CLINICAL PROBLEM-SOLVING

Caren G. Solomon, M.D., M.P.H., *Editor*

A Deficient Diagnosis

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In this Journal *feature, information about a real patient is presented in stages (boldface type) to an expert clinician, who responds to the information, sharing his or her reasoning with the reader (regular type). The authors' commentary follows.*

A previously healthy boy, 2½ years of age, presented with a 6-week history of progressive inability to bear weight on his right leg. His mother noted no recent trauma and reported that his medical history was notable only for speech delay. He had received all the recommended vaccinations and took no medications. He had a slight cough. His mother thought that he felt warm, but a review of systems was otherwise unremarkable. His mother noted no change in his eating or drinking patterns, although she described him as a "picky eater."

This child's apparent inability to bear weight is a worrisome symptom with a broad differential diagnosis. Although no history of injury was reported, the possibility of accidental or nonaccidental trauma must be considered. Nontraumatic causes of gait disturbance include inflammatory, infectious, malignant, and neuromuscular conditions. Transient synovitis is the most common cause of hip pain and limp in young children and may follow a viral infection or trauma. Other possible inflammatory causes include juvenile idiopathic arthritis, myositis, and reactive arthritis. Infectious causes such as septic arthritis, soft-tissue or intraabdominal abscess, or osteomyelitis of the long bones, pelvis, or spine may manifest acutely and require urgent evaluation. The gradual progression of symptoms over a period of 6 weeks and the fact that the child did not look ill at presentation lower the likelihood of a bacterial infection. Mycobacterial, fungal, viral, rickettsial, and tick-borne infections may have a more insidious onset. Several neoplasms such as leukemia, lymphoma, skeletal metastases, primary bone tumors, and retroperitoneal tumors may cause limp and become apparent over this time frame. Determining whether this child is unable to bear weight because of weakness or is unwilling to bear weight because of pain may be helpful in narrowing the diagnosis, but this distinction can be difficult to make in a toddler.

The patient was initially evaluated by his pediatrician after 1 week of limping in which he favored the right leg. A radiograph of the right leg showed a possible fibular fracture. An orthopedic surgeon recommended repeat imaging after a period of relative inactivity. The patient continued to limp. Four weeks after the symptoms in his right leg began, he had signs of pain in the left leg. He began crawling instead of walking and cried when either leg was touched. He was taken to a community hospital for evaluation. Two days before that, his mother had noted that his gums were

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diffusely swollen. He had a black spot on the gingiva between his front teeth; her attempt to wipe it away had resulted in gingival bleeding.

Swollen, friable gingival mucosa can be related to gingival hematomas or an infiltrative process. Thrombocytopenia or other coagulopathy may manifest with gingival bleeding. Given the patient's painful limp and the radiographic evidence of a fibular abnormality, gingival swelling raises concern about an infiltrative process such as acute monocytic leukemia, Langerhans'-cell histiocytosis, or other forms of leukemia and lymphoma. Skeletal metastases from solid tumors — especially neuroblastoma, given our patient's age — may cause the patient to present with limp but would not cause these gingival changes.

On arrival at the emergency department of the community hospital, the patient was afebrile, his blood pressure was 128/51 mm Hg, and his pulse was 164 beats per minute (reference range for age, 90 to 150). Examination revealed an agitated toddler without spontaneous movement in the legs. Both legs were diffusely tender to palpation, with no evidence of bruising or joint swelling. Given concern about nonaccidental trauma, child protective services was notified, and radiographic studies were obtained. Computed tomography (CT) of the head was unremarkable. Skeletal survey showed mild angulation at the left medial proximal tibia, a finding that is consistent with normal osseous development rather than fracture. CT of both legs revealed no evidence of fracture, and the small effusions in the knees bilaterally were considered to be physiologic.

