Stony Brook; vice chairman for academic affairs, Department of Pediatrics; director, Pediatric Hematology—Oncology.

nous drainage may result in hepatosplenomegaly, and if due to venous thrombosis it may produce thrombocytopenia.² Acute blood pooling or sequestration in the spleen may cause hemodynamic instability, with the release of immature elements from the marrow into the circulation, leading to nucleated red cells and immature myeloid elements in the blood smear, as seen in this case. In this infant there was no evidence of venous obstruction on the abdominal ultrasound study, and his hemodynamic condition was stable. In addition, the bone marrow findings would not be explained by that process.

In view of the presence of increased numbers of monocytes and mononuclear leukocytes in the peripheral blood and bone marrow, diseases of monocytes, macrophages, and histiocytes must be considered. Hemophagocytic syndromes in which intrinsic or infection-induced activation of the immune system causes a proliferation of histiocytes and hemophagocytosis may also present with lymphadenopathy, hepatosplenomegaly, and cytopenias.³ Two well-described familial hemophagocytic syndromes, an X-linked form and a non-X-linked form, present in newborns and generally carry a very poor prognosis.⁴ Epstein-Barr virus and cytomegalovirus infections may produce a hemophagocytic syndrome.³ This infant may have been exposed to the Epstein-Barr virus in utero, as suggested by the elevated maternal titer for viral capsid IgG antibody. The diagnosis of an Epstein-Barr virus hemophagocytic syndrome relies on the presence of hemophagocytosis in the bone marrow or peripheral blood, histiocytic infiltration of the marrow or other organs, and the demonstration of the Epstein-Barr virus genome incorporated into somatic cells by in situ hybridization.^{5,6} The absence of hemophagocytosis in the bone marrow and the weak evidence for an Epstein-Barr virus infection in this infant make this class of disorders improbable.

Letterer-Siwe disease, the most aggressive form of Langerhans'-cell histiocytosis,^{7,9} is generally detected in the first few years of life and has been diagnosed in newborns. Infants with Letterer-Siwe disease present with failure to thrive, hepatosplenomegaly, and frequently a skin rash and may have an increase in monocytes and monocytid leukocytes on a peripheral-blood smear.^{7,8} Anemia and thrombocytopenia are frequently present. Langerhans' histiocytes are found in the marrow, the skin, and other organs.⁹ This class of diseases is currently thought to represent a disorder in immunoregulation rather than a neoplastic proliferation.¹⁰⁻¹² Although Letterer-Siwe disease remains a possibility in this case, the absence of histiocytes in the bone marrow and the absence of the characteristic skin rash make this diagnosis unlikely.

Several hematologic tumors merit consideration (Table 3). Juvenile chronic myelogenous leukemia is a clonal panmyelopathic neoplasm distinct from adult Philadelphia-chromosome-positive chronic myelogenous leukemia. The disease is characterized by leukocytosis, the presence of early myeloid and monocyte elements, including blast forms, in the peripheral

Table 3. Hematologic Tumors in the Differential Diagnosis.

Juvenile chronic myelogenous leukemia
Congenital acute leukemias
Chronic monocytic leukemia
Chronic myelomonocytic leukemia
Chronic lymphocytic leukemia

blood, thrombocytopenia, a decreased leukocyte alkaline phosphatase score, skin lesions, and frequently hepatosplenomegaly. Unlike adult chronic myelogenous leukemia, juvenile chronic myelogenous leukemia is not characterized by the presence of either the Philadelphia chromosome or any other consistent chromosomal abnormality.^{13,14} The disease generally presents in the first few years of life and occasionally presents in infancy. The diagnosis is suggested by the clinical presentation and confirmed by laboratory testing. Examination of the bone marrow reveals erythroid and myeloid hyperplasia and an increase in monocytes, with only a slight increase in blast forms. The disease is also characterized by the fetal type of erythropoiesis, with an increase in the hemoglobin F level and the presence of the i antigen on red cells. In this case those studies would not have been helpful in that we would expect to see circulating erythrocytes with fetal characteristics. Although no study is diagnostic of the disease, peripheral-blood progenitor cells have been found to be exquisitely sensitive to the granulocyte colony-stimulating factor and to produce increased colony-forming-unit cells when cultured in vitro.¹⁴⁻¹⁶ When peripheral-blood progenitors obtained from patients with juvenile chronic myelogenous leukemia are cultured, increased numbers of colony-forming-unit cells are produced in the absence of any exogenous cytokine or in the presence of very small amounts of added granulocyte colony-stimulating factor.¹⁴⁻¹⁶

