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## CLINICAL VIGNETTE

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# A Case of Reactive Arthritis

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A 35-year-old male with recently diagnosed salmonella enteritis presented to the emergency room with a new rash and worsening back and hip pain.

His symptoms started 18 days prior with diffuse abdominal pain and watery diarrhea that turned bloody after four days. He presented to another emergency department where he was diagnosed with viral gastroenteritis and discharged home with conservative measures. He continued to have diarrhea and abdominal pain and developed dysuria two days after initial ED evaluation prompting presentation to a different emergency room. He was diagnosed with acute colitis with initial labs which included positive urinalysis, WBC 799 cells/uL, RBC 33 cells/uL, leukocyte esterase 3+. Computed tomography (CT) scan of abdominal/pelvis demonstrated pan colonic wall thickening and hyper-enhancement. His history included tobacco and methamphetamine use with recent incarceration. He was diagnosed with acute colitis and discharged home on ciprofloxacin 500mg bid and flagyl 500mg tid for seven-day course. Stool studies were also ordered. Two days after discharge, salmonella PCR was detected on stool studies, and urine culture was negative. The patient was notified of diagnosis of salmonella enteritis and was instructed to inform his employer. He was working in the kitchen as part of his behavioral program after incarceration. Two other kitchen workers had also been diagnosed with salmonella.

He also reported onset of conjunctival redness with watery discharge and returned to the emergency department and was diagnosed with conjunctivitis and discharged on Polytrim ophthalmic solution.

One week later he returned to the emergency room with a non-pruritic rash on his chest and legs as well as pain in his neck, shoulders, clavicle, cervical and thoracic back, and left hip. He has been taking ibuprofen with minimal improvement. The patient reported resolution of conjunctivitis and dysuria and improvement in diarrhea.

Family history was notable for sister with arthritis on hydroxychloroquine and niece with lupus. Social history was notable for recent incarceration, rodent exposure, and unprotected sexual encounters with multiple female partners.

Vital signs included, T 98.8°F, HR 88, BP 103/81, RR 18, SpO2 94% on room air. Skin exam was notable for 3mm ulcer on left tip of tongue, 2mm erythematous lesion on left side of penile

glans, several small mildly erythematous plaques scattered throughout bilateral hips and buttocks, and scaly lesions over anterior chest. Musculoskeletal exam was notable for tenderness over cervical and thoracic paraspinal areas and bilateral sternoclavicular joints. He had pain with movement of left hip, with no tenderness to palpation over other joints and no joint erythema or effusions.

Labs were notable for elevated WBC  $17 \times 10^3/\mu\text{L}$ , ESR 56mm/hr, and CRP 3mg/dL. Infectious testing included negative hepatitis serology, RPR, MTB-quantiferon, HIV, and urine and rectal chlamydia and gonorrhea. Rheumatologic testing including ANA, dsDNA, and rheumatoid factor were negative.

Imaging was notable for small effusion of bilateral sternoclavicular joints as well as left hip on ultrasound. Plain imaging of cervical and thoracic spine showed mild degenerative disease.

He was admitted and infectious disease, rheumatology, and dermatology consults were obtained. Ciprofloxacin 500mg bid was continued until blood cultures finalized as negative. Given recent salmonella infection and constellation of conjunctivitis and urethritis, there was high suspicion for reactive arthritis. Small effusions in sternoclavicular joints and left hip also supported this diagnosis and he was started on naproxen 500mg bid. After minimal improvement in joint pain two days after starting nonsteroidal anti-inflammatory drugs, prednisone was started. His HLAB27 returned positive and he was discharged home with close rheumatology follow up.

At follow up, the patient reported continued severe pain on prednisone 10mg daily. Prednisone dose was increased to 30mg with slow taper down to 15mg daily. On follow up one month later, sulfasalazine 1g bid was started and prednisone decreased to 10mg. His symptoms improved and over the next three months, prednisone was tapered off and sulfasalazine increased to 1.5g bid. He subsequently contracted COVID-19 and taken off sulfasalazine approximately seven months after hospitalization. He recovered from COVID-19 and has remained off sulfasalazine without recurrence of joint pains.

### *Discussion*

The term "reactive arthritis" was first coined in 1969 as "an arthritis which developed soon after or during an infection elsewhere in the body, in which the microorganisms cannot be

recovered from the joint".<sup>1</sup> We now consider reactive arthritis a form of spondyloarthritis which occurs typically after gastrointestinal (GI) or genitourinary (GU) infections. Historically, reactive arthritis has been associated with Reiter's syndrome -- the triad of conjunctivitis, urethritis, and arthritis. We now know that patients with this triad represent only a subset of patients with reactive arthritis. The term Reiter's syndrome has fallen out of favor after disclosure of Hans Reiter's involvement with the Nazi regimen.<sup>2</sup>

