Case Report

A case of mistaken identity: an enthesitis-related arthritis case report

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ABSTRACT

Juvenile idiopathic arthritis is the most common inflammatory rheumatological condition affecting children. The condition stems from the inability of the immune system to discriminate between self and not-self leading to inappropriate immune reactions against joints. The different subtypes are differentiated by the number of joints involved and the presence or absence of certain exclusion factors. Due to overlapping diagnostic criterion and range of clinical presentation, diagnosis can be a difficult task. Our patient initially presented with joint swelling without pain that was initially diagnosed with traumatic swelling that later was considered to be of an infectious etiology. A biopsy revealed synovitis but current treatment for traumatic and infectious causes continued to fail. Finally, an additional joint showed inflammation leading to additional testing that uncovered that the patient was positive for HLA-B27 as well as a first degree relative with ankylosing spondylitis. This coupled with the inflammatory biopsy findings led to the diagnosis of juvenile idiopathic arthritis. The identification of an HLA-B27 positive patient is important as this population has been shown to have low rates of remission, resistance to certain treatments used for juvenile idiopathic arthritis, specifically DMARDS and corticosteroids which are often first line treatments for juvenile idiopathic arthritis. The HLA-B27 positive patient has also been shown to progress to axial involvement and joint destruction leading to earlier need for arthroplasties. As early identification is important in the determination to begin biologic treatments early in the disease course, physician should maintain a clinical suspicion for JIA when dealing with swollen joints in the pediatric population.

Keywords: Juvenile idiopathic arthritis, Rheumatoid factor, HLA B27, Pediatric, Auto inflammatory

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is a broad term that describes a clinically heterogeneous group of arthritides of unknown etiology which begin before 16 years of age and lasts for at least 6 weeks.1,2 JIA has an estimated prevalence of 1 in 1000 making it one of the most common rheumatological conditions affecting children leading to complications such as joint damage and vision loss.1,2 This childhood condition is inflammatory in nature leading to extraarticular manifestations, permanent joint damage, and significant morbidity with persistence into adulthood.3

The International league of associations of rheumatology (ILAR) developed a classification system in the mid 1990’s, the most recent update in 2001, subdividing JIA
into seven distinct subclassifications based on joint involvement, extraarticular manifestations, and genetic markers. The seven subclassifications of JIA are described in Figure 1.

Spondyloarthropathy (SpA) is another broad term describing an inflammatory arthritis with a genetic predisposition. This class of arthritides typically involves a strong HLA-B27 association, rheumatoid factor (RF) negativity, enthesitis, and axial skeletal involvement. Unfortunately, juvenile spondyloarthropathies (jSpAs) are not a distinct group recognized by the ILAR classification system and a diagnosis for such conditions would fall under enthesitis-related arthritis (ErA), psoriatic arthritis (PsA), or undifferentiated arthritis. Other such jSpAs that do not are specified by the ILAR classification include inflammatory bowel disease (IBD)-related arthritis, reactive arthritis, and juvenile ankylosing spondylitis (jAS).

As mentioned previously, ErA is a special case in that it is also a jSpA. Spondyloarthropathies (SpAs) are oligoarticular, seronegative rheumatological disorders characterized by enthesitis, HLA-B27 positivity, and axial skeletal involvement. These conditions range from ErA, which is an undifferentiated disease seen exclusively in children, to differentiated adult disease such as ankylosing spondylitis. Undifferentiated childhood SpA begins prior to 16 years of age and is typically involves enthesitis and the hip joint. In adults, SpA presents in the spine and sacroiliac (SI) joints which is not typically seen in childhood cases. While age-based differences are present, emerging views are considering these SpAs as a single disease that advances over time.

