

REACTIVE ARTHRITIS SECONDARY TO SALMONELLA GASTROENTERITIS

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ABSTRACT

Reactive arthritis is an inflammatory arthritis triggered by a preceding genitourinary or gastrointestinal infection. The diagnosis of reactive arthritis can be difficult to make, due to the lack of distinct diagnostic criteria. Despite this, evidence of a primary infection followed by articular and extra-articular features after having ruled out other causes is often adequate to make the diagnosis. The case of a middle aged woman with gastroenteritis, arthritis, fever, rash, and episcleritis is described in detail, articulating its nuances from classic reactive arthritis. Despite her overall course of illness being in agreement with the diagnosis, the characteristics of her rash are unique to reactive arthritis, making her presentation worthy of documentation.

CASE HISTORY

What began as gastroenteritis evolved into a more complex case involving a widespread rash, arthritis, fever, and episcleritis. Across multiple care settings and with guidance from Infectious Disease and Rheumatology, an eventual diagnosis of reactive arthritis secondary to salmonella gastroenteritis was made.

In early March, a 49 year old Caucasian woman presented to BTHC emergency with gastroenteritis. Over the past 1.5-2 weeks, she had been experiencing non-bloody diarrhea, nausea, vomiting, and abdominal pain. The diarrhea was occurring up to 8 times daily. This was her 2nd presentation to the ED in the past week, for the same gastro-type symptoms. Her vital signs were normal, and her abdominal exam was unremarkable. She had no recent sick contacts, nor had she recently received any antibiotics. A stool C & S was ordered, and the result was positive for nontyphoidal salmonella. She was admitted to hospital for IV ciprofloxacin and IV fluids.

While in hospital, she developed a widespread rash over her upper extremities, torso, and face, with some involvement of the palms and feet. The rash consisted of minimally raised erythematous plaques,

mostly ovoid in shape, varying in size, some with central bulli. There was no mucosal involvement. The patient took dicyclomine for the first time one day prior to the rash onset. The dicyclomine was stopped, daily Reactine PRN was prescribed, and the working diagnosis for the rash was a drug-related reaction.

She was in hospital for a total of 5 days. During this time, the IV ciprofloxacin was titrated down until she could tolerate oral, at which point she was discharged home.

Just 3 days after the hospital discharge, the patient presented to the Urgent Care Clinic with severe joint pain, redness of the eye, and fever. The patient reported severe bilateral knee pain, worse on the right than the left. Bilateral swelling and tenderness to palpation was evident on exam. There was also joint pain to a lesser degree in the hands and ankles. There was no redness surrounding the joints. Her right eye was erythematous with mild discomfort and no photophobia. The patient also endorsed feeling feverish. There were no symptoms of urethritis. The widespread rash from her recent hospital admission was still present. A working diagnosis of reactive arthritis was made, and the patient was sent to the ED for further work up.

Blood work was performed at the ED, which showed mild leukocytosis and thrombocytosis. The case was discussed with Rheumatology, and it was thought to be reactive arthritis. However, the patient's fever was thought to be suspicious for salmonella bacteremia. Blood cultures, and synovial fluid culture from right knee aspirate had been ordered, but until they came back, it was suggested that the patient receive IV antibiotics. So, she was admitted to the hospital again, for IV ceftriaxone and pain control.

Her second hospital admission lasted 8 days while investigations took place. All cultures came back negative. An optometrist assessed her erythematous right eye to be episcleritis. Her knee pain was managed initially with IV Toradol. Infectious Disease was consulted, and the case was thought to be most consistent with a reactive arthritis secondary to salmonella gastroenteritis. It was felt there were no

REACTIVE ARTHRITIS SECONDARY TO SALMONELLA GASTROENTERITIS

signs of bacteremia; antibiotics were stopped. A punch biopsy of the left forearm was performed for a histopathology assessment of the rash. She was discharged on naproxen and Tylenol for pain management, with plans to follow up with a Rheumatologist in 2 days.

At the follow up, the rheumatologist confirmed that reactive arthritis related to salmonella was the most likely explanation. At that time, all symptoms, including diarrhea, joint pain, and rash, were improving. It was noted that the patient's brother and mother have arthritis, type unknown. She had no history of arthritis previously, and no neck or back complaints. Depo-Medrol and lidocaine was injected into both knees. Rheumatology will continue seeing the patient in follow-up, with the expectation that the arthritis will entirely resolve in a few weeks to a few months time. The punch biopsy result showed lymphohistiocytic vasculitis.

LITERATURE SEARCH

A brief search of the current literature was conducted in an attempt to answer the following clinical questions: How does this case differ from a classic presentation of reactive arthritis? Can a widespread rash, as described in this case, be explained by reactive arthritis?

