Enthesitis as Initial Manifestation of Leukemia in a Pediatric Patient

Baruch Goldberg*

Department of Pediatrics, McGovern Medical School at UT Health, USA

Abstract

This case report highlights the importance of working through a differential diagnosis when a child presents with arthritis or enthesitis, as Juvenile Idiopathic Arthritis (JIA) is a diagnosis of exclusion. A twelve-year-old girl presented to clinic with chronic arthralgias, most notably in her ankles. Some of her symptomatology was characteristic of inflammatory arthritis - morning stiffness and limp. However, the pain was also worse with activity, better with rest, and with occasional night awakenings. Her physical exam revealed no arthritis but she did have enthesitis with swelling, warmth and tenderness over her posterior-lateral malleolus. Nonsteroidal anti-inflammatory drug (NSAID) therapy was started and she had blood work to further investigate the etiology of her enthesitis. Diagnostic considerations were concerning for HLA B27 associated enthesitis related arthritis, psoriatic JIA, Inflammatory bowel disease and chronic recurrent multifocal osteomyelitis. Laboratory findings showed elevated ESR and CRP consistent with inflammation. HLA B27, Rheumatoid Factor and ANA were negative. Her blood count showed mild leukocytosis and anemia. Her differential revealed 17% atypical lymphocytes and 30% blasts. LDH was 251 u/l [normal range 98-192u/l] and uric acid was 6.9 mg/dl [normal range 2.5-7.0mg/dl]. Her peripheral smear showed increased circulating blasts and flow cytometry was consistent with B cell Acute Lymphoblastic Leukemia. The importance of this case is to remember that musculoskeletal symptoms may precede constitutional symptoms in children with leukemia. Thus, it is essential to rule out other differentials prior to diagnosing JIA, especially prior to initiation of steroid or immunosuppressive therapies.

ABBREVIATIONS

JIA: Juvenile Idiopathic Arthritis; ERA: Enthesitis Related Arthritis; CBC: Complete Blood Count; CMP: Complete Metabolic Profile; ESR: Erythrocyte Sedimentation Rate; CRP: C-Reactive Protein; ANA: Anti-Nuclear Antibody; LDH: Lactate Dehydrogenase; ALL: Acute Lymphoblastic Leukemia

INTRODUCTION

Enthesitis is inflammation of an enthesis or insertion point where tendons, ligaments or joint capsules attach to bone. Enthesitis is a predominant feature of children with a subclass of juvenile idiopathic arthritis (JIA) called enthesitis related arthritis (ERA). JIA has an annual incidence rate of six per 100,000 cases in children making it the most common pediatric rheumatic disease [1]. Whereas oligoarticular and polyarticular JIA are subclasses defined by the number of affected joints with arthritis, ERA is categorized by arthritis and/or enthesitis with at least two other features including but not limited to inflammatory back pain or sacroiliac tenderness, presence of HLA-B27 antigen, or acute anterior uveitis. A minimum duration of 6 consecutive weeks of symptoms is necessary to meet criteria for JIA. Furthermore, JIA is a diagnosis of exclusion [2]. This allows for the natural course of transient or reactive processes to self-resolve. Thus, other diagnostic considerations must be ruled out such as trauma, overuse, infections, malignancy, and other autoimmune conditions associated with arthritis. This case emphasizes the essential rule that JIA is a diagnosis of exclusion and the importance of working through a differential prior to committing to a diagnosis of an idiopathic nature.

CASE PRESENTATION

This 12-year-old girl presented to rheumatology outpatient clinic with a chief complaint of arthralgias. Her arthralgias were reported to have started at the age of 4 years old and include her knees, elbows, wrists, low back, but most significantly in her ankles. Recently she felt her pains worsened but was unable to identify when this decline began. During this period, she saw a podiatrist who obtained x-rays of her feet which were reportedly normal. She was diagnosed with Sever’s disease and...
was referred to physical therapy. Her physical therapist referred her for rheumatologic evaluation due to concern for ongoing inflammation in her ankles after several sessions. She described her arthralgias as worsening with activity and unaffected by rest. She endorsed morning stiffness in her ankles lasting up to two hours; yet, evenings were the most painful part of the day for her. Her mother stated that sometimes her ankles would swell up making it difficult to see the outline of her ankle bones, yet this only lasted for a couple days at a time. On days with increased activity, the pain was so severe she would limp and at night would awaken from pain. She reported getting partial relief with an appropriate dose of ibuprofen and massage with essential oils.

Aside from her arthralgias, she endorsed occasional abdominal pain without associated constipation, diarrhea, bloody stools or changes in weight. She occasionally would have headaches that were short lived and responded to essential oil massages on her scalp. Mom remembered that her daughter would sometimes get “small red dots” on her legs that self-resolved after a couple days. Otherwise her review of systems was unremarkable with no history of fevers, psoriasis or other rashes, acute eye pain or vision loss, or ulcers. She is an adopted child and family history was unknown. Her physical exam was notable for warmth, swelling and tenderness overlying her posterior lateral malleolus on her left ankle without palpable joint effusion. Additionally, she had limited flexion in her low back without sacroiliac tenderness when trying to touch her toes.

