Reactive arthritis mimicking inflammatory bowel disease arthritis: a challenging diagnosis

Trabulo D[1], Mangualde J[1], Cremers I[1], Oliveira AP[1]

ACTA REUMATOL PORT. 2014:39;188-192

ABSTRACT

Reactive arthritis comprises a subgroup of infection-associated arthritis, which occurs after genitourinary or gastrointestinal tract infection in genetically susceptible hosts. Studies have proposed *Salmonella, Shigella* or *Yersinia* as microorganisms responsible for the post-dysenteric form. The human leukocyte antigen (HLA)-B27 is a well-recognised predisposing factor. We report a case of HLA-B27-associated reactive arthritis after *Salmonella goldcoast* enteritis, mimicking inflammatory bowel disease arthritis.

Keywords: Reactive arthritis; HLA B27; Inflammatory bowel disease; *Salmonella goldocoast*

INTRODUCTION

Bacterial infections are believed to trigger certain types of arthritis. The strongest support for this theory is based in reactive arthritis and inflammatory bowel disease arthritis.

Reactive arthritis is a sterile arthritis triggered by distant gastrointestinal or urogenital infections, often with some latency. Its pathogenesis is incompletely understood and no optimal treatment is available[1]. *Salmonella spp* infections are implicated in the triggering of enteric reactive arthritis[2]. When arthritis begins, stool cultures are usually negative and the laboratory diagnosis is often dependent on serological tests[2]. In some patients, symptoms resolve within months, while others, may persist for years. HLA-B27 is the strongest predisposing factor of reactive arthritis[3].

Arthritis occurs in a few patients with inflammatory bowel disease, slightly more often in Crohn disease than in ulcerative colitis[4,5]. This enteropathic arthritis is usually nondestructive and reversible. The peripheral arthritis may precede the diagnosis of inflammatory bowel disease and, once established, often parallels the activity of the inflammatory bowel disease. Spondylitis rarely occurs prior to the diagnosis of inflammatory bowel disease and does not correlate with the activity of the underlying bowel disease.

These conditions belong to the category of spondyloarthropathies, which also include ankylosing spondylitis and psoriatic arthritis[6].

Arthritis has also been described in association with other intestinal disorders such as celiac disease, Whipple's disease, and microscopic colitis[6].

This article reports a challenging diagnosis of reactive arthritis in a patient with *Salmonella goldcoast* infection, which mimicked inflammatory bowel disease arthritis.

CASE REPORT

A 28-year-old man was admitted to the emergency room with a clinical picture characterized by fever, bloody diarrhea and abdominal pain for 8 days. He developed arthralgia of the right hip joint two weeks after the onset of the enteritis. Physical examination revealed swelling and tenderness of the hip joint and tenderness over the sacroiliac joints. Laboratory studies showed white blood cell count of 24.300/mm^3, with 87% neutrophils, platelet count of 573.000/mm^3 and C-reactive protein of 18.9 mg/dL (0 to 0.5). Blood and stool cultures were sterile. Synovial fluid from the right hip joint revealed severe inflammation, but Gram staining and culturing were negative. The patient was diagnosed with aseptic arthritis with rapidly progressive hip destruction. He underwent arthroplasty of the right hip joint and was discharged from the orthopedic ward with pain relief medications. However, he maintained bloody diarrhea (with a frequency of six to eight stools, daily and nightly) with abdominal pain, and ele-