The Ovid Medline database was used to search the literature from 1946 to present. The keywords *reactive arthritis AND rash* were initially used, and 3 relevant articles were found. One of these articles gave a thorough overview of the microbiology, epidemiology, pathogenesis, differential diagnoses, and management of the condition. Meanwhile, a different article described in detail the rashes and respective histopathology associated with reactive arthritis microbiological pathogens. In order to make the literature search as all-inclusive as possible, the keywords *reactive arthritis AND skin* were used in a second search. 3 additional articles appropriate to the clinical question were discovered. All articles from this literature search contributed to a deeper understanding of the various typical and atypical clinical presentations of reactive arthritis.

DISCUSSION

Reactive Arthritis is a spondyloarthropathy, characterized by a gastrointestinal or genitourinary infection triggering an inflammatory arthritis. Making a diagnosis of reactive arthritis is often complicated due to the lack of unanimous diagnostic criteria. As detailed in the Case History, it took many weeks, investigations, and consults to arrive at the diagnosis. Even then, the diagnosis given was "most likely," rather than definite. In general however, reactive arthritis can be confirmed by: evidence of a microbiological infection, followed by arthritic and extra-articular clinical features, and after ruling out other causes of arthropathy.¹ These will be the standards used to assess the case in question.

Several bacterial pathogens are known to cause infection commonly associated with reactive arthritis. *Chlamydia*, which causes a genitourinary infection, is strongly associated with reactive arthritis. *Salmonella*, *Shigella*, *Campylobacter*, and *Yersinia*, which cause gastrointestinal infections, are also commonly associated.¹ The stool culture and sensitivity performed on the case patient was positive for Salmonella.

Epidemiology of reactive arthritis is sporadic across the population, but an increased frequency may be seen following infectious outbreaks. As of March 22, 2019, there were 566 confirmed cases of Salmonella across Canada, 27 of which were in Manitoba.² The case patient's Salmonella positive stool result was collected on March 19th. It would be useful to know if any other cases of reactive arthritis have coincided with the outbreak across the region, as well. Health care professionals should remain aware of the outbreak and its possible connection with reactive arthritis. This would ensure more timely diagnosis and appropriate management for future reactive arthritis cases.

The clinical presentation of reactive arthritis progresses from the primary infection to musculoskeletal and extra-articular features. Reiter's syndrome is the well-known and classic triad of urethritis, conjunctivitis, and arthritis. However, reactive arthritis has various

REACTIVE ARTHRITIS SECONDARY TO SALMONELLA GASTROENTERITIS

presentations, and Reiter's syndrome is just one of these subsets.¹

The symptoms of the primary bacterial infection depend on the pathogen involved. Gastrointestinal infection with Salmonella presents with diarrhea, abdominal pain, and fever. During the acute phase of the infection, weight loss and fevers up to 38.8°C have been recorded.³ The case patient had all of the above with severe diarrhea, abdominal pain, and fever. The case patient's fever led clinicians to admit her to hospital, as they were concerned about bacteremia. However, given that the literature indicates that this is a known phenomenon with reactive arthritis secondary to gastroenteritis, perhaps this suspicion and its consequential investigation and admission could have been circumvented. Note, however, that the literature indicates that the fever occurs during the "acute" phase of the illness, and the article did not detail the exact time frame for what is considered "acute." The case patient's fever was noted two weeks into her gastroenteritis symptoms. 2 weeks could be considered more sub-acute than acute, and perhaps the fever doesn't align with what is expected of the clinical course after all.

After enduring the classic diarrhea, abdominal pain, and fever associated with the primary bacterial gastro infection, a patient with reactive arthritis will typically then experience MSK manifestations of the illness. Days to weeks later, often after resolution of the diarrhea, symptoms of arthritis begin. The arthritis is usually in the lower extremities, though involvement of the hands has been reported. The arthritis classically manifests with asymmetric joint involvement, either monoarthritis or oligoarthritis. Enthesitis, dactylitis, and inflammatory lower back pain are also common.⁴ The case patient's arthritis was symmetric, involving her hand joints in addition to her knees. However, her knee joints were her main complaint, and her right knee was significantly more painful than the left. Thus, the case patient's arthritic clinical picture doesn't perfectly match what is to be expected with reactive arthritis, due to its upper extremity involvement and symmetrical nature.

In addition to MSK manifestations, reactive arthritis can present with many extra articular

manifestations, especially if the primary infection was due to *Chlamydia*. The extraarticular manifestations can be very helpful in supporting the diagnosis of reactive arthritis. Common genitourinary symptoms include urethritis, cervicitis, and cystitis. Ophthalmologic symptoms include conjunctivitis, anterior uveitis, and episcleritis, with conjunctivitis being the most common. Cardiac manifestations like pericarditis and heart block are less common though can occur.¹ The case patient did not have any genitourinary symptoms, though this would not be expected given that her infection was gastrointestinal. She did however have unilateral episcleritis. Episcleritis is the least common ophthalmologic manifestation. Thus, the case patient exhibited the absence of genitourinary manifestations, as would be expected with gastroenteritis reactive arthritis, and the presence of one ophthalmologic manifestation, albeit an uncommon one.