Laboratory studies revealed a normal comprehensive metabolic panel. The phosphate level was 3.4 mg per deciliter (1.00 mmol per liter; reference range, 3.8 to 5.8 mg per deciliter [1.20 to 1.90 mmol per liter]); the hemoglobin level 9.5 g per deciliter (reference range, 11.0 to 13.5); the white-cell count 10,700 per cubic millimeter, with a normal differential count; the platelet count 304,000 per cubic millimeter; the mean corpuscular volume 64.1 fl (reference range, 78 to 88); the ferritin level 71.5 ng per milliliter (reference range, 18 to 320); the percent transferrin saturation 3% (reference range, 20 to 50); the partial thromboplastin time 27 seconds (reference range, 22 to 27); the prothrombin time 14 seconds (reference range, 9 to 11); and the international normalized ratio 1.4 (reference range, 0.9 to 1.1). A peripheral blood smear showed hypochromia and microcytosis.

The differential diagnosis of microcytic, hypochromic anemia includes iron deficiency, lead poisoning, and chronic disease. In patients of Southeast Asian, Mediterranean, or African ancestry, thalessemia should be considered. In toddlers, iron-deficiency anemia is commonly the result of excessive consumption of cow's milk or limited intake of iron-rich foods. The mildly elevated international normalized ratio suggests factor VII deficiency; there was no reported family history of bleeding disorders. Dietary deficiency of vitamin K or ingestion of vitamin K antagonists such as rat poison or warfarin should be considered. Potential unifying diagnoses for anemia and weakness in the legs include spinal hematoma or cancer causing bone marrow infiltration, anemia, and spinal-cord compression. Inflammatory myositis or infectious myelitis may also cause weakness or paralysis and anemia associated with chronic inflammation. Further imaging would be helpful in evaluating for these disorders.

Magnetic resonance imaging (MRI) with angiography of the head revealed normal intracranial anatomy. MRI of the cervical, thoracic, and lumbar spine was unremarkable.

The normal results on MRI rule out a spinal-cord disorder, including compression of the spinal cord or nerve roots, tethered spinal cord, or the cauda equina syndrome. The Guillain–Barré syndrome is a consideration, although it is rare in children younger than 3 years of age and would not explain mild elevations in the prothrombin time and the international normalized ratio. In young children, the Guillain–Barré syndrome can manifest initially as poorly localized pain before weakness develops. The findings in the patient's legs are consistent with poliomyelitis, but that disease would be exceedingly rare in the United States in a vaccinated child.

Ascending paralysis related to the Guillain–Barré syndrome was suspected, and a lumbar puncture was performed. Cerebrospinal fluid findings included a white-cell count of 3 per cubic millimeter (reference range, 0 to 7), a glucose level of 53 mg per deciliter (2.9 mmol per liter; reference range,

40 to 80 mg per deciliter [2.2 to 4.4 mmol per liter]), and a protein level of 26 mg per deciliter (reference range, 5 to 40). After the lumbar puncture, a diffuse petechial rash developed. The patient was transferred to our university pediatric hospital for further evaluation.

The normal protein level in the cerebrospinal fluid does not support the diagnosis of either the Guillain–Barré syndrome or poliomyelitis. The differential diagnosis of weakness with a normal MRI and lumbar puncture includes myositis, botulism, or tick paralysis. Rickettisial diseases such as Rocky Mountain spotted fever also warrant consideration, given the musculoskeletal pain, agitation, coagulopathy, and petechial rash.

On transfer to our institution, the patient's oral temperature was 37.4°C, the blood pressure 112/62 mm Hg, and the pulse 174 beats per minute. The respiratory rate was 34 breaths per minute, and the oxygen saturation was 99% while the patient was breathing ambient air. The patient was pale but did not appear ill, and he cried throughout the examination. He had gingival hypertrophy with purplish discoloration of the mucosa between the teeth. There was a diffuse petechial rash with no additional stigmata of bleeding or bruising. Cardiovascular examination revealed a 2/6 systolic ejection murmur that was best heard at the left upper sternal border. Results of physical examination of the lungs and abdomen were normal. The patient held his legs in a frog-legged position; both legs were diffusely tender to palpation with mild, nonpitting edema and no appreciable joint swelling. Tone was diminished in all his arms and legs. He could wiggle his toes, but otherwise he did not actively move his legs or withdraw from painful stimuli. Biceps and brachioradialis reflexes were normal. Patellar reflexes were brisk. There was no ankle clonus. Toes went up bilaterally on plantar stimulation.

