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Case 4-2011: A 4-Year-Old Boy with Back Pain and Hypercalcemia

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PRESENTATION OF CASE

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Dr. Lisa Charo Bain (Pediatrics): A 4-year-old boy was admitted to this hospital because of back pain and refusal to walk.

One week before admission, the patient fell from a single step, after which he reported pain in his lower back and buttocks, which worsened during the following week and was not relieved by acetaminophen. He walked less and slept more than usual. Three days before admission, he was unable to walk more than two steps before falling. His family took him to the emergency department of another hospital. Radiographs of the hips were reportedly normal, and he was discharged home with acetaminophen for pain.

Two days before admission, the patient was found lying on his side in the bathroom, crying; he refused to walk or stand and needed assistance with sitting, because of low back pain. He appeared hot and flushed and asked that shouting be stopped, although there was no shouting; a temperature was not recorded. The next day, the temperature rose transiently to 37.8°C, and oral intake and urine output decreased. On the day of admission, he refused to get out of bed, and his parents brought him to the emergency department of this hospital.

Constipation and hard stools had developed during the previous 5 weeks; the patient's last bowel movement had been 3 days earlier. He had refused to use the toilet and had worn diapers for the previous 3 days. He reported occasional chest and abdominal pain. He seemed to feel more comfortable lying on his left side, and he reported pain predominantly in the lower back. He had been born after a full-term gestation and had had weakness in the right arm since birth, due to right shoulder dystocia; he had otherwise been well and had received all childhood immunizations. He lived with his parents and siblings and attended day care. His father reportedly had a kidney problem; there was no family history of childhood cancers.

On examination, the patient was alert. The temperature was 37.2°C, the blood pressure 97/52 mm Hg, the pulse 113 beats per minute, the respiratory rate 26 breaths per minute, and the oxygen saturation 100% while he was breathing ambient air. The weight was 15.9 kg. The abdomen was soft and neither distended nor tender, and there was no organomegaly or mass. There was tenderness in the lumbosacral region over the bones and paraspinal muscles, more on the left side than on the right side. Pain increased with sitting and leg flexion. Deep-tendon reflexes in the

legs were brisk and symmetric, and plantar responses were flexor; the remainder of the physical and neurologic examinations was normal. The levels of glucose, total protein, albumin, globulin, total and direct bilirubin, alkaline phosphatase, alanine and aspartate aminotransferases, amylase, uric acid, and alpha-fetoprotein were normal, as were tests of renal function and coagulation and a urinalysis; other results are shown in Table 1. Radiographs of the chest were normal, and an abdominal radiograph showed a large amount of feces in the rectum; no other abnormalities were noted. Normal saline was administered intravenously, and acetaminophen and codeine were given orally for pain. The patient was admitted to the hospital.

On the first day, the findings on magnetic resonance imaging (MRI) of the lumbar spine with the administration of gadolinium were considered to be normal. The level of angiotensin-converting enzyme was normal; other laboratory-test results are shown in Table 1. Examination by a neurologist revealed one café au lait lesion (2.5 cm by 1 cm) on the right side of the back and one hypopigmented area on the left thigh. Decreased extension of the right arm at the elbow, which the patient's mother indicated had been present since birth; brisk deep-tendon reflexes (2+); and bilateral clonus, more on the right side than on the left side were observed. The left plantar reflex was equivocal and possibly extensor; the right was flexor. The patient could sit up with minimal help, without ataxia, and refused to walk because of back pain; the remainder of a detailed neurologic examination was normal. A glycerin suppository was administered, and after his mother carried him to the bathroom, a soft stool was produced. Radiographs of the lumbosacral spine showed diffuse osteopenia, slight anterior wedging of the 11th thoracic and 1st lumbar vertebral bodies, and mild loss of height in the 4th lumbar vertebral body. The sacrum was obscured by bowel gas. Ultrasonography of the kidneys and bladder showed normal kidney parenchyma and size, as well as echogenic debris in the bladder, with no nephrocalcinosis or kidney stones.

Overnight, episodes of asymptomatic bradycardia (heart rate <60 beats per minute) were noted, and an electrocardiogram was otherwise normal. Ketorolac tromethamine was administered, with improvement in the pain scores.

On the third hospital day, MRI studies of the

brain, without gadolinium, were interpreted as normal. MRI of the spine and pelvis revealed diffuse T₁-weighted hypointensity of the vertebral bodies throughout the spine and superimposed compressive deformities of several mid-to-lower vertebral bodies of the thoracic and lumbar spine. In retrospect, these changes had been present on earlier studies. Laboratory-test results are shown in Table 1. The temperature remained normal.

On the fifth day, a diagnostic procedure was performed.

DIFFERENTIAL DIAGNOSIS

Dr. Chadi M. El Saleeby: I cared for this patient and am aware of the diagnosis. This patient's complex symptoms necessitated a prompt, three-pronged plan of care. First, his severe pain required age-appropriate assessment and interventions. Second, his serum calcium level was critically elevated, which affected multiple organ systems and required immediate attention. Third and equally important, a unifying cause of these problems needed to be identified.

ASSESSMENT AND MANAGEMENT OF PAIN

This patient was in obvious pain. Pain is often overlooked or inadequately treated in pediatric patients¹⁻³; it is our policy to routinely assess hospitalized patients for pain. We needed to assess the severity of this patient's pain to determine its optimal management. We use standardized scales that take into account behavioral observations for infants and toddlers and self-reports for older children.^{4,5} For a child 3 years old or younger, we would have used the FLACC (face, legs, activity, cry, and consolability) Behavioral Pain Assessment scale.⁴ In patients who are 4 to 7 years of age, self-reporting is usually possible, so for this patient we used the Wong-Baker "faces" pain-rating scale, which involves diagrams of faces showing various degrees of happiness or sadness.⁵ If he had been more than 7 years of age and able to understand the concept of rank and order, we would have used a numeric rating scale. All tools for the assessment of pain in pediatric patients are based on a scale of 0 to 10, with 0 indicating no pain and 10 indicating the most severe pain. At presentation, on the faces scale, the patient ranked his pain at 0 at rest and 6 or 7 intermittently with activity.

