A 16-Year-Old Girl with Leg Pain and Swelling

Robert Listernick, MD

A 16-year-old girl was admitted after a 2-month history of swollen, painful knees, ankles, and feet. She was well until 2 months before admission, when she started developing cramps in her legs without any inciting event. She went to her primary care physician, who sent her to an orthopedic surgeon. The surgeon performed X-rays and a bone scan, both of which were normal.

Subsequently, she was referred to a rheumatologist, who diagnosed her with juvenile idiopathic arthritis (JIA) and prescribed several different treatments that failed to alleviate her symptoms. At the time of admission, she was taking prednisone, methotrexate, hydroxychloroquine, salsalate, and folic acid. Her pain was worsening, so her family sought a second opinion. The second rheumatologist did not believe she had JIA, but increased the prednisone dose.

Throughout this time, the patient had increased pain and swelling in the joints of her legs. She was awaking with pain and had missed most of school during the past several months because of pain. There was no history of weight loss, fever, or other complaints.

Her past history is unremarkable. Her social history was unremarkable. Her family history was remarkable in that her mother had osteoarthritis and bursitis. There was no family history of rheumatologic disease.

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On physical exam, she was an alert, healthy-appearing young woman who was in mild discomfort when she moved. Her weight was in the 90th percentile and height greater than 95th percentile. Vital signs were unremarkable. There were no rashes. HEENT exam was unremarkable. Lungs were clear. S1 and S2 were normal without murmurs or rubs. Abdomen was soft without masses or organomegaly. She was Tanner 5. Multiple joints, including the knees, ankles, elbows, and fingers, were warm and swollen. There were bilateral knee flexion contractures. Neurologic exam was unremarkable.

Pertinent laboratory evaluation included: hemoglobin 10.1 g/dL, white blood cell count 13,000/mm³ with 61% neutrophils and 35% lymphocytes. Urinalysis had trace blood with 3 to 5 red cells/high-powered field. Serum chemistries were normal, save for albumin 2.7 mg/dL. Erythrocyte sedimentation rate was 27 mm/hour and C-reactive protein was 5.6 mg/dL.

Robert Listernick, MD, moderator: Her physical examination sounds very impressive.

Megan Curran, MD, pediatric rheumatologist: It was. After having seen lots of kids with arthritis over the years, her exam was different and unusual. There was more swelling around the bones than I’ve seen in children with arthritis. Her distal phalanges were swollen, which is an unusual finding in JIA. She also had dense painful swelling around her knees and her distal tibiae, which also didn’t resemble the findings generally seen in JIA.

Dr. Listernick: Was this different from digital clubbing?
Dr. Curran: Definitely. There was no hypertrophy of the nailbeds as one sees in clubbing. The main swelling was between the distal interphalangeal joints and the nailbed. This area was very tender, another finding not present in clubbing.

Dr. Listernick: There’s no definitive serologic marker of JIA, and there seem to be so many mimickers. I’ve seen children originally diagnosed with JIA who have, ultimately, had leukemia, Takayasu’s arteritis, or subacute bacterial endocarditis. How can you definitively diagnose JIA?

Dr. Curran: We’re particularly careful to not establish a firm diagnosis of JIA until we have eliminated malignancy and infection. Sometimes, it’s a clinical gestalt; sometimes, we’ll insist on a bone marrow examination before we start immunosuppressive therapy.

Dr. Listernick: Would there be abnormalities on the complete blood count that highlight the possibility of an infiltrative bone marrow process?

Joanna Weinstein, MD, pediatric hematologist: Generally, there will be a clue, such as blasts on the differential count or thrombocytopenia. However, there are cases in which the CBC is totally normal the first time it is checked. Children with leukemia may present with severe bone pain from a densely packed marrow. Rarely, we’ve even seen children with leukemia presenting with polyarticular arthritis.

Dr. Listernick: Perhaps we should outline the different subtypes of JIA.

Dr. Curran: Different groups have defined different subtypes. I prefer to use the International League of Associations for Rheumatology’s seven basic subtypes: systemic-onset JIA; persistent or extended oligoarthritis (four or fewer joints involved); rheumatoid factor positive polyarthritis; rheumatoid factor negative polyarthritis; psoriatic JIA; enthesitis-related arthritis (inflammation at the sites of ligamentous insertion on bones); and undifferentiated forms of arthritis.

Dr. Listernick: So when is “JIA” not JIA?

Dr. Curran: The “typical” teenager with polyarticular JIA is stiff and painful in the morning and feels much better by midafternoon. The pain our patient was experiencing and the presence of large, “boggy” joints were definitely not typical for JIA. Her lack of response to prednisone would have been abnormal for most cases of polyarticular JIA.

Dr. Listernick: What about the presence of joint contractures?

Dr. Curran: We see patients with contractures who have had symptoms long before diagnosis. The contracture develops because the joint is held in a fixed position because of pain, and the muscle tightens up from disuse.