| Subtype                  | Definition                                                                 |
|--------------------------|---------------------------------------------------------------------------|
| Systemic                 | Feve for ≥2 weeks and arthritis in ≥1 joint with one or more additional  |
|                          | symptoms: erythematous rash, generalized lymphadenopathy, hepatomegaly,    |
|                          | splenomegaly, hepatosplenomegaly, or serositis                           |
|                          | Exclusions                                                                |
| Oligoarticular           | Arthritis affecting 4 or less joints during the initial 6 months. Subdivided into: |
|                          | 1. Persistent oligoarthritis in which 4 or less joints are affected throughout the disease |
|                          | 2. Extended oligoarthritis in which more than 4 joints are affected throughout the disease |
|                          | Exclusions                                                                |
| Seronegative Polyarticular| Arthritis affecting 5 or more joints during the initial 6 months and RF positive on 2 occasions 3 months apart |
|                          | Exclusions                                                                |
| Juvenile Psoriatic Arthritis| Psoriasis and arthritis or arthritis 2 of the following:  |
|                          | 1. History of psoriasis, nail pitting, onycholysis, or psoriasis in a first-degree family member |
|                          | Exclusions                                                                |
| Enthesitis-related Arthritis| Arthritis and enthesitis or one of these plus 2 of the following: |
|                          | 1. History of psoriasis, nail pitting, or enthesitis affecting the sacroiliac joint |
|                          | 2. HLA-B27 positive or RF positive |
|                          | Exclusions                                                                |
| Undifferentiated JIA     | Criteria not otherwise categorized or meeting criteria in more than one of the above categories |

* AS - Ankylosing spondylitis
  ErA - enthesitis-related arthritis
  SI with IBD - spondyloarthropathy with inflammatory bowel disease
  RS - Reiter syndrome
  AAU - acute anterior uveitis

Figure 1: Juvenile idiopathic arthritis subtypes as described by international league of rheumatology.
Unfortunately, the difficulties of juvenile SpA, such as ErA, are not only limited to understanding the relationship with adult SpA or differentiating ErA from other JIA subtypes. The wide range of clinical manifestations of rheumatic diseases make the diagnosis a difficult one. While sacroilitis in addition to inflammatory bowel disease can lead to a diagnosis of ErA, a diagnosis of chronic nonbacterial osteomyelitis (CNO) syndrome can be reached with the addition of multiple foci of painful swollen bone. If psoriasis were also present in addition to the previous symptoms, conditions to be considered may include CNO syndrome, synovitis, acne, pustulosis, hyperostosis, osteomyelitis (SAPHO) syndrome, and undifferentiated JIA.

The overlap in diagnostic criteria among these conditions in addition to the complication added as the diseases progress illustrates the need for a revision in the classification system. Martini et al. proposed a new classification system to identify homogenous chronic disorders that fall under the current term JIA using clinical and routine laboratory measures.

Pathogenesis

The etiology of JIA is unknown however, broadly, JIA develops from the inability of the immune system to distinguish self from not self. This has been well documented in the strong association of JIA with Major Histocompatibility Complex alleles perpetrating autoreactive CD4+ T cells as a common driving force in all JIA subtypes. The failure to accomplish self-recognition leads to imbalances in regulatory T cells and the T cell activation of autoreactive B cells promoting this autoinflammatory condition.

Studies have suggested that a genetic susceptibility may be one reason certain people develop JIA which is supported by the prevalence of autoimmune conditions in first degree relatives of patients who have JIA. This is further reinforced by a study published by the International JIA Immunochip consortium in which they confirmed 3 loci that were previously suspected of contributing to JIA as well as 14 new loci some of which are also associated with rheumatoid arthritis (RA), type I diabetes (DM1), and celiac disease. One such association between JIA and other inflammatory diseases, such as ulcerative colitis (UC) and Crohns disease (CD), is that of the LACC1 associated polymorphisms with a purposed mechanism of immunoregulation associated with gut microbiota. This was first mentioned in a study by Tejesvi et al. in 2016, the authors identified an alteration in the microbiome of JIA patients that resembled a similat aberration in patients with DM1 and concluded that in a genetically susceptible population, microbiome alterations may lead to proinflammatory cascades. This has been further substantiated in a paper by Qian et al. in which they found that four genera of short-chain fatty acid (SCFA) producing microbes were useful as a clinical predictor of JIA. As SCFAs have important immunomodulatory functions including differentiation of anti-inflammatory regulatory T cells, IL-10 production, and pro-inflammatory TH17 suppression, the growing evidence continues to find the deregulatory actions of the immune system as the guilty culprit.

This is supported by studies that show that alterations in T-cell populations may promote inflammation and modulation of these populations may be targets for treatment. Studies have shown an increase in CD28-/ T-cells, lacking costimulatory CD28 molecule, in both synovial and peripheral blood samples, as well as T- and B-cell population in JIA patients that have a predisposition of memory cells which may promote ongoing disease activity. Synovial fluid also expressed high levels of pro-inflammatory IL-17A. T-cell involvement is also supported in the studies for treatment alternatives such as histone deacetylases (HDACs). HDACs are being explored for the modulation of epigenetics including increasing T regulatory activity and reducing the inflammatory effects of T effector cells. Toll-like receptor 4 (TLR4) has also become an area of interest due to its link with systemic autoimmunity often associated with bacterial infection as an environmental factor in the development of SpAs, especially reactive arthritis. Single nucleotide polymorphisms (SNPs) have been associated with SpA susceptibility certain populations, such as in those with European origins, but lacks susceptibility influence in others, specifically Indian populations.