Hyperreflexia of the legs raises concern about myelopathy, but imaging did not indicate a spinal-cord disorder. The presence of intact reflexes and hyperalgesia is suggestive of peripheral neuropathy. Although acute inflammatory demyelinating polyradiculoneuropathy and multifocal neuropathy should be considered, there is no unifying neurologic diagnosis for our patient's constellation of symptoms. Serologic studies to evaluate for rheumatologic conditions such as systemic lupus erythematosus, vasculitides, or nutritional deficiencies may be useful.

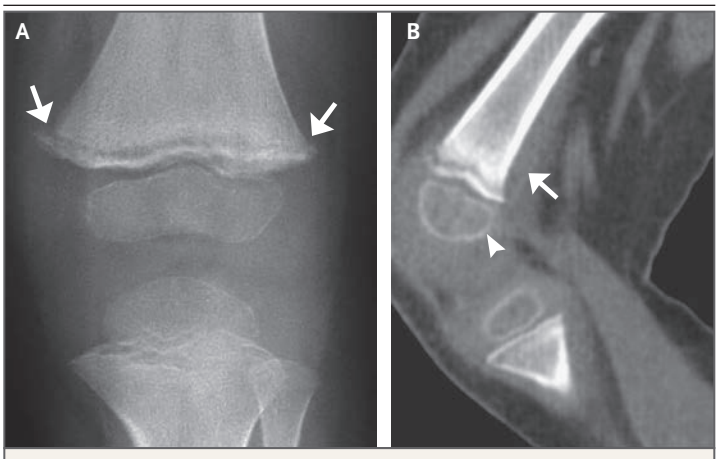

Figure 1. Radiograph and CT of the Femur.
A frontal radiograph of the left femur (Panel A) shows lucent metaphyseal bands (arrows) and subtle cortical thinning. A CT image in the sagittal view (Panel B) confirms the radiographic finding of submetaphyseal band (arrow). There is suggestion of subperiosteal fullness in the femoral metaphysis (arrowhead).

The erythrocyte sedimentation rate and the levels of C-reactive protein, creatine kinase, lactate dehydrogenase, aldolase, thyrotropin, free T_4, and vitamins D and B_{12} were within normal limits. An extractable nuclear antigen panel, rheumatoid factor test, and direct antiglobulin test were unremarkable. The folate level was 2.4 ng per milliliter (5.4 nmol per liter; normal value, ≥3.0 ng per milliliter [6.8 nmol per liter]). Serum samples were sent to an outside laboratory for measurement of vitamins A, B_1, B_2, B_3, B_6, C, and E. Screening for levels of heavy metals — arsenic, lead, mercury, and cadmium — was negative. Testing for the human immunodeficiency virus was negative. Imaging from the community hospital was reviewed by our pediatric radiologists. Lucent metaphyseal bands in the femurs were noted in the plain radiographs and CT scans of the legs (Fig. 1A and 1B).

The normal levels of inflammatory markers and negative serologic tests make connective-tissue disease unlikely. Lucent metaphyseal bands can be a normal variant in a growing child but may also be seen in patients with leukemia, metabolic abnormalities, or nutritional deficiencies such as rickets or scurvy.

