PPID | Private Practice Infectious Disease

MIDC METRO INFECTIOUS DISEASE CONSULTANTS

Syndromic Approach: Reactive Arthritis

Kamo Sidhwa, MD [1]

[1] Metro Infectious Disease Consultants, Burr Ridge, IL 60527; ksidhwa76@gmail.com

Submitted: 17 September 2024, accepted: 30 October 2024, published: 31 December 2024

Keywords: oligoarthritis; seronegative; spondyloarthropathy; urethritis; gastroenteritis

How to cite: Sidhwa, K. Syndromic Approach: Reactive Arthritis. *Priv. Pract. Infect. Dis.*, 2024, 4(4): 9; doi:10.55636/ppid4040009.

Introduction

Reactive arthritis (ReA) is an inflammatory arthritis triggered by an antecedent infection that most commonly originated in the gastrointestinal (GI) or genitourinary (GU) tract [1]. Clinical presentation includes an asymmetric oligoarthritis often accompanied by extra-articular manifestations, including cutaneous, ophthalmologic, cardiac, genitourinary, and skeletal system involvement [2]. Although most patients experience symptom resolution within 3 to 5 months, about 30% of patients will develop chronic seronegative spondyloarthropathies that are often debilitating [1]. Early diagnosis and treatment of this disease process can result in less related organ and joint damage for patients as well as overall improved patient outcomes.

ReA symptoms can be nonspecific, often mimicking a multitude of alternative infectious and noninfectious entities. Here we present a case of ReA which may be similar to one that an infectious disease specialist may be asked to consult on, with a review of the disease process and the most common differential diagnoses that the practitioner should consider.

1.1. Clinical vignette

A 22-year-old female with no past medical history presented to the hospital with a 3-day history of right knee pain and mild swelling, associated with lower back pain. She denied any trauma or prior similar symptoms, and denied any sexual activity in the previous 6 months. The review of symptoms was also negative for any fever, chills, vaginal drainage, abdominal pain, lower extremity weakness, headache, or visual complaints. On further history, the patient acknowledged a 2-day history of self-limited diarrhea that occurred about 2 weeks earlier. Upon evaluation in the emergency room, she was afebrile. Examination confirmed the presence of right-knee swelling with a mild effusion

but no erythema or warmth; range of motion was intact. She did have some palpable lumbar paraspinal back pain, but no focal swelling along the spine was revealed. There was no extremity weakness and neurological exam was otherwise nonfocal. No cardiac murmur was appreciated and no rash was seen. Laboratory data noted a normal complete blood count, normal chemistries, and an unremarkable urinalysis. Erythrocyte sedimentation rate (ESR) was 65 and an antinuclear antibody test was negative. X-ray of the right knee demonstrated a small effusion but no bony changes. Synovial fluid aspiration revealed a white blood count (WBC) of 3200 with 88% neutrophils and no crystals; Gram stain was negative.

Infectious disease consultant was requested for evaluation of inflammatory arthritis.

Differential Diagnosis

After initial assessment of the patient, a differential diagnosis list can be generated using relevant medical history, pertinent physical findings, and laboratory and radiographic data. There are several potential etiologies of inflammatory arthritis in this patient (see Table 1).

Table 1: Etiologies of Inflammatory Arthritis

Diagnosis	Preceding GI/ GU complaints	Joint involvement	Synovial fluid WBC per mcL (if applicable)	Synovial culture positivity
Septic arthritis	-	Typically monoarthritis	>50,000 WBC (>75% neutrophils)	75–95%
Gonococcal arthritis	+/-	Mono- or polyarthritis	34,000–68,000 (>75% neutrophils)	25–70% (Polymerase Chain Reaction (PCR) testing > 75% sensitive)
Crystalline arthropathy	-	Typically monoarthritis	2000–100,000 (>50% neutrophils)	Negative
Lyme arthritis	-	Typically monoarthritis	3000–100,000 (>50% neutrophils)	Negative (PCR testing > 75% sensitive)
Whipples disease	+	Migratory polyarthralgias	200–30,000 (>50% neutrophils)	Negative (PCR testing ~60% sensitive)
Reactive arthritis	+	Mono- or polyarthritis	2000–25,000 (>50% neutrophils)	Negative

2.1. Septic arthritis

Patients with septic arthritis typically present acutely with monoarticular arthritis; most patients have an associated fever. Examination usually reveals a hot, swollen, painful joint with limited mobility. The Academy of Rheumatology supports a diagnosis of septic arthritis with a synovial fluid WBC of 50,000 or more with a predominance of neutrophils, although several studies have noted culture-proven septic arthritis with fewer than 50,000 WBC [3]. Total WBC may also be reduced due to recent antibiotic use or underlying immunosuppression [3].

