A Case of Reactive Arthritis in a Ranger Indoctrination Program (RIP) Student

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ABSTRACT
Musculoskeletal complaints comprise the majority of cases encountered by military physicians when evaluating young active duty Soldier-athletes. This is a case of reactive arthritis in a 19-year-old active duty Soldier-athlete whose failure to improve with conservative therapy initiated further investigation. When evaluating what appear to be routine overuse injuries, it is important to actively include other potential causes of musculoskeletal complaints in the differential diagnosis.

Further investigation of disease in patients whose symptoms and complaints do not improve with routine conservative care is paramount. Reactive arthritis, though self-limiting in two-thirds of those affected, can become a chronic disabling disease affecting as many as 40 out of 100 patients. Current theories suggest the persistent presence of non-culturable bacteria and bacterial antigens residing in the joint synovia as the etiology of the disease state. There is no curative therapy for reactive arthritis and management is focused on the treatment of symptoms with non-steroidal anti-inflammatory drugs (NSAIDs), immunomodulator therapy, and antibiotics if an infectious source is suspected.

CASE PRESENTATION
A 19-year-old active duty white male Ranger Indoctrination Program (RIP) student with a history of bilateral patello-femoral knee pain during high school athletics presented to the Regimental Aid Station with a four-week history of continuous aching bilateral knee pain that worsened with weight bearing and was accompanied by large bilateral knee effusions. The Soldier recently graduated from basic training and the basic airborne course; however, he denied any history of knee or lower extremity trauma or pain during his training. Four weeks prior, the patient was evaluated at the Troop Medical Clinic and treated for bilateral patello-femoral pain syndrome with NSAID and ice therapy. Symptoms progressively worsened and the patient was placed on crutches and a low impact activity profile. His super-

Figure 1: 19 y/o male with bilateral atraumatic knee effusions
visors became concerned about his ongoing symptoms and contacted the Ranger Medical Treatment Facility requesting a second evaluation.

During further investigation, the patient described recent urinary tract infection symptoms to include dysuria and increased frequency of urination approximately four weeks prior to the development of bilateral knee pain. The patient denied fevers, loose-watery stools, urethral discharge, skin lesions, or other joint pains. The patient reported recent casual unprotected sexual intercourse prior to the dysuria and increased frequency and was treated for a “urinary tract infection” at the local Army community hospital with levofloxacin. The urinalysis obtained during this time revealed a white blood cell count of 395, 28 red blood cells, and positive leukocyte esterase; however, no urethral or urine culture was obtained. The patient reported successful resolution of his “urinary tract infection” symptoms after completing the prescribed antibiotic therapy.

The patient was noted to have an antalgic gait (a limp adopted to avoid pain on weight-bearing structures, characterized by a very short stance phase) with pain greater than expected for patella-femoral syndrome. During examination of the lower extremities, bilateral non-erythematous tender joint effusions with warmth to palpation were observed. The patient exhibited mild generalized pain with passive and active range of motion and weight bearing. The patient demonstrated pain and limited range of motion of the knee with flexion bilaterally. Tests for ligamentous and meniscal injury were negative. Urethral discharge, inguinal lymphadenopathy, and epididymal tenderness to palpation were absent. The patient had normal vision with normal light reflex and no photophobia, conjunctivitis, or drainage was observed. No skin lesions or rash were found. Normal range of motion of the spine was present.

Bilateral knee joint aspiration was performed revealing a white blood cell count of 8,389, no red blood cells, negative gram stain, and no visualization of crystals. Initial x-rays of the knees revealed bilateral moderate sized joint effusions with no evidence of tumor, arthritis, or osteochondral abnormality. The erythrocyte sedimentation rate was 98 and the C reactive protein was 16.5. The urinalysis performed during subsequent examination was normal with no gross hematuria or pyuria.

The remainder of the laboratory tests revealed a positive human leukocyte antigen (HLA-B27) (associated with inflammatory disease), negative antinuclear antibody test (ANA) (measures the amount and pattern of antibodies in your blood that work against your own body – autoimmune reaction), no growth of the arthrocentesis culture (joint aspiration), and negative urethral culture for gonorrhea/chlamydia. Samples for hepatitis and human immunodeficiency virus (HIV) were also drawn to evaluate for other possible sexually transmitted diseases and noted to be negative.