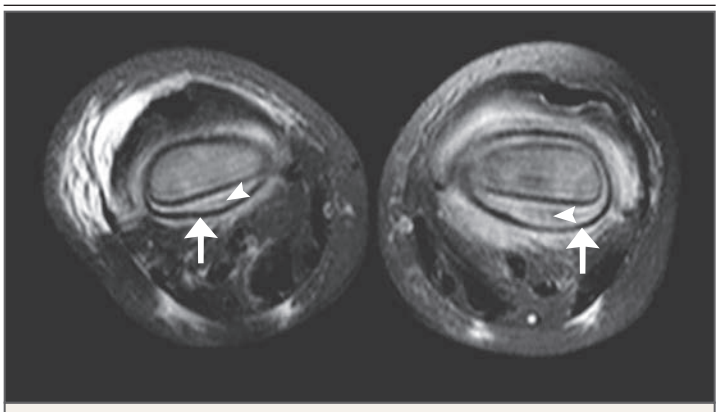

Figure 2. MRI of Distal Femurs.
An axial T_2-weighted fat-saturated MRI at the level of the distal femurs shows bilateral elevated periosteum (arrows) and a heterogeneous subperiosteal signal, possibly representing hematoma (arrowheads).

A bone marrow biopsy was negative for leukemia and for other malignant or infiltrative processes. Flow cytometry was negative for leukemia. Results of electromyelography and muscle biopsy were normal. Repeat MRIs of the total spine, obtained both with and without the use of contrast material, were also normal. MRI of both legs revealed bilateral periosteal elevation (Fig. 2).

Periosteal elevation on MRI is a nonspecific finding. Osteomyelitis is a recognized cause, but it is unlikely given the bilateral findings. Other causes include profound nutritional deficiency or hematologic cancer. This child was described as previously healthy except for a speech delay and as being a picky eater. A diet devoid of vitamin C could produce scurvy. Lack of vitamin C impairs collagen production and, as a result, blood-vessel integrity. Gingival bleeding is common, and subperiosteal hemorrhage may cause bone pain that is severe enough to cause pseudoparalysis. Scurvy can also cause neurologic abnormalities, including irritability, developmental delay, and hypotonia, as well as anemia. The radiographic findings in this patient, including lucent metaphyseal bands, peripheral calcification of the epiphysis, and periosteal elevation, are well-described findings in patients with scurvy.

A thorough dietary history revealed that the patient drank approximately 1.4 liters of chocolate milk and ate two to four graham crackers per day. His mother acknowledged that these items were the mainstay of his diet. A review of nutrition labels revealed a lack of vitamin C in these items. Supplemental ascorbic acid was started at a dose of 100 mg orally three times per day. His vitamin C level that had been drawn before the initiation of therapy was less than 0.1 mg per deciliter (10 μmol per liter; reference range, 0.6 to 2.0 mg per deciliter [30 to 110 μmol per liter]). Over the next several days, the patient began moving his legs. His gingival hypertrophy resolved within 1 week after starting supplementation. His skin was reexamined at the time the diagnosis was made, and his rash was noted to be consistent with follicular hyperkeratosis with perifollicular hemorrhage, a characteristic finding in patients with scurvy; the rash also resolved within 1 week. No "corkscrew" (twisted) hairs that are characteristic of scurvy were noted.

The combination of speech delay and restrictive eating habits raised concern about autism spectrum disorder; the patient was referred for evaluation by a behavioral specialist. He continued to receive vitamin C supplementation for 1 month and received a daily multivitamin and an oral nutritional supplement drink to maintain adequate vitamin and mineral levels. His mother reported that he began walking 10 days after discharge.

At a follow-up visit 4 months later, his hemoglobin level was 14.6 g per deciliter. A behavioral evaluation had not yet been performed, but his language skills had improved with speech therapy.

COMMENTARY

Our patient initially presented with an unwillingness to bear weight on the right leg. The differential diagnosis of limp in the pediatric population is broad and includes both localized and systemic disorders.[1] In our patient, the concomitant signs of hemorrhage, hyperkeratosis, hematologic abnormalities, and irritability were characteristic of scurvy.[1] However, this diagnosis is infrequently encountered in industrialized nations, and diagnosis is often delayed.[2-4] This patient's experience typifies the exhaustive workup that often ensues as clinicians attempt to identify a unifying diagnosis for this ominous constellation of symptoms.

