Alerts, Notices, and Case Reports

Reactive Arthritis Induced by *Clostridium difficile*

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REACTIVE ARTHRITIS without microbial invasion of the joint is associated with various viral, bacterial, parasitic, and mycoplasmal infections. I report an unusual case of reactive arthritis associated with *Clostridium difficile*-induced pseudomembranous enterocolitis.

Report of a Case

The patient, a 66-year-old man with excellent health in the past, was well until three weeks before hospital admission when an abscess developed in a tooth. He was treated with oral penicillin VK, 250 mg four times a day. On the third day of penicillin treatment, intermittent, diffuse, crampy abdominal pain developed. The next day profuse, watery, nonbloody diarrhea accompanied his abdominal pain, occurring 10 to 15 times per day. Over the next ten days the patient's abdominal pain and diarrhea lessened but did not disappear, occurring once or twice a day. Seven days before admission and ten days after the onset of diarrhea, he awakened with a swollen, painful right fourth toe. The following day he had increased pain and swelling in his right knee and right shoulder. The pain progressively worsened and was unrelieved by aspirin. He then sought medical attention, was found to have a fever of 38.9°C (102°F), and was admitted to the hospital.

There was no history of similar episodes of arthritis and diarrhea, foreign travel, shellfish ingestion, chills, skin rash, sore throat, dysuria, urethral discharge, conjunctivitis, uveitis, or photophobia. His daughter had had idiopathic uveitis several years previously.

On physical examination he was alert, thin, and appeared sick, with a pulse rate of 100 beats per minute, a blood pressure of 120/70 mm of mercury, and a temperature of 38.9°C. The right knee, right shoulder, and the proximal interphalangeal joint of the right fourth toe were swollen, with increased warmth, tenderness, and erythema. There were no petechiae, splinter hemorrhages, or rash. The other physical findings were normal, with the exception of deafness and a slightly enlarged prostate.

Synovial fluid from aspiration of the right knee effusion revealed a leukocyte count of 30×10^9 per liter (30×10^3 per mm^3), with 0.60 neutrophils and 0.40 lymphocytes; no crystals; a negative Gram's stain; and no growth on culture. Sigmoidoscopy revealed classic pseudomembranous colitis. Culture of stool specimens was negative for *Yersinia, Salmonella, Shigella,* and *Campylobacter* species. Stool culture grew *C difficile,* but no toxin was identified. Stool examinations did not reveal ova or parasites. Tests for antinuclear antibody, rheumatoid factor, occult blood in the stool, and cultures of blood were negative; the complete blood count, chemistry values, chest film, and electrocardiogram were normal. X-ray films of the right shoulder and right knee were normal with the exception of effusions.

The patient was initially treated with ibuprofen, 600 mg four times a day, and vancomycin hydrochloride, 500 mg orally every six hours. His symptoms disappeared entirely within 48 hours. Therapy was then switched to oral metronidazole, 250 mg three times a day, and he completed an eight-day course of oral antibiotics. He had complete resolution of all joint symptoms and signs at the completion of antibiotic therapy and discontinued taking ibuprofen.

Seven days after completing the course of antibiotics, he again had the onset of diffuse, crampy abdominal pain and profuse, nonbloody, watery diarrhea. Over the ensuing 12 hours, a fever of 38.3°C (101°F) developed, with pain, swelling, and erythema of the right shoulder, right knee, and proximal interphalangeal joint of the right fourth toe. Physical findings were otherwise unchanged from those noted previously.

Stool examination was again negative for *Yersinia, Campylobacter, Shigella,* and *Salmonella* species, *Staphylococcus aureus*, and ova and parasites. Stool culture grew *C difficile,* and *C difficile* toxin was identified. Colonoscopy showed patchy colitis without pseudomembranes. Several colon biopsy specimens were obtained that showed a nonspecific colitis without features of ulcerative colitis or Crohn's disease. HLA typing was positive for B27.

The patient was treated with vancomycin, 500 mg orally every six hours, and ibuprofen, 600 mg four times a day. His symptoms rapidly disappeared, and he remained asymptomatic following a seven-day course of therapy.