The elevated white blood cells count on arthrocentesis, with negative aspirate cultures, and a positive HLA-B27, associated with a prior clinical history of a urinary tract infection favored the diagnosis of reactive arthritis secondary to suspected urethritis. Following the completion of laboratory studies, the patient received bilateral corticosteroid intra-articular injections, and the patient’s symptoms improved over the following days. The patient was referred to physical therapy and was prescribed indomethacin. The patient was also placed on a modified profile (relieved from heavy physical and high-impact activity and placed on bed rest and light duty) and instructed to follow-up daily for re-evaluation. The patient was referred to a local rheumatologist for suspected reactive arthritis.

Interval knee films, six weeks later, revealed continued moderate joint effusion and mild demineralization of the metadiaphyseal junction with no signs of erosive arthritis. Lumbar spine x-rays were normal with no signs of ankylosis. Pelvic x-rays showed no evidence of erosive arthritis or sclerosis.

The historical, clinical, and laboratory findings were most consistent with a reactive arthritis and a presumptive diagnosis was made.

**Reactive Arthritis**

Reactive arthritis is a systemic rheumatologic disease that usually develops after a recent infection and falls within the category of spondyloarthopathies which includes: ankylosing spondylitis, psoriatic arthritis, and the arthropathy of inflammatory bowel disease. The condition typically follows either an enteric or urogenital infection and is characterized by an acute nonpurulent arthritis. Currently, no single diagnostic test exists for reactive arthritis nor have experts universally agreed upon clear clinical and laboratory criteria defining the disease. The American Rheumatism Association criteria committee defines the syndrome as a peripheral arthritis lasting greater than one month and associated with urethritis, cervicitis, or both. The presence of asymmetric oligoarthritis (predominantly lower extremity), sausage-shaped finger or toe (dactylitis), toe/heel pain, enthesitis (inflammation at the site of tendon origin or insertion in bone), cervicitis, conjunctivitis, iritis, genital ulceration, or urethritis on physical exam supports the diagnosis.

Reactive arthritis, formally known as Reiter’s syndrome, was described in early medical literature as
early as the times of Hippocrates and was first formally diagnosed in 1818 by Sir Benjamin Brodie who described the classic symptoms of urethritis, conjunctivitis, and arthritic symptoms. In 1916, Dr. Hans Reiter reported the relationship between urethritis and the development of uveitis and arthritic symptoms in a single case identified in a German soldier. During that same time, the classic description of an arthritic syndrome following urethritis, conjunctivitis, and enteritis was also reported by doctors Feissinger and Leroy of France. Though referred to as Feissinger and Leroy syndrome in France, Reiter’s syndrome became the popularly accepted name of the syndrome after being described in American medical literature by doctors Walter Bauer and Effrain Engelman. Today the term Reiter’s syndrome, has fallen out of favor within the medical community due to Hans Reiter’s unethical medical practices and experiments performed on concentration camp prisoners during his service for the German Nazi Party in the 1930s and 1940s. Instead, the term “reactive arthritis” is recognized by the medical community to describe the syndrome. The frequency of reactive arthritis varies greatly among different populations, races, geographic locations, and sources of disease (enteric is more common in developing nations while urogenital is more common in the developed countries). The prevalence of reactive arthritis has been reported to range between 4.6 and 13 per 100,000 people for the urogenital derived disease and 5 to 14 per 100,000 people for the enteric derived disease. The HLA-B27 genotype is associated with reactive arthritis and carries a significantly increased risk of developing the disease following a urogenital or enteric infection. It has also been noted that specific populations, such as certain Native American tribes, have a higher prevalence of HLA-B27 genotype and therefore, have a higher frequency of reactive arthritis. It is suspected that the incidence of reactive arthritis is underestimated by as much as 40% due to the under-reporting of chlamydial infection. This disease is most common in individuals between 18 to 40 years of age and rarely affects children. The urogenital form of reactive arthritis is more common in males than females with a ratio of 9:1 while the enteric form has been reported to affect males and female equally with a 1:1 ratio. The classic triad is rare occurring in only 5% of patients and is defined by the presence of arthritis, conjunctivitis, and urethritis.