Reactive arthritis is a relatively rare disease, but incidence is highly variable due to different criteria for diagnosis, different causative agents, and population-based versus outbreak associated studies. One population-based US study reported incidence of 0.6-3.1/100,000 after interviewing patients with culture positive cases of *Campylobacter*, *E coli* O157, *Salmonella*, *Shigella*, and *Yersinia* infections.<sup>3</sup> Studies of reactive arthritis in *Salmonella* outbreaks have reported rates from 0-29%. Typically, this condition affects young adults, with mean age of 30-40 years. Males and females are at similar risk after GI infection, but men are more frequently diagnosed after Chlamydial GU infections.<sup>4</sup>

The primary clinical manifestations of reactive arthritis are a preceding GI or GU infection and axial and/or peripheral musculoskeletal signs of symptoms. Extra-articular signs and symptoms including ocular and skin manifestations are also common.

A number of GI and GU pathogens have been identified as causative agents including *Salmonella*, *Yersinia*, *Shigella*, *Campylobacter*, and *Chlamydia trachomatis*; and less common organisms include *Escherichia coli*, *Clostridioides difficile*, *Chlamydia pneumoniae*, *Ureaplasma urealyticum*, and possibly *Mycoplasma genitalium*. Rarely, reactive intravascular arthritis has been associated with BCG infusions for bladder cancer treatments.<sup>5</sup> Initial infection typically occurs 1-4 weeks prior to onset of musculoskeletal symptoms. Patients may have asymptomatic infections, so infectious evaluation of patients presenting with symptoms concerning for reactive arthritis should be pursued even if patient does not have overt enteritis or urethritis. Although preceding infection is necessary for diagnosis, by the time arthritic symptoms appear, the infections may have resolved and no longer detectable. Diagnosis may rely heavily on patient history.<sup>4</sup>

The most typical pattern of arthritis is asymmetrical mono or oligoarthritis, often in the large joints of the lower extremity. However, it can also present as polyarthritis of small joints and involve the upper extremities. Enthesitis (inflammation at the site of insertion of ligaments and tendons), tendinitis, bursitis, dactylitis, and inflammatory low back pain which is typically worse at night and radiates to buttocks, are also common. While most patients have an acute onset arthritis that resolves over time, a minority will develop chronic reactive arthritis, defined as arthritis that lasts for six months or longer.<sup>4</sup>

Extra-articular manifestations include eye disease, most commonly conjunctivitis and less frequently anterior uveitis, episcleritis, and keratitis. Genitourinary tract symptoms including dysuria with urethritis or cystitis without GU infection and cutaneous eruptions including keratoderma blennorrhagica, erythema nodosum, painless oral ulcers and genital lesions such as circinate balanitis can also be seen. Rarely cardiac manifestations including valve disease and pericarditis have been described.<sup>6</sup>

Laboratory evaluation is non-specific and may include elevated inflammatory markers and inflammatory synovitis, if arthrocentesis is performed. Interestingly, while the conventional definition of reactive arthritis includes the absence of pathogen in the affected joint, studies have identified antigens of the triggering microbe and rarely replicating microbes in synovial fluid or tissue.<sup>4</sup> Imaging may help confirm enthesitis, tendinitis, bursitis, or sacroiliitis. Further testing may be necessary to rule out other etiologies such as Lyme arthritis, gout, and rheumatoid arthritis. Testing for HLA-B27 is also frequently ordered, although the association between HLA-B27 and reactive arthritis is weaker than with other forms of spondyloarthritis. Interestingly, in the population-based US study, there was no significant difference in the frequency of HLA-B27 among subjects with confirmed reactive arthritis compared to control,<sup>3</sup> although hospital-based series have shown a stronger correlation with 60-80% of patients with reactive arthritis are positive for HLA-B27 suggesting that HLA-B27 positivity is correlated with more severe disease.<sup>4</sup>

There are no large-scale studies on treatment of reactive arthritis and guidelines are largely based on clinical experience and use in other spondyloarthritis or rheumatologic disorders. For acute reactive arthritis, first line treatment is NSAIDs, and if not effective, intra-articular or systemic steroids. In patients resistant to steroids or who develop chronic reactive arthritis, non-biologic DMARD such as sulfasalazine is appropriate. If symptoms remain refractory, anti-TNF biologics may be necessary. Appropriate antibiotic choice should be based on infection rather than development of reactive arthritis. A systematic review and meta-analysis on antibiotic treatment for reactive arthritis did not show any significant effect of antibiotic treatment on patients' likelihood to reach remission, although the results were highly heterogeneous.<sup>7</sup> There may be a role for antibiotics in certain populations, and some evidence that early antibiotics for infection can prevent recurrent reactive arthritis and a possible role of antibiotics for chronic reactive arthritis associated with *Chlamydia*.<sup>4</sup>

Overall, prognosis for reactive arthritis is very good. Most patients remit or have little active disease within 6-12 months; although 15-20% may experience more chronic persistent arthritis.<sup>6</sup>

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