Vitamin C deficiency emerged as a devastating disease between the 14th and 16th centuries, when sea voyages lengthened and sailors subsisted on diets devoid of fruits and vegetables. In 1747, Scottish surgeon James Lind conducted

what is considered to be the first controlled trial in medicine and determined that citrus fruits were curative of the disease[5] (see the Supplementary Appendix, available with the full text of this article at NEJM.org); however, the daily provision of lemon juice to sailors on long voyages was not implemented until the late 18th century.[6] Scurvy was effectively eradicated at sea but reemerged among the pediatric population during the 19th century, when heated milk and processed foods became staples in the diet of infants.[7]

Humans, unlike most animals, require exogenous intake of ascorbic acid for the biosynthesis and hydroxylation of hormones, neurotransmitters, and mature collagen.[6] Generalized symptoms of scurvy include fatigue, myalgias, arthralgias, weakness, anorexia, weight loss, and irritability. Dermatologic manifestations include follicular hyperkeratosis with perifollicular hemorrhage surrounding twisted, brittle hairs (corkscrew hairs), ecchymoses, poor wound healing, and swelling in the legs. In dentulous patients, gingival swelling and hemorrhage may occur.[6] Soft-tissue or subperiosteal hemorrhage, most commonly affecting the legs, may cause pain so severe that affected persons are unwilling to walk.[3,8] Left untreated, scurvy may result in cardiorespiratory failure and death, the mechanisms of which are incompletely understood.[6]

Anemia occurs in 75% of patients with scurvy[9] and is the only routine laboratory abnormality. Multifactorial causes of the anemia include blood loss into tissues or from the gastrointestinal tract, intravascular hemolysis, and coexisting folate and iron deficiencies.[9] Our patient had a microcytic, hypochromic anemia that was consistent with iron deficiency. Iron-deficiency anemia in children should prompt careful dietary review; cow's milk is a poor source of iron, and excessive consumption may satiate the child and decrease the ingestion of iron-rich foods.[10] Our patient's intake of milk was twice the recommended daily maximum, and simultaneous vitamin C deficiency adversely affected the absorption of iron. Coagulation abnormalities do not result from vitamin C deficiency[9]; given our patient's markedly restricted diet, the elevated prothrombin time and international normalized ratio suggest concurrent vitamin K deficiency.

The diagnosis of scurvy depends on history, physical examination, and clinical improvement after the administration of ascorbic acid; however, serologic and radiologic studies may also be helpful. Although a low plasma vitamin C level is specific for the diagnosis of scurvy, plasma vitamin C levels quickly normalize with enteral intake of ascorbic acid and do not reflect tissue levels.[11] In humans, leukocytes serve as a storage pool for ascorbic acid. The measurement of ascorbic acid levels in leukocytes may be considered, although such levels may not be easily obtainable and may also be affected by dietary intake.[11] Findings on plain radiographs include a lucent transverse metaphyseal band with an adjacent dense sclerotic band, metaphyseal spurring, and nonspecific evidence of diffuse osteopenia and cortical thinning.[12] MRI may reveal an abnormal bone marrow signal, periosteal elevation, and heterogeneous subperiosteal fluid consistent with hemorrhage.[12]

It is important that clinicians maintain a low threshold for considering scurvy in at-risk populations, including elderly persons, patients in psychiatric institutions, and persons with restrictive eating habits or alcohol use disorders.[13,14] Scurvy is rare among children[2] but has been described in children with autistic spectrum disorder, oral aversion, and global developmental delay.[2,3] Although much attention has been devoted to the learning and behavioral challenges facing patients with autism spectrum disorder, their feeding difficulties and resulting nutritional deficiencies are still underrecognized by many physicians.[15]

Our patient had speech delay, and the mother alluded to restrictive eating patterns early in the clinical history. Unfortunately, a comprehensive dietary review was performed only after an exhaustive and costly workup had been pursued. This circuitous diagnostic route frequently occurs when providers are faced with this rare, yet easily treated, condition.[4,5] Providers who are familiar with the clinical presentation of scurvy and are aware of the demographic groups that may be vulnerable to the condition will be equipped to make a diagnosis of vitamin C deficiency, thereby averting diagnostic deficiency.

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

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