Our initial choice of analgesics was based on the severity of pain, as it is in all cases; to prevent adverse effects, we choose the lowest effective

Table 1. Laboratory Data.*

Variable	Reference Range, Age-Adjusted†	On Admission	Day 1	Day 3
Hematocrit (%)	34.0–40.0	31.1		
Hemoglobin (g/dl)	11.5–13.5	11.5		
White-cell count (per mm ³)	5500–15,500	8300		
Differential count (%)				
Neutrophils	27–55	67		
Lymphocytes	36–52	26		
Monocytes	4–11	5		
Eosinophils	0–8	1		
Basophils	0–3	1		
Platelet count (per mm ³)	150,000–450,000	264,000		
Mean corpuscular volume (μm ³)	75–87	75		
Erythrocyte sedimentation rate (mm/hr)	0–11	49		
Sodium (mmol/liter)	135–145	134		141
Potassium (mmol/liter)	3.4–4.8	4.0		4.1
Chloride (mmol/liter)	100–108	95		105
Carbon dioxide (mmol/liter)	23.0–31.9	23.8		21.6
Phosphorus (mg/dl)	4.5–5.5	5.7	4.3	5.2
Magnesium (mmol/liter)	0.7–1.0	0.8	0.6	0.6
Calcium (mg/dl)	8.5–10.5	15.5	12.4	11.5
Ionized calcium (mmol/liter)	1.14–1.30		1.63	
Lactate dehydrogenase (U/liter)	110–210	384		
Lipase (U/dl)	13–60	84		
Creatine kinase (U/liter)	60–400 (boys)	42		
C-reactive protein (mg/liter)	<8.0	19.1		
25-Hydroxyvitamin D (ng/ml)	>32		15	
1,25-Dihydroxyvitamin D (pg/ml)	24–86		<9	
Thyroxine (μg/dl)	4.5–10.9		11.3	
Free thyroxine (ng/dl)	0.9–1.8		1.3	
Thyrotropin (μU/ml)	0.40–5.00		2.27	
Parathyroid hormone (pg/ml)	10–60		5	
Spot urine sample				
Calcium (mg/dl)	Not defined		27.7	
Creatinine (mg/ml)	Not defined		0.15	
Calculated calcium:creatinine ratio	<0.21		1.85	

* To convert the values for phosphorus to millimoles per liter, multiply by 0.3229. To convert the values for magnesium to milligrams per deciliter, divide by 0.4114. To convert the values for calcium to millimoles per liter, multiply by 0.250. To convert the values for ionized calcium to milligrams per deciliter, divide by 0.250. To convert the values for thyroxine to nanomoles per liter, multiply by 12.87. To convert the values for free thyroxine to picomoles per liter, multiply by 12.87.

† Reference values are affected by many variables, including the patient population and the laboratory methods used. The ranges used at Massachusetts General Hospital are age-adjusted and are for those who are not pregnant and do not have medical conditions that could affect the results. They may therefore not be appropriate for all patients.

dose. A general guide for pediatric analgesia at our hospital suggests the use of acetaminophen and nonsteroidal antiinflammatory drugs, singly or in combination, for mild pain (score, 1, 2, or 3); acetaminophen with codeine or intravenous ketorolac or both for moderate pain (score, 4, 5, or 6); and opioids with morphine, unless contraindicated, for severe pain (score, 7 through 10).

This child's pain was initially rated in the moderate range and was controlled with oral acetaminophen with codeine, followed by intravenous ketorolac. However, pain scores escalated on hospital days 3 and 4, ranging from scores of 4 to 8 at rest and 8 with activity, and periodic intravenous morphine and subsequently patient-controlled administration of morphine with continuous infusion were introduced. Unfortunately, hypoxemia and bradypnea developed in association with mounting doses of morphine, and we needed assistance from the pediatric pain team to fine-tune the drip. Despite these measures, the patient remained unable to walk during the first 5 days.

TREATMENT OF SYMPTOMATIC HYPERCALCEMIA

This patient's serum calcium level was more than 15 mg per deciliter (3.8 mmol per liter). Symptoms of hypercalcemia are dependent on both the serum level of calcium and the rate of rise. With mild hypercalcemia (<12 mg per deciliter [3 mmol per liter]), patients are usually asymptomatic. With moderately elevated calcium levels (12.0 to 13.5 mg per deciliter [3.0 to 3.4 mmol per liter]), weakness, anorexia, constipation, polyuria and polydipsia due to intravascular volume contraction usually develop. Severe hypercalcemia (>13.5 mg per deciliter), as seen in this patient, can manifest as a life-threatening metabolic emergency with cardiac and central nervous system effects including encephalopathy, seizure, and coma. This patient had constipation, anorexia, dehydration, abdominal pain, and polyuria on presentation. Of particular concern were his history of auditory hallucinations and somnolence with a depressed affect, reflecting central nervous system involvement. Thus, his hypercalcemia required urgent treatment.

The patient was vigorously hydrated with normal saline to replenish intravascular volume, dilute the serum calcium, and enhance renal calcium excretion. If calcium levels had not responded promptly after volume repletion, we would have considered administering furosemide to enhance

calciuresis. Although calcitonin and a bisphosphonate have been used in recalcitrant cases, experience with the use of bisphosphonates in children is limited and there are concerns about side effects.^{6,7} This patient had prompt improvement of his serum calcium level within 24 hours after therapy (Table 1), and his alertness and affect also improved.