2.2. Gonococcal arthritis

Gonococcal arthritis occurs as a result of the migration of *Neisseria gonorrhoeae* from the mucosal tract to the blood, ultimately settling in one or several joints. It is an important cause of acute arthritis in young adults who are otherwise healthy. The spectrum of disseminated gonococcal infection ranges from the classic triad of tenosynovitis, dermatitis, and polyarthralgia to a frank purulent arthritis

consistent with the presentation of a classic septic arthritis. Positive cultures (either in the blood or synovial fluid) may be seen in up to 50% of patients [4].

2.3. Crystalline arthropathy

Approximately 80% of initial crystalline arthritis occurs in a singular joint. An acute gouty attack classically involves the great toe, whereas pseudogout (calcium pyrophosphate dihydrate) usually involves the knee. Synovial fluid analysis demonstrates a high total WBC count with a predominance of neutrophils, although generally not seen with the degree of elevation noted in septic arthritis. Diagnosis is made by the presence of uric acid or calcium pyrophosphate crystals within the fluid itself [5].

2.4. Lyme arthritis

Monoarthritis, usually involving the knee, can complicate late stages of Lyme disease in about 10% of cases. Typically, patients present with chronic swelling that progresses over time, rather than an acute hot, swollen joint. Occasionally patients may recall an antecedent tick bite or classic skin lesion, i.e. erythema chronicum migrans. Synovial fluid cultures usually remain negative and the diagnosis is made by serological testing [5].

2.5. Whipple's disease

Whipples disease is a typically a chronic, multisystem disease process caused by *Tropheryma whipplei* in which patients present with joint symptoms, chronic diarrhea, and malabsorption that often leads to weight loss. Eighty percent of patients present with joint symptoms, which most often constitute migratory arthralgias of the large joints. A true arthritis with an associated effusion or joint destruction is rare. Most patients are initially misdiagnosed as having a seronegative arthropathy; thus, Whipples disease should be considered in a patient who presents with consistent symptoms and who does not respond to immunomodulatory therapy. Diagnosis is made by a small bowel biopsy noting periodic acid-Schiff– (PAS–) positive macrophages or by two different *T whipplei* tests (polymerase chain reaction [PCR], PAS, or immunochemistry) from the same specimen or one positive test in each of two different specimens [6].

2.6. Systemic disorders

Several systemic disorders can also present similarly with monoarthritis as a primary complaint. Rheumatologic diseases, including rheumatoid arthritis and Behcets, as well as seronegative arthritides (including psoriatic arthritis, ankylosing spondylitis and inflammatory bowel disease–associated arthritis) can occasionally present with single-joint arthritis, most commonly involving the lower extremities. These arthritic complaints are usually chronic in nature and patients often have other systemic complaints or objective findings that may serve as clues to the underlying diagnosis [5]. The presence of a rash, pathergy or recurrent oral and genital ulcers may lead to the diagnosis of Behcets. Chronic diarrhea may signal that a patient may have IBD-associated disease.

Discussion

Reactive arthritis is an inflammatory arthritis resulting from an aberrant autoimmune response to an antecedent gastrointestinal or genitourinary infection occurring 1 to 4 weeks prior. Incidence following a genitourinary infection is from 2% to 4% and occurs most commonly after *Chlamydia trachomatis* infection. After gastrointestinal infection, incidence of ReA ranges more broadly, from 1% to 15%, but

appears more likely to occur with *Campylobacter* and *E coli* O157:H7 gastroenteritis [2]. Rare cases have been described after *Clostridium difficile* infection and there have been at least 16 cases of ReA following infection with COVID-19 [7].

ReA is characterized by articular as well as extra-articular complaints. Patients typically present with an oligoarthritis involving the lower extremity joints, most commonly the knee. Axial complaints appear to be underrecognized as well. About half of patients presenting with ReA have lower back pain as their presenting complaint [7]. Extra-articular symptoms include those related to the genitourinary system (urethritis, cervicitis), ocular system (conjunctivitis, uveitis), skin (keratoderma blennorhagicum, aphthous ulcers, erythema nodosum), and cardiac system (heart block, valvular disease, pericarditis) [7].

Guidelines for the diagnosis of ReA have been established. A patient with definitive ReA is one that presents with both major criteria (arthritis and preceding enteritis or urethritis) and one minor criterion (a positive urine, cervical, urethral, or stool culture signifying a triggering infection) or persistent synovial infection as evidenced by positive immunohistology or PCR [7]. A patient has probable ReA if they satisfy both major criteria or one major and one minor criterion. Our patient as described in our clinical vignette carries a diagnosis of probable ReA based on this classification (both major criteria were met).