The onset of reactive arthritis typically occurs one to four weeks after an initial urethral or gastrointestinal infection. The presence of urethritis is often asymptomatic in women; however, males usually present with urethral discharge or dysuria. In some patients, hematuria may be the only symptom. Conjunctivitis is most likely to be mild and bilateral in nature and is more prevalent following genitourinary or Shigella-associated infection. Conjunctival cultures are negative and the conjunctivitis normally resolves in approximately 10 days without treatment. Anterior uveitis occurs in five percent of patients and is most often acute, unilateral, and recurrent. Oligoarthritis is most frequently seen in the lower extremities and onset usually occurs rapidly, often times resulting in large effusions. Smaller joints of the wrists and fingers may also present with similar symptoms. Inflammation may involve ligaments and tendons, otherwise known as enthesopathy, at sites of insertion of the achilles, patellar, and quadriceps tendons (in order of prevalence). The duration of arthritis is quite variable and most patients recover within one year; however, others develop chronic complications. Recurrence of symptoms ranges from 15 to 30% and most commonly occurs after the urogenital form of disease. Low back pain is a common symptom secondary to spondylitis and inflammatory asymmetrical sacroilitis. Skin lesions that are histologically similar to psoriasis may be present. Keratoderma blennorrhagica begins as clear vesicles on a red base and progresses to flat macules, papules, or nodules found on the soles, palms, and mucus membranes. Balanitis cinctinata presents as painless penile ulcers on the glans and shaft of the penis. Painless oral ulcers have also been associated with reactive arthritis. Other symptoms such as fever and weight loss can be significant. Cardiac involvement is rare but, when present, can include aortic valvular insufficiency and conduction disturbances leading to heart block.

Serum laboratory studies often reveal a nonspecific anemia, elevated erythrocyte sedimentation rate, and elevated C reactive protein. Patients may exhibit a slight neutrophilic leukocytosis. Urethral swabs may be performed to evaluate for chlamydia, but direct fluorescent antibody, enzyme immunoassay, polymerase chain reaction (PCR), ligase chain reaction (LCR), or a probe for ribosomal ribonucleic acid (rRNA) are more accurate as cultures are unreliable and a negative culture does not rule out an ongoing reactive process. Following a history of diarrhea, stool cultures should be obtained to determine the infectious agent. Joint fluid examination reveals inflammatory synovitis with 15,000-30,000 white blood cells per millimeter, with a predominance of neutrophils. Joint aspirate is negative for crystals, cultures are negative, and glucose count is normal. Plain films generally are unremarkable with the exception of an effusion. Juxtaarticular osteoporosis, erosions...
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with indistinct margins, may be noted. In addition, unilateral or bilateral sacroiliitis may be noted with asymmetric paravertebral comma-shaped ossification involving the thoracic or lumbar spine. Synovial biopsy can be informative but not practical for acute treatment. Biopsy findings may include Reiter cells (macrophages with vacuoles containing nuclear debris and white blood cells), nonspecific inflammatory changes, infectious antigens, and Chlamydia trachomatis organisms (found utilizing in-situ hybridization) in the synovial tissue.

In addition, antichlamydial antibodies have been demonstrated in serum.

**Differential Diagnosis**

The differential diagnosis of an atraumatic knee effusion includes infectious processes from hematogenous seeding of the joint, reactive arthritis, psoriatic arthritis, autoimmune polyarthritis (i.e. rheumatoid arthritis, juvenile rheumatoid arthritis, systemic lupus erythematosus, sarcoid arthritis), crystal-induced arthritis (gout or pseudo-gout), coagulopathy (hemophilia), sickle-cell disease, neoplasia (benign or malignant tumors) and osteoarthritis.

Though infectious arthritis is possible with hematogenous spread of many microorganisms to a bony joint, the most common causes of infectious arthritis in young, sexually active populations is gonococcal in origin. It is associated with the formation of a pustule with an erythematous base and is often associated with a migratory polyarthralgia involving the small joints of the hands and wrists.

Autoimmune arthritis usually presents with an insidious onset associated with other systemic signs and symptoms such as skin and mucous membrane lesions and multiple symmetric joint involvement. Clinical suspicion is often confirmed by the presence of positive auto-immune markers.