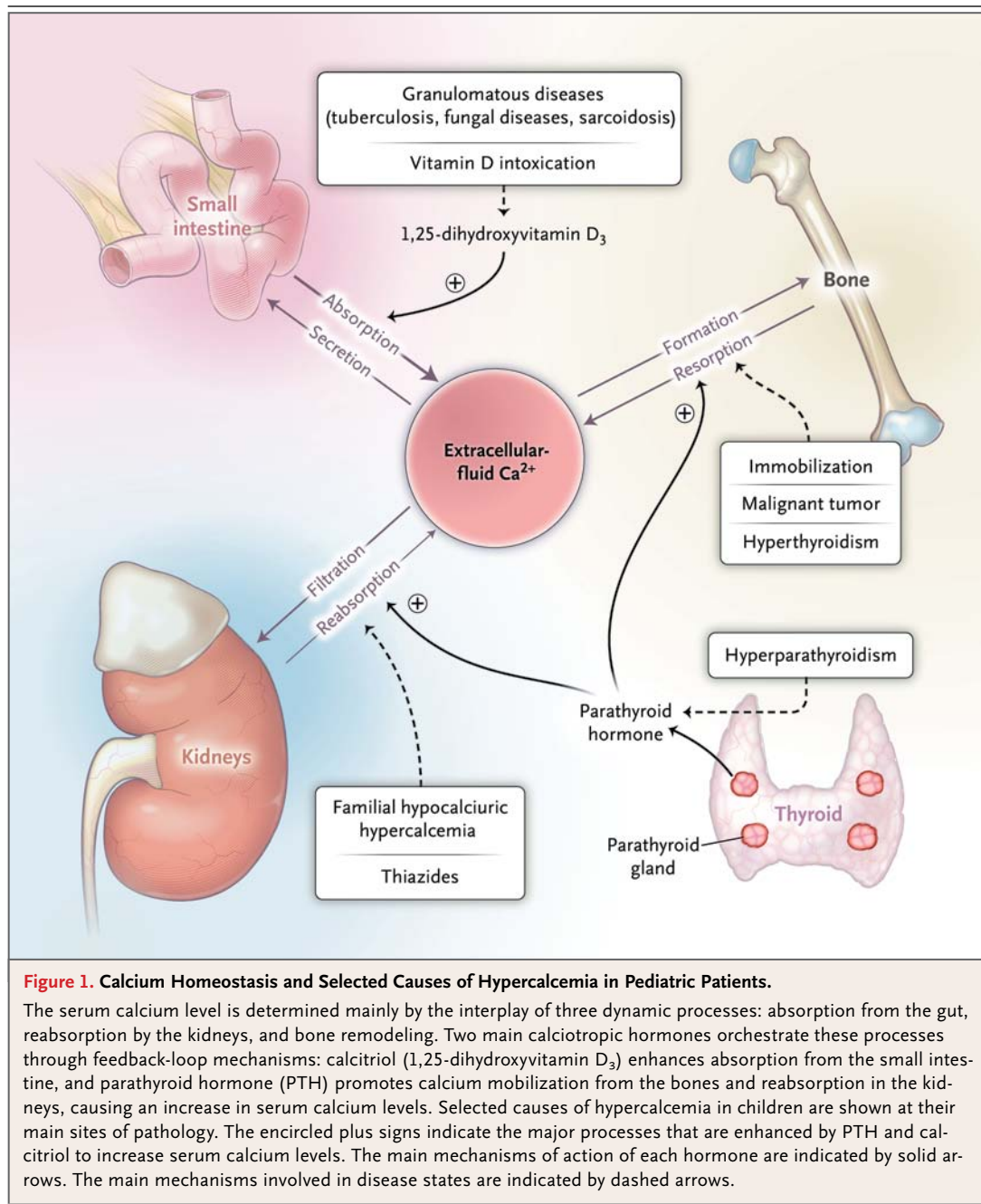
DIFFERENTIAL DIAGNOSIS OF HYPERCALCEMIA

Hypercalcemia is uncommon in children. The most common causes of hypercalcemia in adulthood are primary hyperparathyroidism and malignant tumors; those in children are more diverse (Fig. 1). Evaluation of pediatric hypercalcemia necessitates a systematic approach. Physical examination is usually not helpful, but the underlying process can often be identified with the use of a short biochemical evaluation, including studies of urinary calcium excretion and serum levels of intact parathyroid hormone (PTH), phosphate, vitamin D, and PTH-related protein (PTHrP).⁸

This patient had hypercalciuria (calcium:creatinine ratio from a spot urine sample, 1.85; normal for age, <0.21), effectively ruling out familial hypocalciuric hypercalcemia, a relatively common but usually asymptomatic cause of mild pediatric hypercalcemia caused by a mutation in the calcium-sensing receptor, that leads to increased renal tubular reabsorption of calcium and low urinary calcium and, in most cases, normal PTH values.⁹ Primary hyperparathyroidism is unusual in young children,¹⁰ with less than 0.5% of all cases manifesting before the patient is 10 years of age. PTH was suppressed in this patient, ruling out this diagnosis.

Toxic effects of thiazide diuretics or other hypercalcemia-causing substances (e.g., lithium and vitamin A or D) were ruled out by meticulous history taking and normal vitamin D levels. Normal calcitriol levels also ruled out infectious and non-infectious granulomatous disorders that could be associated with ectopic production of vitamin D. In the newborn, hypercalcemia may be caused by subcutaneous fat necrosis, a rare entity of the neonate that is usually associated with traumatic delivery or perinatal asphyxia.