The prognosis for patients with juvenile chronic myelogenous leukemia is guarded, with an aggressive, nonlymphoid acute leukemia developing ultimately in most children.^{13,15} Aggressive therapy with antineoplastic agents while the patient is in the chronic, stable phase of the disease does not improve survival and may enhance progression to acute leukemia.^{13,17} In some cases low doses of cytarabine have produced some in vivo myeloid differentiation and clinical improvement.¹³ Recently, the use of cis-retinoic acid has caused stabilization and in some cases regression of disease.¹⁸ In a limited number of children bone marrow transplantation has been curative.¹⁹

Both chronic monocytic leukemia and chronic myelomonocytic leukemia are rare disorders in children that are characterized by abnormal proliferation of monocytes and myeloid elements. Both diseases are characterized by anemia, thrombocytopenia, hepatosplenomegaly, and an increase in monocytes, with or without immature myeloid elements in the peripheral blood and bone marrow.¹³ Aggressive antineoplastic therapy is not indicated in the stable phase for the

same reasons that it is not indicated in juvenile chronic myelogenous leukemia. Both diseases have a propensity for transformation to acute nonlymphoid leukemia. Chronic lymphocytic leukemia, a neoplastic clonal proliferation of relatively mature lymphocytes, is rare in young children.¹³ The patient under discussion had a clinical presentation consistent with a congenital chronic leukemia, and on the basis of the peripheral-blood picture I would consider juvenile chronic myelogenous leukemia in particular. However, the bone marrow findings, particularly the decreased cellularity, are not strongly suggestive of any of these disorders.

The bone marrow findings, especially the thickened bony trabeculae, lead me to consider two other disorders: systemic mastocytosis and osteopetrosis.

I am unaware of any neonatal presentations of systemic mastocytosis. In adults the bone marrow is the extracutaneous site most commonly involved,^{20,21} either as focal collections of mast cells, eosinophils, and lymphocytes or as a diffuse infiltration by mast cells. Also, fibrosis and thickened bony trabeculae may be prominent features.^{20,21} Many patients with systemic mast-cell disease have increased early myeloid or monocytic elements in the peripheral blood that are consistent with chronic myelomonocytic leukemia, as did this patient. In pediatric mast-cell disease, however, there are few or no peripheral-blood changes, and only small perivascular collections of mast cells and eosinophils are found in the bone marrow.²² In this patient the absence of mast cells on Giemsa staining of the bone marrow-biopsy specimen and the absence of skin lesions consistent with mast-cell disease rule out this diagnosis.

I am brought, perhaps "out on a limb," to a consideration of osteopetrosis as a possible diagnosis in this case. It is an inherited disorder of bone formation characterized by decreased bone resorption, resulting in dense, fragile bones.²³ The disease occurs in several forms, including an autosomal recessive "malignant" form that presents in early infancy, a milder adult or juvenile autosomal dominant form, an autosomal recessive form associated with renal tubular acidosis, less well-defined mild autosomal recessive forms, and a lethal form associated with a marked reduction of osteoclasts.²⁴ In some animal models and in some human beings, decreased osteoclast activity appears to result from defects in the generation of superoxide or macrophage colony-stimulating factor, and some investigators have described functional leukocyte defects as well.²⁵⁻²⁷ The oncogenes *src* and *c-fos* have been implicated in this disease in animal models,^{28,29} but to my knowledge specific oncogenes have not been described in human disease.

Infants with the "malignant" autosomal recessive form of osteopetrosis generally present in the first few months of life with visual loss, hepatosplenomegaly, leukocytosis, lymphadenopathy, thrombocytopenia, and later, anemia.³⁰ Gerritsen et al.,³⁰ in a recent review of 33 cases of this disorder, found that visual changes are the most frequent presenting manifesta-