Gout and pseudo-gout arthritis often present with similar symptoms as reactive arthritis but usually involves only one joint, presents and resolves acutely, and is confirmed by the presence of crystals in the joint aspirate.

Blood dyscrasias, such as sickle-cell disease and coagulopathy, can be confirmed by a prolonged prothrombin time (PT) or partial thromboplastin time (PTT), the absence of specific coagulation factors or serum proteins and prolonged bleeding times, and hemoglobin electrophoresis. Often a bloody fluid collection is present on aspiration of the joint space indicating hemarthrosis.

Though rare, Still’s disease (a disease of unknown etiology characterized by recurrent fever, arthritis, and rash), Behcet’s syndrome (a disease of unknown etiology characterized by mucocutaneous ulcers and polysystemic inflammatory manifestations to include arthritis), and rheumatic fever must also be considered in the differential diagnosis.

**Causative Organisms**

Multiple organisms can trigger reactive arthritis but the condition usually follows a genitourinary infection or infectious enteritis. The most common urethral organism is Chlamydia trachomatis. Gonococcal venereal disease, however, has been implicated as a causative organism. Other genitourinary pathogens include ureaplasma. The most common causative organisms of enteritis induced reactive arthritis include Salmonella, Shigella, Campylobacter, and Yersinia. Other infectious organisms such as Clostridium difficile, Lyme disease (Borrelia burgdorferi), Brucella, beta-hemolytic Streptococcus, parvovirus, HIV, and rickettsia are believed to be possible culprits. In addition, parasites such as strongyloids and amoebae, have been suspected.

**Pathogenesis**

Current theories on the pathogenesis of reactive arthritis postulate the cause of reactive arthritis is from the persistent presence of non-culturable bacteria and bacterial antigens residing in the joint synovia or other tissues of the body. These metabolically active non-culturable bacteria continue to illicit a local immunological and inflammatory response by the host despite resolution of the initial acute infection. The presence of mitochondrial (mRNA) and RNA of Chlamydia trachomatis identified by PCR techniques using biopsied synovia has been demonstrated in multiple patients. These findings suggest the continued presence of metabolically active infectious organisms that continue to produce bacterial antigens triggering an immune response. It is thought that monocytes are likely involved in the transportation of chlamydia from the genitourinary tract to the synovium.
and the persistence of chalmydiae species may be a result of an impaired T-cell response to infection. In other studies of biopsies of synovial tissue or synovial fluid, the presence of antigens from enteric pathogens has been identified using immunohistochemistry techniques. This may indicate persistent infection of the gastrointestinal tract by these organisms and intra-cellular transport of the bacterial antigens to the intra-articular space via monocytes. 

Reactive arthritis most often occurs in genetically predisposed persons. The major serological marker is HLA-B27 and is present in nearly 50% of patients. If negative for HLA-B27, persons may be positive for cross-reactive human leukocyte antigens such as B7, B22, B40, and B42. Recent studies reveal similar peptide binding sites on gram negative organisms and B27 molecules. Current theories suggest this molecular mimicry may produce a serological cross-reactivity thereby allowing tolerance of the foreign pathogens by the host immune system. Some theories suggest HLA-B27 inhibits the host’s ability to clear infected macrophages which could lead to persistent infection and possible dissemination of infectious agents. Other theories postulate an impaired immune response and the inability to clear infected macrophages in some predisposed subjects with HLA-B27 marker.

**Course**

The course of reactive arthritis can be highly variable ranging from a short, self-limiting process to a continuous, unremitting and progressive disease state. Reactive arthritis was once considered a benign, self-limiting condition. The average disease duration has been reported to be between three and six months; however, up to 20% of patients report symptoms at 12 months post initial symptoms. A cohort study of 432 Ontario (Canada) policemen who developed acute gastroenteritis secondary to *Salmonella typhimurium* food poisoning revealed that 27 patients developed reactive arthritis and 18 remained symptomatic five years after the inciting event. Several patients were forced to seek new employment secondary to continued arthritic symptoms. Of the 18 patients with persistent symptoms, 14 continued to exhibit axial disease including sacroiliitis and spondylitis. In another study, 40 of 100 patients developed chronic disability 25 years after the onset of disease.

