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CASE REPORT

A case of reactive arthritis due to *Clostridium difficile* colitis

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Reactive arthritis is an acute, aseptic, inflammatory arthropathy following an infectious process but removed from the site of primary infection. It is often attributed to genitourinary and enteric pathogens, such as *Chlamydia*, *Salmonella*, *Shigella*, *Campylobacter*, and *Yersinia,* in susceptible individuals. An uncommon and less recognized cause of this disease is preceding colonic infection with *Clostridium difficile*, an organism associated with pseudomembranous colitis and diarrhea in hospitalized patients and those recently exposed to antibiotics. Recognition of this association may be complicated by non-specific presentation of diarrhea, the interval between gastrointestinal and arthritic symptoms, and the wide differential in mono- and oligoarthritis. We present the case of a 61-year-old, hospitalized patient recently treated for *C. difficile* colitis who developed sudden, non-traumatic, right knee pain and swelling. Physical examination and radiographs disclosed joint effusion, and sterile aspiration produced cloudy fluid with predominant neutrophils and no growth on cultures. Diagnostic accuracy is enhanced by contemporaneous laboratory investigations excluding other entities such as gout and rheumatoid arthritis and other infections that typically precede reactive arthritis. Contribution of *Clostridium* infection to reactive arthritis is an obscure association frequently difficult to prove, but this organism is warranted inclusion in the differential of reactive arthritis.

Keywords: *Clostridium*; *reactive arthritis*; *Reiter's*; *arthritis*

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The patient is a 61-year-old white male with a past medical history significant for diverticulosis and small bowel obstructions who was admitted with severe abdominal pain. His past surgical history was significant for many intraabdominal surgeries including internal hernias. He had recently been hospitalized at a different institution for incisional hernia causing small bowel obstruction, managed non-operatively, when diarrhea developed. At that time, he tested positive for *Clostridium difficile* by stool antigen and was started on a 2-week course of oral vancomycin. That regimen completed 3 days prior to presentation to our institution with abdominal pain, nausea, and vomiting. He was admitted for symptom management with intravenous hydration, antiemetics, and analgesia.

Despite treatment, symptoms of abdominal pain, diarrhea, nausea, and vomiting persisted. His prolonged intolerance to oral intake would eventually necessitate parenteral nutrition, but this resolved over the course of the hospitalization. Within 1 year prior to presentation, the patient had colonoscopy which revealed only diverticulosis, suggesting that these symptoms were unlikely inflammatory bowel disease manifestations. Gastroenterology was consulted on this admission, and biopsy of the sigmoid colon showed no significant pathologic abnormality. Stool toxin assay was positive, and another course of oral vancomycin was initiated.

On Day 6 of admission, 23 days after the initial treatment of *C. difficile* colitis was started, the patient awoke to the first instance of pain and swelling in his right knee. The joint was edematous without erythema or warmth, and range of motion was reduced in both active and passive flexion and extension. He sustained no trauma precipitating the effusion and denied prior history of joint effusion and gout. Relevant laboratory studies on the day of effusion development included leukocyte count 3.0 thou/mcL, platelet count 142 thou/mcL, erythrocyte sedimentation rate 37 mm/h, and uric acid 2.2 mg/dL. The patient was found to be positive for HLA-B27. Rheumatoid factor and anti-cyclic citrullinated peptide

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studies were negative. Amplified RNA probes for *Gonorrhea* and *Chlamydia* were negative. Serologic testing for Lyme disease was negative. Three-view radiograph of the knee revealed only mild joint space narrowing in the medial tibiofemoral compartment and joint capsular distension (Fig. 1). Arthrocentesis of the affected knee revealed cloudy appearance of synovial fluid with white blood cell (WBC) count 3,960/mm^3, 98% neutophils, 1% lymphocytes, 1% mononuclear cells, and no crystals under light microscopy. Gram stain and cultures of synovial fluid were negative.

No other acute effusions developed while the patient was under medical surveillance following initial aspiration. Pain resolved with injection of a mixture solution containing lidocaine, triamcinolone, and dexamethasone at the time of aspiration, and he was given further treatment for inflammatory symptoms with oral ibuprofen. He was able to bear weight on both lower extremities, and the range of motion improved following aspiration. Three days later he was discharged to complete second antibiotic course as outpatient. He experienced no recurrence of mono- or oligoarthritis and never endorsed urethritis or uveitis.

Discussion

The Centers for Disease Control and Prevention reported nearly half a million cases of healthcare-associated infection with *C. difficile* in 2011. Those affected tend to be older patients who frequently or recently received antibiotics and healthcare in the hospital setting. Interdiction of this epidemic has involved changing prescribing practices and hygienic and disinfectant guidelines in hospitals. The importance of this infection to hospitals has increased drastically with its incidence. Reactive arthritis is more often an outpatient concern and a cause of morbidity rather than mortality, but recognition of its associated etiologies, including occult ones such as *Clostridium*, can help a clinician more holistically appreciate a clinical presentation.