The chronic inflammation that results from the misdirected immune system leads to inflammation of the synovium, synovitis, and synovial hypertrophy. Without appropriate and early aggressive treatment, JIA may result in significant morbidity, such as leg-length discrepancy, joint contractures, permanent joint destruction, or blindness from chronic uveitis. Although none of the available drugs has a curative potential, prognosis has greatly improved as a result of substantial progresses in disease management.

CASE REPORT

Informed consent was obtained from the parent of the patient to publish case details, lab results, and images. The patient is a 3 years old, Indian female child who initially presented in March 2019 with prominent large swelling with dull skin and no redness on the 5th proximal interphalangeal joint, seen in Figure 2. There were no other signs of joint stiffness, joint pain, reduced joint range of motion (ROM). She was diagnosed with a traumatic swelling with normal x-ray and was prescribed Ibuprofen.

Due to the lack of improvement over the course of a month, the patient was taken to a pediatric orthopedic physician where she underwent magnetic resonance imaging (MRI) and a biopsy because of suspected tuberculosis. The MRI showed altered marrow signal intensity involving distal metadiaphyseal region of proximal phalanx and epiphysis of middle phalanx of little finger. Moderate joint infusion...
was seen with capsular distension and effacing extensor apparatus at proximal interphalangeal (PIP) joint level. Thinning of cortex is seen involving distal end of proximal phalanx. Minimal extra osseous soft tissue edematous changes were seen adjacent to proximal phalanx. Contrast study revealed homogeneous enhancement of the above-described lesion. An infective etiology was suspected.

The biopsy revealed inflammation that led to the diagnosis of an acute-on-chronic synovitis presumed to be of infective origin, however, the culture turned out to be negative. The patient was prescribed naproxen oral suspension and oral corticosteroids and advised to follow up.

The case remained diagnosed as traumatic infective swelling for 10 months. During this period, another minor, almost unnoticeable swelling with dull skin and no inflammation presented on the right 1st interphalangeal joint during normal investigation during follow up eight months later (Figure 3).

Family history revealed that the patient’s father suffers from HLA-B27 positive ankylosing spondylitis and bone marrow cancer in 2nd degree relative of the patient. The patient was tested and found positive for HLA-B27 and additional testing for rheumatic factor (RF) and anti-cyclic citrulline peptide antibody (anti-CCP) bared negative results (Table 1). Finally, the patient received a diagnosis of JIA. Uveitis screening was negative. The patient’s history was also negative for signs of gastrointestinal symptoms that may indicate the presence of IBD, so no further testing was performed. Due to the absence SI joint tenderness and gait abnormalities, imaging of the SI joint has been declined at this time.

The patient was initially treated with 5mg of prednisolone for 10 days followed by 2.5 mg of prednisolone for another 10 days. Methotrexate was started at 5mg once a week for 2 weeks followed by the patient’s current treatment dose of 7.5 mg once a week. Naproxen oral suspension was also prescribed to be taken as needed. The treatment is still ongoing and the progress of the disease is at an acceptable stage with decrease in the swelling on both the joints (Figure 4). At this point, there have been no complaints regarding medication side effects.

**DISCUSSION**

JIA is an umbrella term describing various types of arthropathies affecting the pediatric population before the age of sixteen. Our patient would most likely is classified into the category of juvenile spondyloarthropathies, or enthesitis-related arthritis (ErA). According to the International League of Associations for Rheumatology classification of subtypes of JIA, our patient fits the classification for ErA due to the presence of HLA-B27 antigen and history of ankylosing spondylitis in at least one

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**Table 1: Test results.**

| Test parameter      | Result(s) | Biological Reference Interval |
|---------------------|-----------|------------------------------|
| HLA B 27            | Positive  | Negative                     |
| Rheumatoid Factor c(RF) | 10 IU/ml | 0 - 14                      |
| Anti CCP            | <7.00 U/ml| Up to 17.0                  |