Mucocutaneous manifestations are present in up to 50% of patients with reactive arthritis. These include painless oral ulcerations, erythema nodosum, circinate balanitis, and keratoderma blennorrhagica. Erythema nodosum affects the extremities, and is predominantly associated with *Yersinia* induced reactive arthritis. Circinate balanitis presents as sharply demarcated erythematous plaques on the glans penis. Keratoderma blennorrhagica involves the palmoplantar region, scrotum, trunk, and scalp. It appears as erythematous vesicles that evolve into papules, nodules, or hyperkeratotic plaques that resemble pustular psoriasis.⁵ Skin lesions tend to occur with prolonged disease, with most patients experiencing joint symptoms for months to years before skin involvement.¹ Although the case patient had extensive skin involvement, the clinical picture matches none of the expected mucocutaneous manifestations. There were no oral ulcers. The patient's rash began as large plaques, not vesicles. It was widespread, with more extensive involvement than that described in hyperkeratotic plaques. There was also minimal sole and palm involvement. Not to mention that the rash began before the onset of the arthritic symptoms. For these reasons, the case patient's rash challenges the diagnosis of reactive arthritis. From the brief literature review conducted, there wasn't a single mucocutaneous manifestation

REACTIVE ARTHRITIS SECONDARY TO SALMONELLA GASTROENTERITIS

described as typical of reactive arthritis that matched the presentation of the patient's rash.

However, one article found in the literature search may demonstrate a link between the patient's rash and reactive arthritis after all. According to Magro and Crowson, microbial pathogens associated with reactive arthritis may have distinct cutaneous manifestations and histopathology. In their article, 16 patients were described who developed skin eruptions resembling Sweet's syndrome, erythema nodosum or erythema multiforme post-infection with a pathogen typical of reactive arthritis. Clinically, Sweet's syndrome and erythema multiforme appears as erythematous/violaceous, targetoid, and infiltrative plaques on the arms, legs, and trunk.⁶ The lesions erupt within 24 hours, often affecting the upper limbs more than lower. The lesions are initially well demarcated, round, red/pink and flat, then gradually enlarge to form plaques that darken in color with surface changes like blistering or crusting.⁷ An argument could be made that this clinical picture resembles that of the case patient's rash. Although not targetoid in morphology, the case patient's rash appeared and evolved in similar manor as described here. And, atypical types of erythema multiforme exist that are not distinctly targetoid. Magro and Crowson's article notes that although the clinical presentation may be variable, the histopathology of these skin lesions is uniform: diffuse interstitial histiocytic inflammation, focal lymphocytic dermatitis, and mononuclear cell predominant vasculopathy/vasculitis. The case patient's pathology report identified the biopsy as lymphohistiocytic vasculitis. Thus, perhaps the patient's rash was a cutaneous expression of the gastroenteritis infection after all.

Overall, the case patient followed a course of illness that corresponds with reactive arthritis, with some notable discrepancies. She first experienced diarrhea, and abdominal pain as the manifestation of her primary salmonella gastroenteritis. There is nothing odd about this initial presentation. Next, the case patient developed symmetric arthritis, fever, and episcleritis. The overall appearance of the arthropathy and inflammatory eye condition is also no surprise. Yet, the arthritis being symmetrical, rather than asymmetrical, and the eye being inflamed with episcleritis rather than conjunctivitis

is a far less common presentation of reactive arthritis. Additionally, the case patient developed a unique rash, atypical from reactive arthritis' commonly reported erythema nodosum, circinate balanitis, and keratoderma blennorrhagica. One article found in the literature search describes an association between reactive arthritis pathogens and Sweet's syndrome or erythema multiforme. This combined with the patient's histopathology finding of lymphohistiocytic vasculitis, may provide a possible explanation of the patient's rash as a cutaneous manifestation of the primary bacterial infection. Overall, the patient's condition appears to resemble reactive arthritis with notable inconsistencies, the rash being most significant.

CONCLUSION

The diagnosis of reactive arthritis can be difficult to make, due to the lack of clearly defined diagnostic criteria. The case patient presented initially with gastroenteritis, confirmed to be salmonella. She later presented with rash, fever, arthropathy, and episcleritis. Given the overall course of her illness, from showing signs of a primary microbiological infection, to exhibiting arthritic and extra-articular features, reactive arthritis was the most likely explanation. However, some details of her clinical picture, notably her unique rash, were inconsistent with the typical course of reactive arthritis.

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REACTIVE ARTHRITIS SECONDARY TO SALMONELLA GASTROENTERITIS

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