**Treatment**

Currently no curative treatment exists for reactive arthritis. Approximately two thirds of persons will have a self-limiting disease. Primary treatment consists of high dose oral NSAIDs such as Indocin. Cyclooxygenase-2 (COX-2) inhibitors may be beneficial and better tolerated due to their lower gastrointestinal side-effect profile. Though useful in some of the other spondyloarthropathies, no evidence suggests treatment with oral corticosteroids is effective.

Antibiotic therapy is indicated for the treatment of chlamydial disease and has been shown to decrease the incidence of reactive arthritis in individuals receiving early intervention during acute infection. For recurrent urethritis in patients with a history of reactive arthritis in the past, erythromycin and tetracycline therapy have been shown to reduce recurrence rates to 10%, versus 37% recurrence in untreated individuals. Another study evaluating the effects of prolonged antibiotic therapy using lymecycline for a period of three months in individuals with reactive arthritis secondary to chlamydial infection revealed a decreased duration of disease symptoms in 50% of the patients being treated. However, it was noted that long-term lymecycline therapy did not change the natural course of the disease and musculoskeletal complaints were common in the majority of patients treated. Short-term use of antibiotic therapy in individuals who have already developed reactive arthritis secondary to a chlamydial infection has generally been considered ineffective. When treating chlamydia, it is important to appropriately treat the sexual partner of the affected individual.

Utilizing antibiotic therapy to treat enteric infections has been ineffective in the prevention of reactive arthritis and has not been shown to decrease the length or recurrence of disease. One study revealed an exception: ciprofloxacin treatment of enteritis caused by *Yersinia* prevented reactive arthritis but did not change the disease prognosis if administered after reactive arthritis had already ensued.

Intra-articular corticosteroid injections may temporarily improve symptoms in patients with mono or oligo-articular disease.

For patients with reactive arthritis refractory to first line therapy, disease-modifying anti-rheumatic drugs (DMARDs) are indicated. The utilization of sulfasalazine (azulfidine) appears to be effective for the persistent disease state. Patients with physical or radiologic findings of arthritis or sacroiliitis may benefit from immuno-suppressive medications such as methotrexate or azathioprine (Imuran) therapy. Recently, new treatments have included etanercept and infliximab which suppress tumor necrosis factor, a protein involved in the immune response cascade, and show promising results though large studies have not been performed. Immuno-suppressive therapy should be
managed by a rheumatologist. Bed rest may be counterproductive and a gradual increase in physical activity, to include walking, swimming, and range of motion exercises may reduce stiffness and improve flexibility. Persistent symptoms and failure to respond to therapy should lead to testing for human immunodeficiency virus as reactive arthritis is often the presenting symptom.8

PROGNOSIS

The majority of patients become asymptomatic after six months, but symptoms may continue to present after 12 months. The 20-year prognosis of reactive arthritis is determined by four major factors: the nature of the triggering infection, the presence of HLA-B27, the patient’s gender, and presence of recurrent arthritis. Overall, a relapsing course appears less common in enteric-related disease than in chlamydia-associated reactive arthritis. HLA-B27 is associated with chronic disease and bears a less favorable prognosis. Male gender is associated with a poorer prognosis. Other predictive factors that may occur during the first two years and are associated with a poor prognosis include: hip arthritis, erythrocyte sedimentation rate > 30mm/h, poor response to NSAID therapy, limited range of motion of the lumbar axis, dactylitis, oligoarthritis, and onset of disease prior to 16 years of age.6 As noted above, the likelihood of permanent disability is high and it is not possible to predict outcome. Per 2007 U.S. Army fitness standards for retention, Army personnel diagnosed with the condition must undergo a medical evaluation board (MEB) and will likely be medically discharged as this condition is disqualifying for military service.16

CONCLUSION

Though most musculoskeletal complaints in the young active duty Soldier-athlete stem from mechanical and overuse injury, it is important to remain vigilant for other causes of disease especially when symptoms do not improve with initial conservative therapy. This case of reactive arthritis illustrates the importance of further investigation, identification, and treatment of a Soldier-athlete with progressively worsening knee pain despite conservative therapy.

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