Hyperthyroidism, prolonged immobilization (>2 weeks), or malignant tumors can precipitate hypercalcemia that is due to a pathological increase of bone resorption. Results of this patient's thyroid tests were normal, and at presentation, he had been bedridden for about 1 week. Hyper-



calcemia that is associated with malignant disease is rare in children,¹¹ but when present, it is usually due to bone destruction either directly, by the tumor or tumor metastases, or after the production of lytic factors (e.g., PTHrP, interleukins, or prostaglandins).¹² This patient's PTHrP level was pending at the time of the diagnostic procedure but was later reported as undetectable.

After this extensive workup, we suspected either an occult cancer (with or without the pro-

duction of PTHrP) or, less likely, an occult vertebral fracture that had caused immobilization owing to pain, with resulting hypercalcemia.

DIFFERENTIAL DIAGNOSIS OF BONE PAIN IN CHILDREN

Dr. Brian E. Grottkau: I was asked to see this child because of his acute back pain and limping. Back pain is surprisingly frequent in children, but in this case it was long-lasting, which is unusual. The

most likely cause of the patient's limping was pain, which results in an antalgic gait; other causes we considered included proximal muscle weakness, which can cause Trendelenburg's gait; limb-length discrepancy, which causes a short-leg gait; and diseases affecting the spinal pyramidal tracts, which can cause a spastic gait. We could not evaluate this patient's gait, because the pain was so severe that he refused to walk. Our differential diagnosis included trauma, infection, osteochondrosis, inflammatory processes, and neoplasms.

An important consideration in this young child was either a fracture of the tibia (toddler's fracture) or a nondisplaced physeal fracture of a long bone, both of which are common in toddlers and young children, and both of which result in an antalgic gait pattern or a refusal to bear weight on the involved leg.^{13,14} Radiographs are frequently normal, at least initially, as they were in this case; abnormalities may appear after 2 weeks or so during the healing process.¹³ Tibial fractures are characterized by pain on palpation along the shaft of the tibia and pain with external rotation of the tibia relative to the femur. Physeal fractures are generally characterized by pain on palpation over the involved growth plate, with or without swelling in the region. This patient's pain and tenderness on examination were limited to the back.

We also considered infectious causes, including osteomyelitis, spondylodiskitis, and septic arthritis, which are typically characterized by fevers, with an elevated erythrocyte sedimentation rate and C-reactive protein level, present in this case; blood cultures are negative in more than half of untreated patients.¹⁵ Pain is associated with motion of the involved joint in septic arthritis and with weight bearing and palpation in osteomyelitis. Finally, we considered Lyme disease, which is endemic in the northeast region of the United States and is characterized by acute synovitis that results in joint pain and a positive Lyme titer.¹⁶

Legg-Calvé-Perthes disease, an osteochondrosis of the femoral head in children, usually presents with a painless limp; pain is elicited in the hip during range-of-motion testing. There may be no radiographic abnormalities initially; later, radiographic findings may include subchondral flattening of the femoral head, a feature that is consistent with early osteonecrosis.¹⁷ Inflammatory causes of back pain and refusal to walk, including juvenile rheumatoid arthritis and other inflammatory arthritides, are generally character-

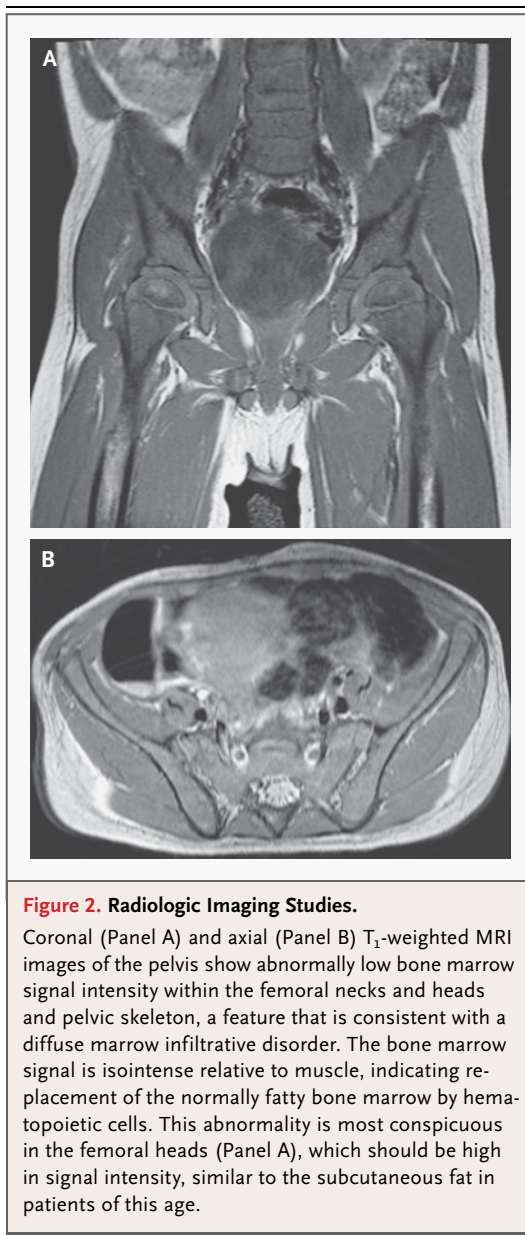
ized by a positive family history, with or without positive tests for antinuclear antibody and rheumatoid factor, and thus seemed unlikely.¹⁸

Vitamin deficiencies were also considered; vitamin C and vitamin D deficiencies (resulting in scurvy and rickets, respectively) can be seen in this age group and result in bone pain and the gradual inability to walk. The rapid onset of this patient's pain argues against vitamin deficiency as a cause, and although his serum vitamin D levels were low, the severe hypercalcemia would be unusual.