tion. In some cases the visual problems are part of a generalized neurodegenerative process. At times the presentation mimics that of a primary hematologic neoplasm. Indeed, Toren et al.³¹ have reported a case of osteopetrosis in a newborn who presented with a clinical picture highly suggestive of juvenile chronic myelogenous leukemia. The organomegaly and some of the blood findings in osteopetrosis are the direct result of extramedullary hematopoiesis, which compensates for the obliteration of the marrow by the abnormal bone formation. However, the anemia and thrombocytopenia result in large part from hypersplenism and extravascular hemolysis.^{23,32} The alkaline phosphatase level, although markedly elevated in older patients with osteopetrosis, is frequently normal in newborns. Radiologic studies reveal dense bones with a thickened cortex, a "bone-in-bone" appearance of the vertebrae and long bones of the hands, and widened, rachitic-appearing metaphyses of the long bones.³³ CT evaluation of the skull may reveal thickening and sclerosis of the calvarium, shallow orbital cavities, and occasionally intracranial calcifications. Untreated infants have progressive organomegaly, cytopenia, blindness due to optic atrophy, and frequent fractures and generally do not thrive. They usually die of infection, hemorrhage, or both, within the first few years of life. The infants in whom early visual or hematologic impairment develops appear to have the worst prognosis.³⁰

Therapeutic approaches in patients with osteopetrosis have included limitation of calcium intake, administration of vitamin D and parathyroid hormone to enhance bone resorption and prednisone to improve hematologic indexes, and splenectomy.^{32,34} Bone marrow transplantation has been curative in some patients.^{35,36} Key et al.³⁷ documented both clinical and biochemical improvement in eight children whom they treated with recombinant human interferon gamma. With the exception of allogeneic bone marrow transplantation, however, all the therapies attempted to date at best ameliorate but do not correct the osteopetrotic defects.

In summary, this infant's physical examination and hematologic findings may be explained by juvenile chronic myelogenous leukemia, although this diagnosis would not account for the radiologic abnormalities in the ulna and femur or the hypocellular bone marrow with thickened bony trabeculae. Both of these findings, in addition to the other findings on hematologic evaluation and physical examination and the elevated lactate dehydrogenase level, are best explained by a diagnosis of autosomal recessive "malignant" osteopetrosis.

DR. NANCY L. HARRIS: Dr. Grabowski, will you tell us your diagnostic impressions?

DR. ERIC F. GRABOWSKI: Two additional diseases that we considered early in the course are the Wiskott-Aldrich syndrome and a malignant teratoma, but neither of these diagnoses would explain the elevated white-cell count. We subsequently favored the diagnosis of juvenile chronic myelogenous leu-

kemia, especially when the total white-cell count rose to 56,800 per cubic millimeter.

CLINICAL DIAGNOSIS

Juvenile chronic myelogenous leukemia.

DR. ROBERT I. PARKER'S DIAGNOSIS

Autosomal recessive "malignant" osteopetrosis.

PATHOLOGICAL DISCUSSION

DR. PHUONG L. NGUYEN: The diagnostic procedure was an open-liver biopsy, which revealed an extensive portal and sinusoidal infiltrate composed of immature-appearing mononuclear cells, abundant eosinophils, scattered mature segmented neutrophils (Fig. 6 and 7), and rare erythroid precursors and megakaryocytes. Immunohistochemical stains demonstrated the myeloid origin of the infiltrate, with many mononuclear cells having reactivity for myeloperoxidase (Fig. 8) and lysozyme. Our diagnosis was a leukemia, consistent with juvenile chronic myelogenous leukemia.

Juvenile chronic myelogenous leukemia accounts for approximately 2 percent of all cases of childhood leukemia. Most of the patients are under two years of age,^{19,38,39} and over 90 percent are under four years of age.³⁹ The clinical presentation can be acute or subacute, depending on the associated physical and laboratory findings. Abdominal discomfort due to splenomegaly is an almost constant finding.³⁹ Hepatomegaly and lymphadenopathy are less common. Hemorrhagic manifestations, ranging from petechiae to overt bleeding, are related to the thrombocytopenia. A skin rash occurs in approximately 40 percent of the patients, most often involving the face. Leukemic infiltration of the lungs may result in a cough, tachypnea, and bronchospasm, with a radiologic interstitial pattern. The hematologic findings include leukocytosis with monocytosis, thrombocytopenia, and variable normoblastemia. The blast-form count at presentation can vary but never reaches the level seen in acute leukemia.