1. Serviço de Gastrenterologia - Hospital de São Bernardo - Centro Hospitalar de Setúbal

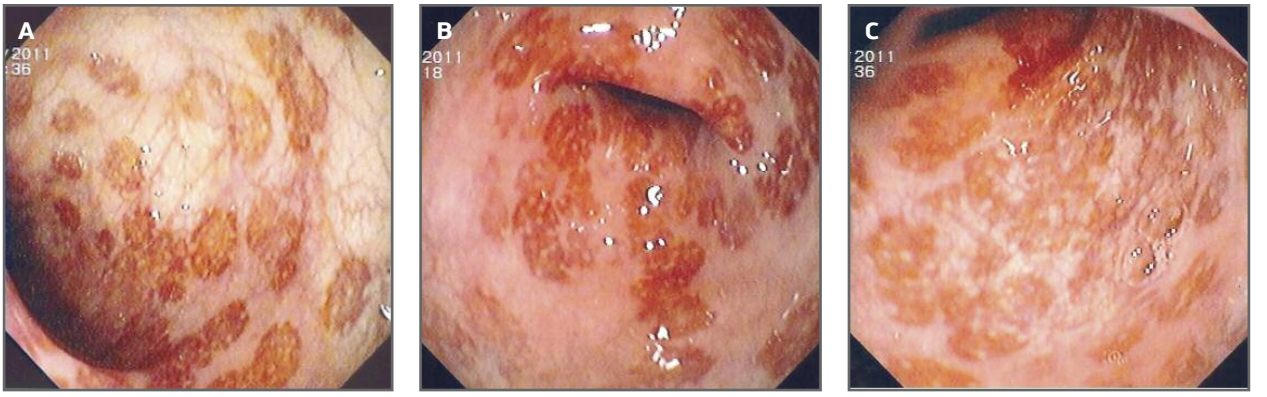

FIGURE 1. Aspects of the colonic mucosa in rectossigmoidoscopy: focalized and irregular areas with hyperemia and superficial erosions, surrounded by areas of normal mucosa

vation of inflammatory parameters so he was referred to outpatient clinic of Gastroenterology.

In this consultation, besides abdominal symptoms, he presented intermittent mild fever, headache and prostration. He also presented pain, swelling and morning stiffness of the right wrist joint, metacarpophalangeal joints, sacroiliac joints and left ankle, withoutbalanitis, urethral discharge, hematuria, or genital ulcers.

Occupational history revealed daily work with an aquarium with tropical fishes and regular mouth water suction for cleaning. He denied contact with other animals, drug habits, recent travel or ingestion of contaminated food. He had never received a blood transfusion and had no history of sexual contacts. He also denied familiar similar history.

At physical examination, the patient presented tachycardia and fever (38,2ºC). He presented diffuse abdominal pain, without palpable masses, organomegalies or signs of peritoneal irritation. He had polyarthritis of the previously mentioned joints, with gait ataxia. He had no cutaneous rash. Cardiac and pulmonary auscultation, as well as neurological exam, were unremarkable.

Laboratory studies showed white blood cell count of 17.900/mm3, with 80% of neutrophils, platelet count of 426.000/mm^3, an erythrocyte sedimentation rate of 75 (0 to 15) mm/hr, and C-reactive protein of 16.7 (0 to 0.5) mg/dL. Liver and renal function tests showed no abnormalities. Urinalysis and urine culture were negative. The patient underwent a flexible rectossigmoidoscopy, which revealed focalized and irregular areas with hyperemia and superficial erosions, surrounded by areas of normal mucosa, in the whole extension observed (60 cm) (Figures 1A, 1B and 1C).

In this context, the differential diagnosis with reactive arthritis following gastrointestinal infection, inflammatory bowel disease arthritis, Whipple's disease or vasculitis with gastrointestinal involvement was considered.

The pathological examination revealed vascular congestion, hemorrhagic foci, crypt abscesses and lymphoplasmacytic and neutrophilic inflammatory infiltrate of the lamina propria, with no distortion of the architecture (Figures 2A, 2B and 2C).

Whipple's disease was excluded by normal, biopsies of the second portion of the duodenum. Immunological markers were negative including antinuclear antibody, extractable nuclear antigen antibodies panel, anticardiolipin antibody, lupic anticoagulant antibody, antibeta2-glycoprotein-1 antibody, anti-DNA antibody and rheumatoid factor antibodies. HLA class I serotyping was positive for B27. VDRL, HIV, CMV, EBV, Borrelia and Ricketsia antibody tests were also negative.

Radiographs of the sacroiliacs showed signs of sacroiliitis grade I/IV; however ankle, wrist and metacarpophalangeal x-rays showed only soft tissue swelling, without enthesopathic lesions or erosive joint damage. Ultrasound of wrist, ankle and metacarpophalangeal joints showed synovitis grade II in grey scale without erosions. MRI of the sacroiliac joints showed edema with incipient periosteal resorption and mild erosions in the lower third.

The stool culture was positive for *Salmonella goldcoast* in 3 samples. Parasitological and mycological cultures were sterile.