Finally, the patient's symptoms could be caused by a neoplastic process. Childhood leukemia is manifested with bone pain in 20% of the cases.¹⁹ Radiographic abnormalities include metaphyseal bands and osteopenia. Fevers, pallor, lymphadenopathy, hepatosplenomegaly, and easy bruisability are signs of leukemia that were absent in this case. Intracranial and intraspinal tumors must be ruled out; patients with these tumors may present with headache or back pain, long-tract signs, and other neurologic abnormalities. Ewing's sarcoma is an uncommon cancer that can occur in this age group. Children generally present with constitutional symptoms, bone pain, and radiographic abnormalities within the diaphyseal region of long bones or within the pelvis.²⁰ Neuroblastomas from abdominal or other primary sites need to be ruled out by means of physical examination and imaging. Eosinophilic granuloma of bone (Langerhans'-cell histiocytosis) can be manifested with vertebral collapse and pain.

This 4-year-old boy had severe, debilitating back pain that had progressed to the point at which he refused to walk and required a diaper. Because initial imaging studies had not provided an explanation for his pain, we repeated them and obtained additional studies.

Dr. Sjirk J. Westra: I became involved in the care of this child on the third hospital day, when I analyzed the repeated spinal and new pelvic MRI studies that had been obtained in an effort to find an explanation for his persistent bone pain. I noticed that the signal intensity of the patient's bone marrow was diffusely low on the T₁-weighted images (Fig. 2 and 3A), a finding that was most conspicuous in the femoral heads (Fig. 2A). In normal development, there is a gradual transition from hematopoietic marrow, which normally populates the entire skeleton in newborns and confers a low signal intensity on T₁-weighted images, to fatty marrow, which becomes more



prevalent in the appendicular skeleton than in the axial skeleton as children mature and confers high signal intensity on T₁-weighted images.^{21,22} This conversion progresses in an orderly fashion from diaphysis to metaphysis and from the peripheral marrow to the central marrow. In this patient, we should have seen high T₁-weighted signal intensity in the bone marrow in most locations. Since there were no corresponding abnormalities of the bone marrow signal on the fat-suppressed, T₂-weighted images (there was no bone marrow edema) and there was no abnormal enhancement after the administration of

gadolinium, I suspected that there was a diffuse marrow-replacing neoplastic process, such as leukemia or lymphoma, or a storage disease such as Gaucher's disease. There was no evidence of a primary tumor (neuroblastoma is the most common in patients at this age) to suggest diffuse metastatic disease.

Plain-film radiographs showed diffuse osteopenia of the spine, with mild wedge deformities from osteoporotic compression fractures (Fig. 3C); the lack of increased T₂-weighted signal intensity on MRI indicated that these were chronic. Areas of metaphyseal demineralization were evident in the growth centers around the knee, reflecting a disturbance at the growing ends of the bone caused by the packing of the marrow with neo-plastic cells (Fig. 3D).

Dr. Grottkau: In view of the findings on the imaging studies, a number of diagnoses could be eliminated, including infection, Legg–Calvé–Perthes disease, inflammatory conditions, and neuroblastoma. Instead, diffuse marrow processes such as leukemia and Gaucher's disease topped the list. The characteristic Erlenmeyer-flask deformity of Gaucher's disease (flaring of the long-bone metaphyses due to interruption of normal remodeling) was not seen, which suggests a more acute process such as leukemia.

Dr. Alison M. Friedmann: When I was first asked to see this boy, he had been in the hospital for 4 days. The pertinent features that I considered were hypercalcemia, which had improved with hydration; severe back pain and refusal to walk; imaging studies showing osteopenia and diffuse signal abnormalities in the bone marrow; and mild anemia.

In contrast to adults with malignant tumors, approximately 20 to 30% of whom have hypercalcemia,²³ only 0.4 to 0.7% of pediatric cancer patients present with hypercalcemia.^{11,24} Hypercalcemia occurs in association with rhabdomyosarcoma, hepatoblastoma, some brain tumors, neuroblastoma, and hematologic cancers, including lymphoma and acute leukemia. The imaging studies did not show evidence of an extramedullary primary tumor, such as an abdominal mass to suggest neuroblastoma. In two large series, hypercalcemia was reported in 0.3 to 0.4% of patients with acute leukemia; all but one of the patients had acute lymphoblastic leukemia (ALL).^{11,25}

Bone pain is a more common presenting feature in patients with acute leukemia than is hy-

percalcemia; bone pain is also more common in ALL than in acute myeloid leukemia (AML) and is more common in children than in adults.²⁶⁻²⁹ It is interesting that most patients with hypercalcemia, including this patient, have bone pain as a prominent symptom, and patients with bone pain or hypercalcemia often do not have the striking abnormalities in the complete blood count that are typically present at the time of diagnosis of ALL.^{11,25,30} Thus, ALL should be considered in the differential diagnosis of bone pain or hypercalcemia in a child, even in the presence of a normal complete blood count.

Therefore, our leading diagnosis was acute leukemia, most likely ALL. We recommended a repeat complete blood count and a bone marrow aspiration, which were performed on the fifth hospital day.

PATHOLOGICAL DISCUSSION

Dr. Aliyah R. Sohani: Samples of the bone marrow aspirate were sent for morphologic examination, flow cytometry, and cytogenetic analysis. Morphologic examination of the aspirate smear revealed a predominant population of small-to-medium-size cells that had finely dispersed nuclear chromatin, small prominent nuclei, and scant basophilic cytoplasm, features that are consistent with blasts (Fig. 4A). Review of a peripheral-blood smear from the time of the bone marrow procedure showed a small population of circulating blasts. According to flow-cytometric studies (Fig. 4B and 4C), the blasts were positive for the pan-B-cell marker CD19, CD10, and terminal deoxynucleotidyl transferase (an immature lymphoid marker) and weakly positive for CD45 (leukocyte common antigen), the mature B-cell marker CD20, and the stem-cell marker CD34, features that are consistent with a precursor B-cell phenotype. The findings in the bone marrow and peripheral blood were diagnostic of B lymphoblastic leukemia.