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first degree relative, her father. It has been documented that other juvenile arthropathies do present with HLA-B27 antigen positivity, such as extended oligoarthritis or psoriatic arthritis, however these are unlikely classifications for our patient since she did not have a history of any rashes, large joint involvement, or more than four joints affected after 6 months of disease. ErA and other juvenile spondyloarthropathies have a strong association with the HLA-B27 antigen. As with our patient, the pediatric forms specifically present upon initial onset with a peripheral pattern and limited axial involvement. It takes several years before this type of arthritis develops into ankylosing and according to one study, half of the cases developed axial involvement five years after initial symptom onset. This may indicate that this patient may slowly develop these axial symptoms in the later years. Additionally, familial history is a strong prognostic factor of persistent disease and sacroiliac involvement and as our patient’s father has ankylosing spondylitis, our patient has increased risk. Furthermore, HLA B27 has been shown to have increased association with uveitis. Considering these various associations with the HLA-B27 antigen, we recommend that children diagnosed with arthritis and who are also positive for HLA-B27 antigen should have a team of physicians on board. Not only is an experienced pediatric rheumatologist needed, but also an ophthalmologist due to strong association with uveitis, an orthopedist due to various joints involved, a physiotherapist, and a pediatric radiologist in order to catch early axial involvement.

Additionally, it has been suggested that HLA-B27 antigen has various severe prognostic factors on JIA. One study, prior to the age of biologics, showed that the most severe cases had the HLA-B27 antigen as well as lower rates of remission and very early development of joint destruction leading to arthropahties. Furthermore, it was found that over the course of eight years of follow up appointments, patients with HLA-B27 exhibited less frequent clinical remission. Another study showed that the major factors at diagnosis that are related to poor remission include thrombocytosis, HLA-B27 positivity and high CRP levels.

Current recommendations to treat JIA include the first-line treatment with non-steroidal anti-inflammatories (NSAIDs), disease-modifying anti-rheumatic drugs (DMARDs) such as methotrexate (MTX), leflunomide and sulfasalazine depending on disease activity. These can be combined with corticosteroids. In cases of moderate and high disease activity or failure of previous treatment course, biological agents are utilized, such as anti-tumor necrosis factor agents, anti-interleukin-1 agents, anti-interleukin-6 agents, and T-cell regulatory agents. Standard DMARD therapies have been successful in certain populations of JIA patients, more often in oligoarthritis. However, Bava et al. determined that remission was less likely achieved with standard DMARD therapy such as methotrexate with or without corticosteroid injections in patients with ErA and determined that systemic JIA, ErA, and polyarthritis with elevated CRP were found to be independently associated with failure of MTX as sole DMARD therapy. Several studies have found that it is difficult to attain remission in ErA and that earlier advancement to biologic DMARDs (bDMARDs) can be protective against development of axial disease and have significant effect on both clinical and patient reported outcomes. One study was successful in achieving remission with the use of anti-TNF agents. However, it is difficult to assess this association as insurance often requires the failure of standard and synthetic DMARDs to allow advancement to bDMARDs.

This patient falls into a category of nonspecific jSpA with limited information regarding treatment. While she falls into the subtype ErA, she does not have active enthesitis, therefore should the patient be treated as an oligoarticular patient or a patient with active enthesitis? This is an important consideration as the patient has increased risk for debilitating conditions that must be weighed against the risks of bDMARD treatment at younger ages. We recommend that bDMARDs be given earlier consideration in the treatment course for those suffering from ErA in effort to mitigate the development of more severe symptoms in the future. The growing body of evidence supports the premise that standard and synthetic DMARDs are not sufficient to curb the course of the disease and earlier implementation of bDMARDs can have a significant effect on both clinical and patient-reported outcomes in the HLA-B27 population. Physicians must use their best clinical judgement when these cases arise with the most current body of evidence to make the decision that is in the best interest of their patients.

CONCLUSION

This non-severe presentation of the patient demonstrates another case in which the overlap in presentation and classification of JIA subtypes needs clarification to match the accumulating information and range of manifestations. The time to reach a diagnosis translates to time taken from treatment. This is especially concerning as HLA-B27 positive patients often progress to severe disease leading to a poor quality of life as the future for these children. This case further promotes awareness with the difficulties concerning treatment that physicians must face in seeking the appropriate care for their patients. It is important to screen patients for HLA-B27 and consider earlier initiation of bDMARD treatment when appropriate.

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