Reactive arthritis is commonly referred to by its eponym Reiter's syndrome for Dr. Hans Reiter, who described a triad of non-gonococcal urethritis, arthritis, and uveitis in a German officer during World War One. It is an inflammatory arthritis which is reactive to some other infection. Classically, this infection is genitourinary *Chlamydia*, but in the intervening century a wider range of infections producing this syndrome have been accepted. Reactive arthritis most often involves joints asymmetrically. While infection plays a role in its etiology, it is distinguished from septic arthritis by lack of organisms in the involved joint and characteristic inflammatory rather than infectious findings on synovial fluid analysis.

Many mild cases of reactive arthritis are certainly unrecognized and may not present to medical attention (1). In this case, the duration of time between diarrhea, or at least when it was first recognized and treated, and arthritis symptoms was 23 days. The interval between diarrhea and onset of arthritis is variable (2). Had the patient not been under medical surveillance as inpatient for recurrent abdominal pain, the stiff knee may have been left to resolve on its own. If the preceding infection was unknown, the association between it and the joint involvement may not have been drawn. If the effusion developed in the outpatient setting, it may initially be attributed to trauma. Confidence in the diagnosis of this case is enhanced by knowledge of the recent medical history and active surveillance in the inpatient setting when reactive arthritis developed.

Synovial fluid analysis is an important laboratory investigation and can distinguish normal synovial fluid from inflammatory, non-inflammatory, septic, and hemorrhagic effusions on the basis of color, clarity, number of leukocytes, and percentage of polymorphonuclear leukocytes (PMN). Crystal analysis under polarized light

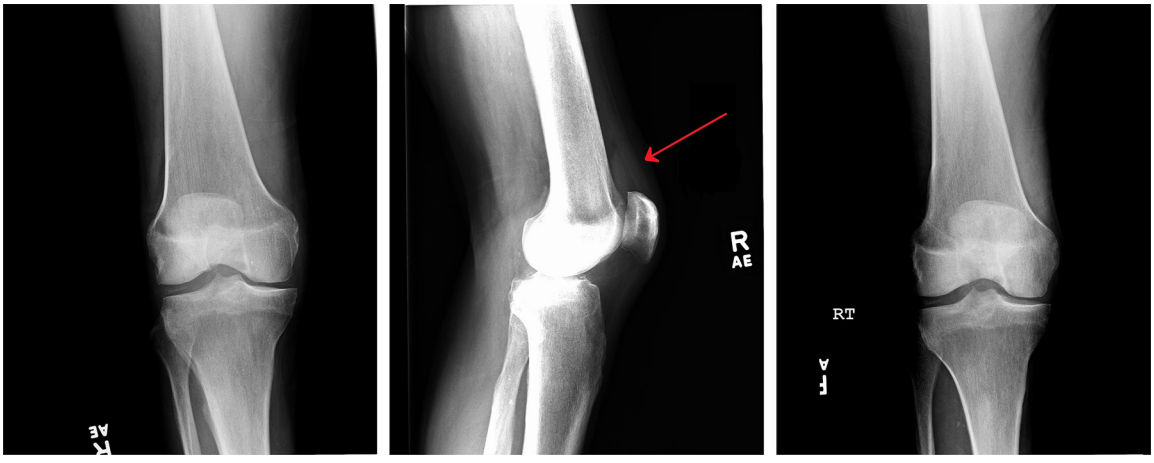

Fig. 1. Three-view radiographs of the right knee demonstrate mild joint space narrowing of the medial tibiofemoral compartment and capsular distension.

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can illuminate gout and pseudogout, and Gram stain and culture can isolate the infectious species in septic arthritis. Exact reference values vary slightly, but in general normal synovial fluid should be transparent and clear with less than 200 leukocytes per cubic millimeter, less than 25% of which are PMNs. Non-inflammatory exudates are of larger volume and tend toward a yellow color; leukocyte count may be as high at 1,000, but still less than 25% of these are PMNs. Inflammatory synovial fluid can appear translucent or opaque. Leukocyte counts range from 1,000 to 100,000, of which greater than 50% are PMNs. Some sources use 4,000 leukocytes per mm^3 as the lower limit. We theorize that our patient's synovial fluid WBC count sitting on the lower end of this spectrum is reflective of his systemic leukopenia; recall that his serum WBC count on the day of effusion development was 3.0. 98% neutrophils in our patient's synovial fluid was an important finding, as synovial fluid WBC count and percentage of polymorphonuclear cells perform well as discriminators between inflammatory and non-inflammatory disease (3). Septic arthritis will present with opaque synovial fluid which contains leukocytes numbering 15,000 to over 100,000, greater than 75% of which are PMNs. Cultures are usually positive. This is a critical diagnosis. Finally, hemorrhagic effusions will be bloody and red. If investigated similarly, hemorrhagic effusions will be found to have WBC count 200–2,000 with 50–75% of them being PMNs.