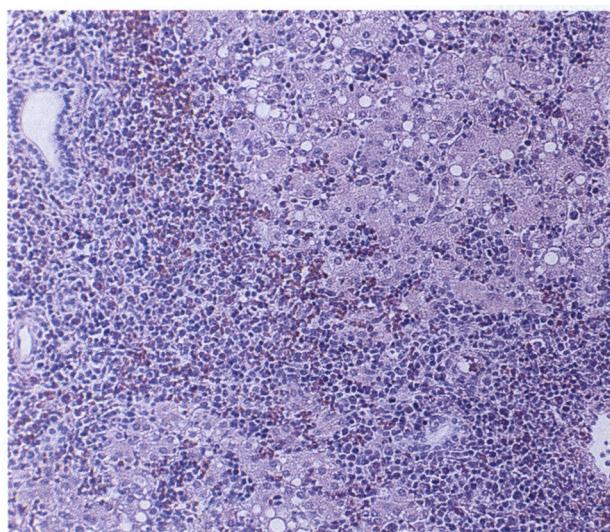


Figure 6. Liver-Biopsy Specimen ($\times 60$).

The infiltrate has a portal and sinusoidal pattern of distribution.

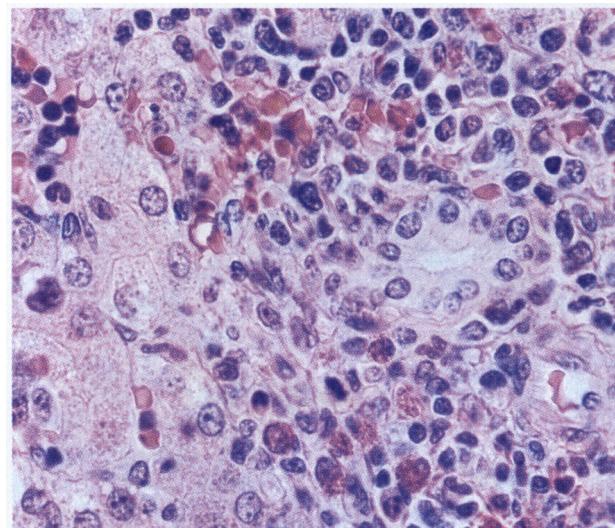


Figure 7. Liver-Biopsy Specimen ($\times 350$).

The infiltrate is composed of immature-appearing mononuclear cells with admixed eosinophils and segmented neutrophils.

The count may have prognostic value.¹⁹ The bone marrow is typically hypercellular, with normal to increased granulocytopenia; megakaryocytes are often decreased.

Additional laboratory findings include an increased level of hemoglobin F (fetal hemoglobin) in approximately 60 percent of the patients^{40,41} and a decreased leukocyte alkaline phosphatase level in approximately 40 percent.³⁹ Hemoglobin F was not measured in this patient. The leukocyte alkaline phosphatase level, measured on the day of the liver biopsy, was 26 U per liter (normal, 30 to 160). Although thrombocytopenic purpura and anemia are uncommon manifestations of persistent Epstein-Barr virus infection, Herrod et al.⁴² described rare cases of children who presented with organomegaly and hematologic abnormalities mimicking juvenile chronic myelogenous leukemia. In contrast to the findings in juvenile chronic myelogenous leukemia, however, these abnormalities resolve spontaneously.⁴³ Serologic studies would be necessary to document recent acute infection with Epstein-Barr virus.

Of the myeloproliferative disorders of childhood, monosomy 7 shares many similarities with juvenile chronic myelogenous leukemia, including the young age at presentation, organomegaly, a leukoerythroblastic blood picture with monocytosis, and thrombocytopenia.^{44,45} The hemoglobin F level is less elevated in monosomy 7 than in juvenile chronic myelogenous leukemia. The distinguishing diagnostic criterion is the finding of monosomy 7 in the bone marrow. In contrast, 80 percent of patients with juvenile chronic myelogenous leukemia have a normal karyotype,^{46,47} as this patient did, and the remainder have no consistent cytogenetic abnormalities.⁴⁷

Although some investigators have proposed that juvenile chronic myelogenous leukemia should be classified as a histiocytosis syndrome,⁴⁸ others have suggested that it be viewed as a panmyelopathy, with a