Laboratory and radiographic findings in patients with ReA are highly nonspecific. Acute phase reactants, including ESR and C-reactive protein elevation, have not been consistently seen in cases of ReA. Similarly, plain radiographs do not demonstrate any unique findings that point to a diagnosis of ReA. Synovial fluid analysis usually reveals a mild inflammatory response with between 2000 and 25,000 WBC/mL and a predominance of neutrophils. Synovial cultures typically remain negative, but PCR testing can occasionally be positive, especially in cases related to *C trachomatis* [2].

The course of ReA is variable in terms of symptomology, frequency of relapses, and duration. Factors predictive of worse prognosis in ReA include HLA-B27 positivity, chlamydia-induced infection, family history of spondyloarthropathy, or a personal history of inflammatory bowel disease [7]. Most patients with ReA experience a resolution of their symptoms within 5 months, yet 30% of patients typically develop chronic disease with symptoms persisting for 6 months or more. Potential complications related to chronic ReA include recurrent arthritis (in up to 50%), sacroiliitis, ankylosing spondylitis (with a higher likelihood in people who are HLA-B27 positive), urethral stricture, aortic root stenosis, cataracts, and cystoid macular edema [2].

First-line treatment for acute ReA includes the use of nonsteroidal anti-inflammatory drugs (NSAIDs) prescribed for at least 2 weeks. In those patients who clinically fail with NSAID therapy or who do not tolerate their use, intra-articular glucocorticoids should be considered to provide symptomatic relief, and to avoid potential adverse effects related to systemic steroids [8]. Antibiotics have not been shown to provide any clinical benefit in patients with acute ReA [7].

The treatment of chronic ReA is more difficult and often requires either disease-modifying antirheumatic drugs (DMARDs) or biological agents. Although clinical trials have not definitively demonstrated efficacy with methotrexate, it is still considered to be the most used DMARD to treat patients with chronic disease and is often the first line of therapy [7]. When chronic ReA is refractory to both NSAIDs and DMARDs or in situations of progressive disease, clinical studies support the use of tumor necrosis factor alpha antibodies (including infliximab, etanercept, adalimumab) or interleukin-6 receptor antibodies (including tocilizumab) [7].

ReA is a seronegative spondyloarthropathy often associated with extra-articular manifestations. Clinical presentation can initially be nonspecific but given its propensity for progression to chronic disease, early diagnosis and treatment are imperative to avoid excessive morbidity in these patients.

Funding: This research received no external funding.

Conflicts of Interest: The author declares no conflict of interest.

References

1. Jubber, A.; Moorthy, A. Reactive arthritis: a clinical review. *J. R. Coll. Physicians Edinb.* **2021**, *51*, 288–297. [CrossRef] [PubMed]
2. Cheeti, A.; Chakraborty, R.K.; Ramphul, K. Reactive Arthritis. In *StatPearls*; StatPearls Publishing: Treasure Island, FL, USA, 2 January 2023.
3. McGillicuddy, D.C.; Shah, K.H.; Friedberg, R.P.; Nathanson, L.A.; Edlow, J.A. How sensitive is the synovial fluid white blood cell count in diagnosing septic arthritis? *Am. J. Emerg. Med.* **2007**, *25*, 749–752. [CrossRef] [PubMed]
4. Holmes, K.K.; Counts, G.W.; Beaty, H.N. Disseminated gonococcal infection. *Ann. Intern. Med.* **1971**, *74*, 979–993. [CrossRef] [PubMed]
5. Helfgott, S.M. Monoarthritis in adults: Etiology and evaluation. In UptoDate; Post, T.W., Ed.; 2024. Available online: https://www.uptodate.com/contents/monoarthritis-in-adults-etiology-and-evaluation (accessed on 9 September 2024).
6. Apstein, M. Whipples Disease. In *UptoDate*; Post, T.W., Ed.; 2024. Available online: https://www.uptodate.com/contents/whipples-disease (accessed on 9 September 2024).
7. Bentaleb, I.; Abdelghani KBen Rostom, S.; Amine, B.; Laatar, A.; Bahiri, R. Reactive Arthritis: Update. *Curr. Clin. Microbiol. Rep.* **2020**, *7*, 124–132. [CrossRef] [PubMed]
8. Horowitz, D.L.; Katzap, E.; Horowitz, S.; Barilla-LaBarca, M.-L. Approach to septic arthritis. *Am. Fam. Physician* **2011**, *84*, 653–660. [PubMed]