Further classification of B lymphoblastic leukemia relies on cytogenetic analysis.^{31,32} In many cases, cytogenetic abnormalities define specific entities that are associated with distinctive clinicopathologic features or that have important prognostic implications.³¹ In this patient, cytogenetic analysis revealed a normal male karyotype (46,XY). Fluorescence in situ hybridization showed normal numbers of chromosomes 4, 10, and 17 and no evidence of rearrangements involving TEL,

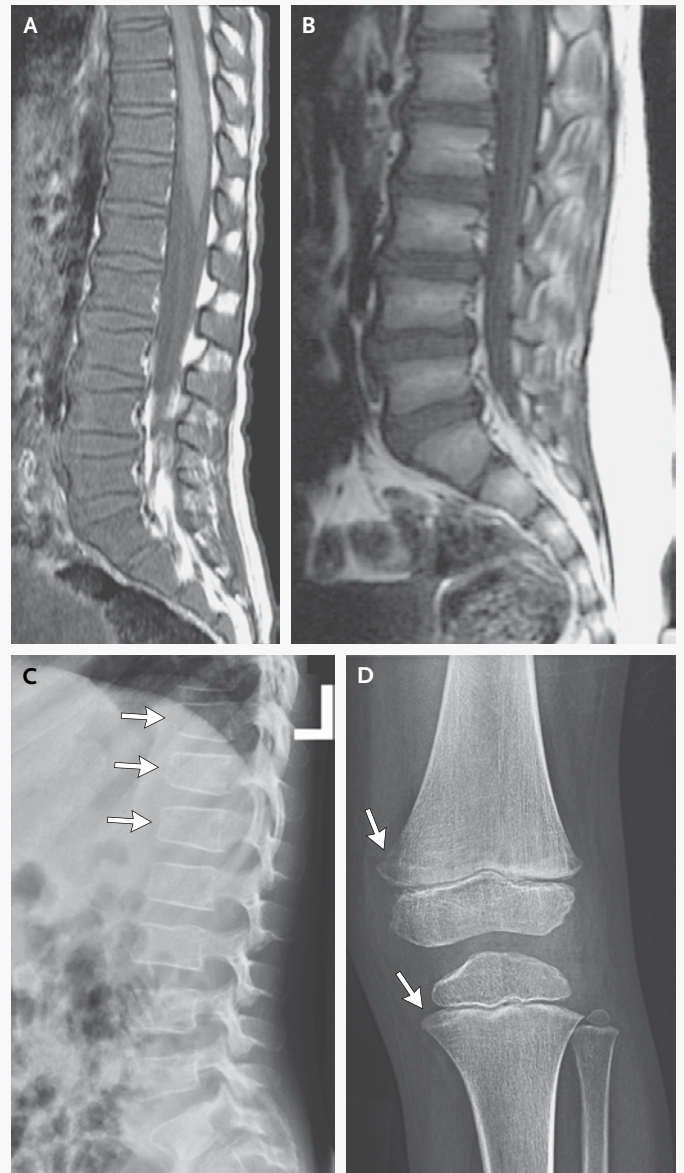


Figure 3. Radiologic Imaging Studies.

Sagittal T₁-weighted MRI of the lumbosacral spine (Panel A) shows abnormally low signal intensity in the vertebral bodies, which are hypointense as compared with the disks. Corresponding MRI of an age-matched normal child (Panel B) shows the higher signal intensity that is indicative of partial conversion of hematopoietic marrow to fatty marrow within the central portions of the vertebral bodies. Corresponding T₂-weighted and gadolinium-enhanced T₁-weighted images of the pelvic and axial skeleton of the patient (not shown) were normal, which indicated an absence of bone marrow edema and an absence of a focal tumor process. A lateral radiograph of the lumbar spine (Panel C) shows diffuse osteoporosis and anterior wedging of vertebral bodies at the thoracolumbar junction (arrows), due to osteoporotic compression fractures, which are subacute to chronic in nature. A frontal radiograph of the left knee (Panel D) shows metaphyseal lucent bands due to focal demineralization (arrows).

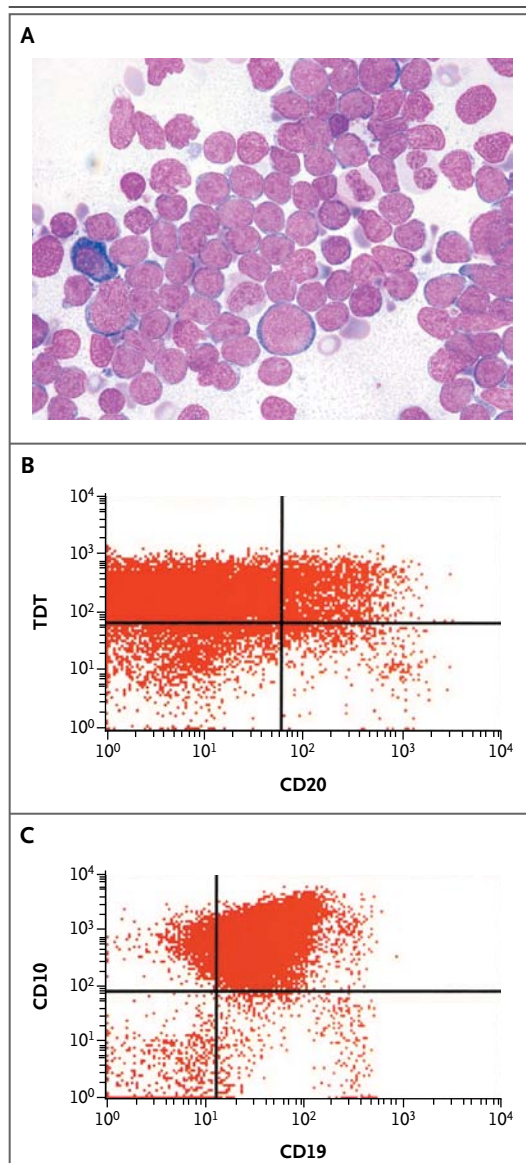


Figure 4. Findings on Examination of Bone Marrow Aspirate.