Dr. Listernick: What is the role of laboratory testing in diagnosing JIA?

Dr. Curran: With this degree of diagnostic uncertainty, you can understand why we order so many tests. A great deal of the abnormal testing in JIA is not very specific: elevated total WBC counts; platelets; ESR; and CRP. We hope that the patterns of autoantibodies that we find will be helpful diagnostically.
Dr. Listernick: Her antinuclear antibody, rheumatoid factor, and anticytoplasmic nuclear antibody were all negative.

Dr. Curran: Unfortunately, not helpful since polyarticular JIA may be seronegative.

Dr. Listernick: When she arrived, we performed radiographs of her extremities.

Ellen Benya, MD, pediatric radiologist: There was intense periosteal new bone formation along the diaphyseal portions of her femurs, tibias, and fibulas bilaterally, as well as in the diaphysis of the long bones of both upper extremities. It’s fairly solid and uniform.

Dr. Listernick: Differential diagnosis?

Dr. Benya: This is extremely unusual. We can see periosteal new bone formation as a manifestation of leukemia or fluorosis or hypervitaminosis A, but generally it’s not as symmetric and diffuse as it is in this patient.

Dr. Weinstein: We can see “leukemia lines” or diffuse osteopenia in some patients, or discrete lytic lesions in children who have skeletal metastases, but nothing like this.

Dr. Listernick: For what it’s worth, she wasn’t receiving any over-the-counter or alternate and complementary formulations.

As in all clinicopathologic conferences, “a diagnostic study was performed.” Anyone care to name that diagnostic study?

Anonymous audience member 1: Synovial biopsy.

Anonymous audience member 2: Endoscopy looking for inflammatory bowel disease.

Anonymous audience member 3: Bone marrow biopsy.

Dr. Listernick: The correct answer is chest X-ray.

Dr. Benya: The chest X-ray revealed a round mass at the left lung base. The margins are distinct, making a “round pneumonia” unlikely. The lung base would be a good location for a pulmonary sequestration, although unlikely with this configuration. Other potential chest masses would include bronchogenic cyst or primary lung tumors, the latter being rare in children. Metastatic disease could be a possibility, but we would generally see multiple lesions.

Dr. Listernick: How should we proceed?

Dr. Benya: Computerized tomography (CT) of the chest would help decide if this was fluid-filled, as would be seen in bronchogenic cyst, or solid. We also could determine whether it has systemic arterial supply, making it a sequestered lung. We could see if there were smaller metastatic nodules not seen on chest X-ray. The CT scan revealed a solitary solid mass abutting the pericardium.

Dr. Listernick: The chest X-ray was performed because she had some nonspecific respiratory symptoms. It was only after she came here that our astute radiologist, Dr. Tamar Ben Ami, suggested the pathologic diagnosis.

Reema Jaffar, MD, pediatric pathologist: We received a well-circumscribed fleshy mass with several areas of calcification. The most prominent cell type was spindle-shaped cells, with eosinophilic cytoplasm that were myofibroblastic spindle cells. There were numerous plasma cells and lymphocytes. Immunohistochemical stains were negative for anaplastic lymphoma kinase (ALK). ALK staining may be positive either as the result of a fusion gene in several cancers (anaplastic large cell lymphoma,
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non–small cell lung cancer), or as a point mutation in some cases of familial neuroblastoma. However, this child’s final diagnosis is inflammatory myofibroblastic tumor (IMT), in which ALK is positive approximately half the time.

Dr. Weinstein: The literature on IMT is very confusing because it has been called various terms, including “inflammatory pseudotumor,” “plasma cell granuloma,” and “immune myofibroblastic tumor.” IMTs are classified as intermediate, rarely metastasizing neoplasms made up of dense, spindle-shaped myofibroblasts and surrounding mature lymphocytes and plasma cells. They may arise anywhere in the body, but most commonly in the lung, liver, bladder, and gastrointestinal tract.

Dr. Listernick: How do these tumors generally present clinically?

Dr. Weinstein: They may cause symptoms due to mass compression of adjacent structures. However, many of these tumors produce high levels of IL-6, which can lead to constitutional symptoms such as weight loss, recurrent fever, or chronic microcytic anemia refractory to iron therapy. Malignant transformation is uncommon.

Dr. Curran: There have been isolated case reports of secondary hypertrophic osteoarthropathy associated with IMTs. Presumably, the tumor elaborates growth factors such as vascular endothelial growth factor or platelet-derived growth factor, which lead to fibroblast proliferation and periosteal new bone formation.

Dr. Weinstein: The constitutional symptoms generally abate if the tumor is completely removed. There have been reports of using indomethacin to block the effects of the prostaglandin excess in children whose tumors could not be completely removed. I would expect that her bone disease will slowly disappear.

Dr. Listernick: Thank you, everyone.