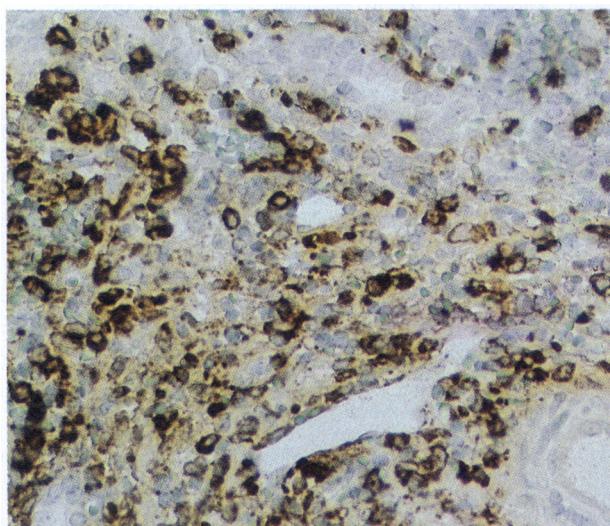


Figure 8. Liver-Biopsy Specimen Stained with Antimyeloperoxidase Antibody, Demonstrating the Myeloid Origin of the Infiltrate in the Liver (Immunoperoxidase Stain, $\times 350$).

prominent monocytic involvement.¹⁸ European hematologists use the term "subacute or chronic myelomonocytic leukemia" instead of juvenile chronic myelogenous leukemia,¹⁹ because when the mononuclear cells in the peripheral blood or bone marrow are cultured in a semisolid or liquid medium, a large number of predominantly monocytic colony-forming units are observed. In contrast, when mononuclear cells from the blood or bone marrow of patients with the adult type of chronic myelogenous leukemia are cultured, a large number of granulocyte colony-forming units with fewer monocytic and erythroid blood-forming units are observed.^{20,49-51} The frequent finding of a disordered pattern of hemoglobin F synthesis is evidence of involvement of the erythroid lineage in juvenile chronic myelogenous leukemia. In addition, when patients with this disorder present with a cytogenetic abnormality, it involves erythroid precursors as well as the monocytes and granulocytes.

The prognosis of juvenile chronic myelogenous leukemia is poor, with a median survival of less than two years in most of the reported cases.³⁹ In the largest reported series to date, comprising 38 patients with juvenile chronic myelogenous leukemia, the median survival with or without chemotherapy was only 16 months.¹⁹ Factors associated with a shorter survival included an age of more than two years, hepatomegaly, bleeding, thrombocytopenia, and high counts of blast forms and normoblasts in the peripheral blood.¹⁹ Six of 14 patients with juvenile chronic myelogenous leukemia who received allogeneic bone marrow transplants have remained in remission for as long as 11½ years after transplantation.²³ A preliminary study describes the use of cis-retinoic acid in eight children with juvenile chronic myelogenous leukemia; two had a complete response, and two had a partial response.²²

In summary, the diagnosis of juvenile chronic myelogenous leukemia in this case is based on the con-

stellation of characteristic clinical, hematologic, and cytogenetic findings.

DR. PARKER: Did you consider osteopetrosis in this patient?

DR. NGUYEN: We interpreted the area of thickened trabeculae as endochondral ossification in a newborn.

DR. PARKER: The thickened trabeculae in the medullary cavity, the poor cellularity of the bone marrow specimen, and the radiographic appearance of the long bones led to my diagnosis of osteopetrosis.

DR. GRABOWSKI: The patient received a bone marrow transplant from a sister whose marrow was HLA-compatible on mixed-lymphocyte culture; the transplantation was performed at another hospital when he was 3½ months of age. His white-cell count decreased considerably, his liver size approached normal, and the lymphadenopathy vanished. We were disappointed, however, when we found that three of four of his marrow cells were male, and one was his donor sister's. This situation is not uncommon in cases of adult chronic myelogenous leukemia and has also been reported in juvenile chronic myelogenous leukemia after bone marrow transplantation.⁵² The finding is a failure of full engraftment due to an inadequate graft-versus-leukemia effect and a tendency to "underdose" infants when one undertakes cytoreduction before transplantation. We subsequently transfused whole blood from the sister to induce further graft-versus-host disease and enhance the graft-versus-leukemia effect. That approach in adults has been described recently.⁵³ We then gave mononuclear-cell transfusions from the sister over a period of four weeks. With the first two infusions we produced some graft-versus-host disease but not enough to be effective, so we are continuing that treatment.

ANATOMICAL DIAGNOSIS

Juvenile chronic myelogenous leukemia.

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