A smear from the bone marrow aspirate (Panel A, Wright-Giemsa) shows a predominant population of small-to-medium-size monomorphous blasts with finely dispersed nuclear chromatin, multiple small prominent nucleoli, and scant pale and basophilic cytoplasm. Flow-cytometric analysis of the bone marrow aspirate revealed a predominant population of blasts that were weakly positive for the mature B-cell antigen CD20 and positive for terminal deoxynucleotidyl transferase (TDT) (Panel B, anti-TDT fluorescein isothiocyanate and anti-CD20 peridinin chlorophyll protein); they were also positive for the pan-B-cell marker CD19 and for CD10 (Panel C, anti-CD10 phycoerythrin and anti-CD19 allophycocyanin). This immunophenotype is consistent with B lymphoblasts. Blasts were negative for the myeloid-associated antigens myeloperoxidase and CD117 (not shown).

AML1, BCR, ABL1, or MLL. Cases with normal cytogenetics are classified as B lymphoblastic leukemia, not otherwise specified; however, such cases may contain cryptic chromosomal rearrangements or genetic mutations that play a role in leukemogenesis and that may have specific clinicopathologic associations.^{33,34}

DISCUSSION OF MANAGEMENT

Dr. Friedmann: At the time of this boy's admission to the hospital, the complete blood count was fairly normal, showing only mild anemia. However, the complete blood count obtained 5 days later showed that the white-cell count had fallen from 8300 to 4300 per mm³, the hematocrit had declined from 31 to 25%, and on close inspection, there was a small number of circulating lymphoblasts. These changes illustrate the natural history of acute leukemia, in which an abnormal clone in the bone marrow gradually replaces the bone marrow and inhibits normal hematopoiesis and the peripheral blood contains increasing numbers of peripheral blasts and declining numbers of normal leukocytes, platelets, and red cells.

One day after the diagnosis of ALL was confirmed, a lumbar puncture was performed, with the administration of intrathecal methotrexate. The cerebrospinal fluid did not show evidence of leukemic cells. The patient was considered to have standard-risk ALL because of his age (older than 1 year and younger than 10 years) and the low white-cell count at diagnosis.³⁵ He started a standard three-drug induction regimen with daily dexamethasone, weekly vincristine, and a single dose of the polyethylene glycol (PEG) conjugate of L-asparaginase. He had a good response to treatment; his pain decreased within a few days. His pain management was transitioned from intravenous morphine sulfate to oral pain medications, and he was able to walk independently by the time of his discharge from the hospital, on day 10 of the induction therapy. The calcium level normalized on day 3 of induction therapy.

Bone marrow examination on day 13 of induction therapy showed no residual leukemic blasts, and flow-cytometric analysis of peripheral blood on day 29 of induction therapy showed less than 0.1% blasts, indicating a rapid early response to treatment. This information, together with the cytogenetic results, put the patient in a standard-risk group, according to the current Children's Oncology Group (COG) risk-group stratification.³⁶

The patient subsequently received multiagent chemotherapy according to the current COG trial for standard-risk ALL. He has suffered two major complications of treatment: pancreatitis, attributed to PEG-L-asparaginase and managed with supportive care; and a generalized tonic-clonic seizure, which occurred 4 months after diagnosis and 1 week after a lumbar puncture with intrathecal methotrexate. These are both well-described side effects of ALL therapy. He is currently doing well 2 years after diagnosis, is in complete remission, and is receiving maintenance chemotherapy on an outpatient basis, which will continue for a total of just over 3 years.

A Physician: Given the rapid change in the peripheral-blood smear but evidence of chronic changes in the patient's bones, do you have any idea how long the leukemia might have been present before it became apparent?

Dr. Westra: The presence of compression frac-

tures without edema suggests that it had been going on for a matter of weeks, not days.

Dr. Nancy Lee Harris (Pathology): This case illustrates the importance of experience and subspecialization in radiology. The initial MRI images were interpreted as normal; when the pediatric radiologist was consulted, the abnormality was recognized. The message for clinicians is that if the studies do not explain the symptoms, it may help to have someone else look at the studies.

ANATOMICAL DIAGNOSIS

B lymphoblastic leukemia, not otherwise specified.

This case was presented at the postgraduate course Primary Care Pediatrics, sponsored by the Harvard Medical School Office of Continuing Education.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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REFERENCES