Discussion

Reactive arthritis is a well-recognized sequela of a variety of gastrointestinal disorders that include inflammatory bowel disease, jejunoileal bypass, and various gastrointestinal infections, including those caused by *Salmonella, Shigella, Yersinia,* and *Campylobacter* species and *Strongyloides stercoralis, Taenia saginata*, and *Ancylostoma duodenale.*[1]

Antibiotic-induced pseudomembranous enterocolitis has become common and widespread with the increasing use of broad-spectrum antibiotics. In 1977 Larson and coworkers identified a fecal toxin neutralized by *Clostridium sordellii* antitoxin as the cause of antibiotic-induced pseudomembranous enterocolitis,[2] and soon afterward en-

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terotoxin-producing strains of *C difficile* were identified as the source of this toxin.[3] Although pseudomembranous enterocolitis induced by *C difficile* is now commonly recognized, reactive sterile arthritis associated with this disorder has been rare. Several cases of reactive arthritis associated with pseudomembranous enterocolitis were reported before the discovery of *C difficile* that had the characteristic history of this disorder.[4,5] In 1980 Fairweather and associates reported a case of reactive arthritis associated with documented *C difficile*-induced enterocolitis.[6] Since then there have been scattered reports in the English-language literature.

Reactive arthritis induced by *C difficile* typically presents as an asymmetric oligoarthritis or polyarthritis of predominantly the large joints, occurring one to two weeks after the onset of the enteral infection. The arthritis may be migratory and appear as an enthesopathy predominantly involving tendons and their insertions.[4,7] The arthritis can last from weeks to years, and there may be other nongastrointestinal manifestations associated with it. Urethritis with *C difficile* reactive arthritis was described by Hayward and colleagues.[8] The classic triad of Reiter's syndrome—urethritis, conjunctivitis, arthritis—has been described in 2 of the 15 cases reported to date.[9,10] Iritis and pleuritis have been described with *C difficile*-induced reactive arthritis, but the skin, cardiac, and neurologic manifestations of reactive arthritis associated with other infections have not been reported.[7,10]

The exact mechanism through which reactive arthritis occurs is unclear. It has been postulated that systemic absorption of *C difficile* toxin with resultant antibody production may be important in the pathogenesis of reactive arthritis associated with *C difficile*-induced enteritis. In reactive arthritis induced by *Salmonella* species, the severity of the arthritis appears to fluctuate with the levels of *Salmonella* antibodies,[11] and in inflammatory bowel disease the severity of the arthritis appears to correlate with the level of circulating immune complexes.[12] Urticaria has occurred before the onset of arthritis associated with *C difficile*-induced diarrhea, supporting an immune-complex cause.[4,13] Antitoxin has been shown in 2 patients with *C difficile*-induced reactive arthritis,[6,14] but not in 11 others with *C difficile* enterocolitis without arthritis.[6] This further suggests that the cause of arthritis is immune-complex disease or antibody cross-reactivity with synovial tissue. *Clostridium difficile*-induced reactive arthritis, however, has not been described with the other signs or symptoms associated with immune-complex disease, and there are cases of *C difficile*-induced reactive arthritis occurring without the presence of antitoxin.[8,9] In this patient the presence of antitoxin was unfortunately not determined.

The association of HLA-B27 with postinfectious Reiter's syndrome and reactive arthritis following infection with *Salmonella, Shigella,* or *Yersinia* species is clear, occurring in 80% to 90% of the cases.[15] It is speculated that HLA-B27 is a marker for an immune response gene determining susceptibility to an environmental trigger for reactive arthritis. The role of HLA-B27 in *C difficile*-induced reactive arthritis is unclear. The patient described herein was HLA-B27-positive. Although the number of cases reported in the literature is small, *C difficile*-induced reactive arthritis appears to be associated with HLA-B27 in 10 of 15 patients (66%).[7-10,13-19]

The success of the treatment of *C difficile*-induced reactive arthritis has been variable, with symptoms resolving in two weeks to two years. Cope and co-workers suggested a correlation between the presence of HLA-B27 and prolonged arthritis in patients with *C difficile*-induced diarrhea. Review of all the published cases does not support this assumption.[6-10,13-19] A wide variety of anti-inflammatory agents has been used in the treatment of *C difficile*-induced reactive arthritis, including oral adrenocorticosteroids, intra-articular adrenocorticosteroids, and nonsteroidal anti-inflammatory agents with the last used most often. Although the course of the arthritis does not clearly correlate with the resolution of diarrhea or the eradication of *C difficile* and toxin from the stool, it appears to be shorter in patients treated with oral vancomycin. In the case reported herein, there was a definite correlation between the resolution of the patient's gastrointestinal symptoms with oral vancomycin therapy and that of his reactive arthritis, as has been shown in another patient with relapsing *C difficile*-induced reactive arthritis.[8]

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