An x-ray of her sacral joints was obtained and without radiographic abnormalities. A set of baseline screening labs were obtained including complete blood count (CBC), complete metabolic profile (CMP), Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), HLA-B27 antigen, rheumatoid factor, and anti-nuclear antibody (ANA). She was negative for HLA-B27, rheumatoid factor and ANA. Her CMP was unremarkable. ESR and CRP were elevated at 50mm/hr and 44.1mg/l (normal <2.9), respectively. CBC showed mild leukocytosis at 16.2 K/ CMM, mild normocytic anemia with hemoglobin of 10.6 g/dl and normal platelets. Differential on CBC showed 30% blasts and 17% atypical lymphocytes. LDH was elevated at 251 u/l (normal range: 98-192) and uric acid was in the upper limit of normal at 6.9mg/dl (normal range: 2.5-7.0). Peripheral smear revealed increased circulating blasts and flow cytometry showed an expanded population of B-lymphoblasts consistent with acute B-cell lymphoblastic leukemia.

DISCUSSION

In about 15-30% of children, acute lymphoblastic leukemia (ALL), the most common childhood malignancy, can initially present with musculoskeletal complaints prior to noticeable peripheral blood abnormalities [3]. Typically, children with ALL present with fevers, organomegaly, cytopenias and possible mucosal bleeding [4]. However, if blood findings are without expected cytopenias or blasts, then this can lead to incorrect diagnosis and delay in appropriate care. A study conducted by Jones, O, et al. in 2005 showed that the strongest factors associated with ALL rather than JIA were leucopenia, low to normal platelet counts and reported nightime awakenings due to pain [3]. With raised awareness to features that may not fit classic JIA, often times oncologic evaluation with possible bone marrow examination is needed to confirm suspicion of malignancy, especially if not yet evident in peripheral blood. This can be crucial as in some cases JIA may be treated with local or systemic steroids which may lead to partially treating malignancies or increasing resistance to chemotherapy.

Arthritis as a manifestation of ALL is typically secondary to bone or periosteal lesions [4]. Although no frank arthritis was found in this patient, her enthesitis could be reflective of nearby bone or periosteal involvement.

This twelve-year-old girl presented to the rheumatology outpatient clinic lacking the constitutional symptoms that could be suggestive of underlying ALL. Furthermore, her arthralgias per report were of a chronic nature. Although it is not plausible to attribute her chronic arthralgias to such a long duration of initial musculoskeletal manifestations secondary to ALL, per report her arthralgias had worsened recently - perhaps indicating a new acute on chronic process indicative of the developing malignancy. Her enthesitis plus suspicion for inflammatory back pain could give justice to ERA being on the differential; however, she did not have a history of acute anterior uveitis, ankylosing spondylitis, irritable bowel disease, or Reiter’s syndrome, and she lacked the presence of HLA-B27 antigen. Her elevated inflammatory markers and mild anemia, although can be seen in some subtypes of JIA, were more than typical for her clinical presentation. Her CBC unmasked 30% blasts lending to a high degree suspicion of leukemia which was subsequently confirmed by peripheral smear and flow cytometry.

Often times, for rheumatologists, one of the best tests for a suspected diagnosis is the test of time. Autoimmune diseases

Table 1: Criteria for Diagnosis of Enthesitis Related Arthritis.

<table>
<thead>
<tr>
<th>Enthesitis Related Arthritis Definition: Arthritis and enthesitis, or arthritis or enthesitis plus 2 or more of the following:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Sacroiliac joint tenderness and/or inflammation lumbosacral pain</td>
</tr>
<tr>
<td>2. Onset of arthritis in male older than 6 years of age</td>
</tr>
<tr>
<td>3. HLA B27 antigen positive</td>
</tr>
<tr>
<td>4. Acute symptomatic anterior uveitis</td>
</tr>
<tr>
<td>5. First degree relative with a history of ankylosing spondylitis, ERA, sacroiliates with inflammation bowel disease, Reiter’s syndrome, or acute anterior uveitis.</td>
</tr>
</tbody>
</table>

*Exclusive to this sub-classification apply to ensure all classification of JIA are mutually exclusive. The exclusions for ERA are history of psoriasis in patient of first degree relative diagnosis of systemic JIA, or presence of rheumatoid factor.
tend to develop over time, some with less acuity than others. This patient, although had exam findings consistent with enthesitis, shows us the importance of understanding JIA to be a diagnosis of exclusion with its own set of criteria. Fortunately, her diagnosis was secured via baseline and screening lab results. Yet, should her peripheral blood have not shown blasts, there would have been a delay in diagnosis and likely a poorer outcome. When dealing with diseases that are known mimickers, even the most classic of presentations are still at best - classic mimickers. Strong consideration should be given to leukemia on the initial differential of enthesitis or arthritis as both presentations relate to underlying bone involvement and may lack other key differentiating features early on.

REFERENCES