1. The assessment and management of acute pain in infants, children, and adolescents. *Pediatrics* 2001;108:793-7.
2. Ellis JA, O'Connor BV, Cappelli M, Goodman JT, Blouin R, Reid CW. Pain in hospitalized pediatric patients: how are we doing? *Clin J Pain* 2002;18:262-9.
3. Taylor EM, Boyer K, Campbell FA. Pain in hospitalized children: a prospective cross-sectional survey of pain prevalence, intensity, assessment and management in a Canadian pediatric teaching hospital. *Pain Res Manag* 2008;13:25-32.
4. Merkel SI, Voepel-Lewis T, Shayevitz JR, Malviya S. The FLACC: a behavioral scale for scoring postoperative pain in young children. *Pediatr Nurs* 1997;23:293-7.
5. Wong DL, Hockenberry-Eaton M, Wilson D, Winkelstein M, Schwartz P. *Essentials of pediatric nursing*. St. Louis: Mosby, 2001.
6. Mathur M, Sykes JA, Saxena VR, Rao SP, Goldman GM. Treatment of acute lymphoblastic leukemia-induced extreme hypercalcemia with pamidronate and calcitonin. *Pediatr Crit Care Med* 2003;4:252-5.
7. Shaw NJ, Bishop NJ. Bisphosphonate treatment of bone disease. *Arch Dis Child* 2005;90:494-9.
8. Sperling MA. *Pediatric endocrinology*. 3rd ed. Philadelphia: Saunders Elsevier, 2008.
9. Brown EM. Familial hypocalciuric hypercalcemia and other disorders with resistance to extracellular calcium. *Endocrinol Metab Clin North Am* 2000;29:503-22.
10. Kollars J, Zarroug AE, van Heerden J, et al. Primary hyperparathyroidism in pediatric patients. *Pediatrics* 2005;115:974-80.
11. McKay C, Furman WL. Hypercalcemia complicating childhood malignancies. *Cancer* 1993;72:256-60.
12. Mundy GR, Guise TA. Hypercalcemia of malignancy. *Am J Med* 1997;103:134-45.
13. Tenenbein M, Reed MH, Black GB. The toddler's fracture revisited. *Am J Emerg Med* 1990;8:208-11.
14. Mizuta T, Benson WM, Foster BK, Patterson DC, Morris LL. Statistical analysis of the incidence of physical injuries. *J Pediatr Orthop* 1987;7:518-23.
15. Pääkkönen M, Kallio MJ, Kallio PE, Peltola H. Sensitivity of erythrocyte sedimentation rate and C-reactive protein in childhood bone and joint infections. *Clin Orthop Relat Res* 2010;468:861-6.
16. Steere AC, Glickstein L. Elucidation of Lyme arthritis. *Nat Rev Immunol* 2004;4:143-52.
17. Wada I, Horiuchi O, Wakabayashi K, Otsuka T. Bone disease with pain: Legg-Calvé-Perthes' disease (LCPD). *Clin Calcium* 2008;18:239-48. (In Japanese.)
18. Pugh MT, Southwood TR, Gaston JS. The role of infection in juvenile chronic arthritis. *Br J Rheumatol* 1993;32:838-44.
19. Nies BA, Kundel DW, Thomas LB, Freireich EJ. Leukopenia, bone pain, and bone necrosis in patients with acute leukemia: a clinicopathologic complex. *Ann Intern Med* 1965;62:698-705.
20. Grier HE. The Ewing family of tumors: Ewing's sarcoma and primitive neuroectodermal tumors. *Pediatr Clin North Am* 1997;44:991-1004.
21. Foster K, Chapman S, Johnson K. MRI of the marrow in the paediatric skeleton. *Clin Radiol* 2004;59:651-73.
22. Laor T, Jaramillo D. MR imaging insights into skeletal maturation: what is normal? *Radiology* 2009;250:28-38.
23. Stewart AF. Hypercalcemia associated with cancer. *N Engl J Med* 2005;352:373-9.
24. Leblanc A, Caillaud JM, Hartmann O, et al. Hypercalcemia preferentially occurs in unusual forms of childhood non-Hodgkin's lymphoma, rhabdomyosarcoma, and Wilms' tumor: a study of 11 cases. *Cancer* 1984;54:2132-6.
25. Inukai T, Hirose K, Inaba T, et al. Hypercalcemia in childhood acute lymphoblastic leukemia: frequent implication of parathyroid hormone-related peptide and E2A-HLF from translocation 17;19. *Leukemia* 2007;21:288-96.
26. Miller DR. Hematologic malignancies: leukemia and lymphoma. In: Miller DR, Boehrer, RL, eds. *Blood diseases of infancy and childhood*. 7th ed. St. Louis: Mosby, 1994:660-804.
27. Rogalsky RJ, Black GB, Reed MH. Orthopaedic manifestations of leukemia in children. *J Bone Joint Surg Am* 1986;68:494-501.
28. Appell RG, Bühler T, Willich E, Brandeis WE. Absence of prognostic significance of skeletal involvement in acute lymphocytic leukemia and non-Hodgkin lymphoma in children. *Pediatr Radiol* 1985;15:245-8.
29. Gallagher DJ, Phillips DJ, Heinrich SD. Orthopedic manifestations of acute

pediatric leukemia. *Orthop Clin North Am* 1996;27:635-44.

30. Jonsson OG, Sartain P, Ducore JM, Buchanan GR. Bone pain as an initial symptom of childhood acute lymphoblastic leukemia: association with nearly normal hematologic indexes. *J Pediatr* 1990; 117:233-7.

31. Borowitz MJ, Chan JKC. B lymphoblastic leukaemia/lymphoma with recurrent genetic abnormalities. In: Swerdlow SH, Campo E, Harris NL, et al., eds. WHO classification of tumours of haematopoietic and lymphoid tissues. 4th ed. Lyon, France: IARC Press, 2008:171-5.

32. *Idem*. B lymphoblastic leukaemia/lymphoma, not otherwise specified. In: Swerdlow SH, Campo E, Harris NL, et al., eds. WHO classification of tumours of haematopoietic and lymphoid tissues. 4th ed. Lyon, France: IARC Press, 2008:168-70.

33. Mullighan CG, Collins-Underwood JR, Phillips LA, et al. Rearrangement of CRLF2 in B-progenitor- and Down syndrome-associated acute lymphoblastic leukemia. *Nat Genet* 2009;41:1243-6.

34. Russell LJ, Capasso M, Vater I, et al. Deregulated expression of cytokine receptor gene, CRLF2, is involved in lymphoid transformation in B-cell precursor acute

lymphoblastic leukemia. *Blood* 2009; 114:2688-98.

35. Smith M, Arthur D, Camitta B, et al. Uniform approach to risk classification and treatment assignment for children with acute lymphoblastic leukemia. *J Clin Oncol* 1996;14:18-24.

36. Pui CH, Evans WE. Treatment of acute lymphoblastic leukemia. *N Engl J Med* 2006;354:166-78.

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