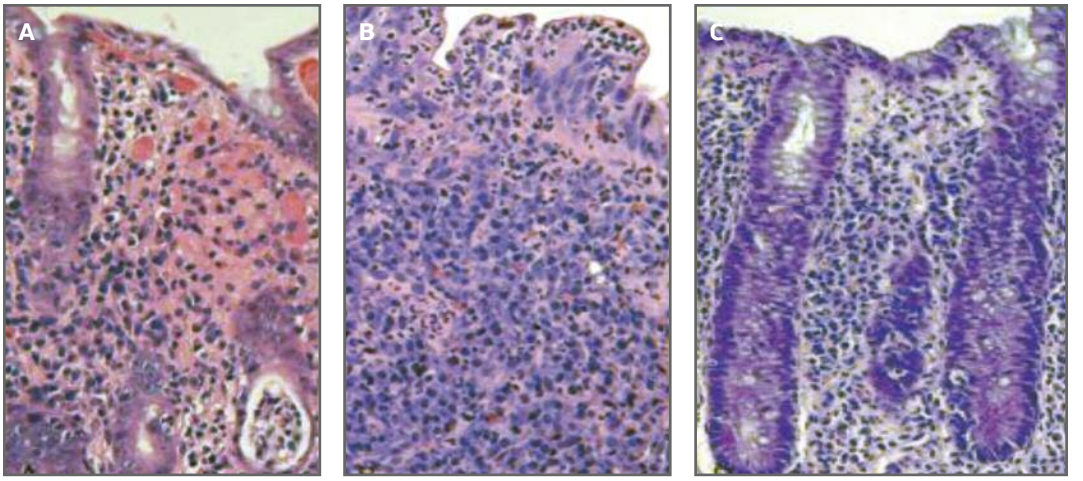

FIGURE 2. Pathologic examination of the biopsies of colonic mucosa showing hemorrhagic foci, crypt abscesses, lymphoplasmacytic and neutrophilic inflammatory infiltrate of the lamina propria, with mild distortion of the architecture

The patient was treated with ciprofloxacin 200 mg every 12h and ibuprofen 400 mg every 8 hours, for 8 days, and was advised to abandon the habit of sucking water from the aquarium. He significantly improved his gastrointestinal symptoms after one week. Colonoscopy 3 weeks later was normal. Musculosqueletal symptoms resolved with non-steroidal anti-inflammatory drug (NSAID) without corticosteroids or disease modifying antirheumatic drugs (DMARDs). Currently, after a 12 months follow-up, he remains asymptomatic, with no chronic pain or muscle wasting.

DISCUSSION

Considering the clinical features, the preceding symptomatic enteritis, the occupational history and the positive stool cultures for *Salmonella goldcoast*, we proposed a diagnosis of reactive arthritis to salmonellosis, triggered by the recreational habit of sucking contaminated water from an aquarium, possibly the source of maintained infection.

Reactive arthritis is a sterile synovitis triggered by a distant infection of the genitourinary or gastrointestinal tract. Researchers have proposed its classification into HLA-B27-associated and non-associated forms and have observed a number of other clinical features associated with reactive arthritis[7]. According to the American Rheumatism Association criteria, patients with reactive arthritis generally have asymmetric polyarthritis that lasts at least one month, as well as one or more of the following features: urethritis, inflammatory eye disease, mouth ulcers, balanitis, or radiographic evidence of sacroilitis, periostitis, or heel spurs[8].

Generally, the diagnosis of reactive arthritis is clinical; there are no definite diagnostic laboratory tests or radiographic findings[2]. In the present case, apart from the elevated sedimentation rate, C-reactive protein, and neutrophilic leukocytosis, which suggested a bacterial infection, all laboratory investigation results were negative. Reactive arthritis cases commonly show elevated sedimentation rate and acute phase reactants. It is closely associated with HLA-B27, as our patient presented. HLA-B27 antigen, increases the risk of the disease and 70 to 80% of patients with reactive arthritis have this antigen[7-9]. HLA-B27 probably shares some molecular characteristics with bacterial epitopes and researchers have suggested that an autoimmune cross-reaction takes part in its pathogenesis[9].

The etiology of reactive arthritis is still incompletely understood. However, the development of reactive arthritis is closely associated with certain bacterial infections, including *Salmonella*, *Shigella*, *Yersinia*, and *Chlamydia*[2,7,9]. The incidence of *Salmonella*-induced reactive arthritis varies greatly, from 5 to 14 per 100.000 people[3]. In this case, the patient had three stool cultures positive for *Salmonella goldcoast* which belongs to serogroup C. It was first isolated in Ghana in 1953[10]. *S. goldcoast* was identified as the agent responsible for outbreaks in Europe involving the consumption of meat, vegetable, dried food products or contact with domestic animals/pets[10-12]. In general, the prevalence of

Salmonella in fish and shellfish is considered to be low (0,4-2,3%). However, they can be contaminated if the water becomes contaminated[13].