Many individuals afflicted by reactive arthritis carry an allele for a human leukocyte antigen-B, one of the three main components of major histocompatibility class 1, of subtype 27. Positivity for HLA-B27 is associated with seronegative spondylarthropathies, a group of autoimmune disorders negative for rheumatoid factor. In addition to reactive arthritis, this includes psoriatic arthritis and ankylosing spondylitis. Inflammatory bowel disease is also associated with this allele. While not all patients with reactive arthritis will test positive for HLA-B27, the finding in this patient further suggested a seronegative spondylarthropathy of which only reactive arthritis was a reasonable diagnosis.

Reactive arthritis is associated with several gastrointestinal pathogens. Among these, *Shigella*, *Salmonella*, *Campylobacter*, and *Yersinia* are the best recognized. A small but growing body of literature now includes *Clostridium* on this list of enteric bacteria (2, 4–11), including in pediatric cases (12). In total, 23 cases of proposed reactive arthritis due to *C. difficile* prior to this have been published. Classically, this syndrome is associated with sexually transmitted *Chlamydia trachomatis* (although it is actually more associated with other *Chlamydia trachomatis* serovars). The eye, urinary tract, and asymmetric joint involvement in classical presentation led to the clinical mnemonic 'can't see, can't pee, can't climb a tree'. Some sources reserve the term Reiter's syndrome for only those cases involving this complete triad and refer to others, such as our case, as reactive arthritis. Other sources have discontinued using the term Reiter's syndrome altogether and refer to all triggered autoimmune reactions from remote infection as reactive arthritis. The most commonly involved joints are the large and medium joints of the lower extremities, and articular involvement may be solitary or multiple. Unlike rheumatoid arthritis, multiple joint involvement is typically asymmetric.

The pathogenesis of reactive arthritis secondary to a Chlamydial infection and ankylosing spondylitis are active subject areas of study accelerated by genomic investigation. Of the seronegative spondylarthropathies, ankylosing spondylitis is used as the prototypical disease (13). In laboratory investigations specifically focused on reactive arthritis, the genetics, anatomic localization of, and response to *Chlamydia*, *Salmonella*, and *Yersinia* have received far more attention than *Clostridium* (14). The similarity of the pathogenesis of reactive arthritis due to *C. difficile* is assumed but not directly studied. *Salmonella*, *Shigella*, *Campylobacter*, and *Yersinia* likely share more in common with *Clostridium* in the pathogenesis of induction of reactive arthritis than *Chlamydia* due to the unique development cycle and antigenicity of *Chlamydia*. Research suggests that the implicated enteric pathogens persist *in vivo* subclinically, possibly in gut mucosa–associated lymphoid tissue or lymph nodes, with variation in the specific distribution or duration based on species (15, 16). Nevertheless, antibiotics are not the mainstay of treatment. Gut inflammation, interleukins, tumor necrosis factors, and genetic susceptibility interplay, but this has not been specifically described in reactive arthritis due to *C. difficile*. As this association becomes better recognized and *Clostridium* infections become a heavier nuisance to the healthcare system, the specific pathogenesis may receive more focused attention in primary research.

C. difficile, a Gram-positive, spore-forming bacteria, is most commonly associated with colonic infection. This case highlights its involvement in precipitating reactive arthritis. Other extracolonic manifestations of *Clostridium* include bacteremia/sepsis, visceral abscesses, prosthesis infection, and osteomyelitis. Encephalopathy attributed to high titers of circulating *C. difficile* toxins has been proposed (17). While articular involvement may persist after gastrointestinal symptoms resolve, the long-term prognosis of *C. difficile*–associated reactive arthritis properly treated with anti-inflammatory drugs seems to be excellent (8, 10, 18).

Conclusion

Reactive arthritis is an inflammatory, asymmetric, aseptic arthritis associated with recent bouts of certain gastrointestinal and genitourinary infections, particularly in susceptible individuals positive for HLA-B27. This case

adds to the small but growing body of literature necessitating the inclusion of *C. difficile* as a causative agent of reactive arthritis, and confidence is enhanced as pertinent investigations of alternate diagnoses were undertaken immediately in inpatient setting. Physicians should consider this association in patients recently presenting with or completing treatment for colonic symptoms who have new arthritis or when investigating the source of an arthropathy inconsistent with other rheumatologic entities.

Competing interests and funding

The authors declare that there is no conflict of interests regarding the publication of this paper.

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