This patient had enteritis prior to reactive arthritis onset and jointsymptoms accompanied intestinal symptoms and persisted over the time. They were probably triggered by the persistent habit of sucking contaminated water from an aquarium with tropical fish. However, we cannot exclude another source of *Salmonella goldcoast* infection, since no cultures of the aquarium water were made to confirm that hypothesis.

Arthritis may also occur as an extraintestinal manifestation of inflammatory bowel disease (IBD), making differential diagnosis sometimes challenging. There are no pathognomonic findings to distinguish arthritis associated with IBD from reactive arthritis, thus it remains a diagnosis of exclusion. Acute phase reactants usually reflect the activity of the intestinal disease and are not useful in assessing peripheral arthritis or spondylitis. Radiograph study of the sacroiliac joints often presents abnormal findings even in IBD patients without gastrointestinal symptoms. Plain radiographs of the peripheral joints may present soft-tissue swelling, juxta-articular osteoporosis and mild periostitis usually without erosions or destruction[14,15].

Relevant conditions for differential diagnosis of patients with both intestinal involvement and arthritis, include Whipple's disease, Behçet's disease, celiac disease, parasitic infestation, pseudo-membranous colitis and as a result of intestinal bypass surgery, which were excluded by the tests performed.

General treatment of reactive arthritis most commonly employs NSAIDs[2,3,7]. Low dose steroids may help in acute symptomatic arthritis, especially when inflammatory symptoms are resistant to the NSAIDS. About 15% of the patients develop chronic spondyloarthritis after recurrent acute arthritides. In such patients, treatment with DMARDs has been tried, with different results and limited published data. Sulphasalazine has been shown to be effective when used in chronic reactive arthritis[16]. Methotrexate and leflunomide has also been used, but with limited efficacy, similar to ankylosing spondylitis[17,18]. Biologicals are a new class of drugs shown to be effective in chronic HLA-B27 associated diseases such as in ankylosing spondylitis[19], chronic spondyloarthritis[20] and psoriatic arthritis[21]. Our patient showed a good response to NSAID treatment.

The natural history of reactive arthritis varies considerably, depending on the triggering pathogen, the patient's genetic background and gender, and the presence of recurrent arthritis[3]. Most patients remit completely or have little active disease 6 months after presentation[22].

Chronic persistent arthritis, lasting more than 6 months, occurs in only a small proportion of patients. Patients with reactive arthritis, who are HLA-B27 positive, usually have more severe involvement and a worse prognosis than patients who are HLA-B27 negative in some studies, suggesting that they are more likely to develop a chronic spondyloarthropathy[23].

Some patients with chronic reactive arthritis can develop features of another spondyloarthritides, e.g. psoriatic arthritis, ankylosing spondylitis or arthritis associated with inflammatory bowel disease. Patients with the triad of postinfectious arthritis, urethritis, and conjunctivitis may also have a poorer prognosis[24,25].

CONCLUSION

Reactive arthritis is a form of arthritis associated with a co-existing or recent history of extra-articular infection. Certain enteric pathogens are commonly accepted as capable of causing reactive arthritis, which include *Salmonella spp*. Musculoskeletal features of reactive arthritis typically develop one to four weeks following an acute infection and include asymmetric oligoarthritis, often affecting the lower extremities.

Disorders that can cause acute mono or oligoarthritis, particularly those associated with bowel diseases, make the diagnosis with inflammatory bowel diseases difficult and sometimes challenging. In this case report, the diagnosis was based upon the presence of characteristic musculoskeletal features and ongoing enteric infection, excluding other causes of arthritis. Occupational history and stool cultures are essential tools to confirm infection in patients with gastrointestinal symptoms.

CORRESPONDENCE TO
Daniel Trabulo
Rua Arminda Correia, Lote 4 – 8º B
1750 Lisboa
E-mail: danieltrabulo@yahoo.com

REFERENCES

1. Granfors K, Jalkanen S, Lindberg AA, et al. Salmonella lipopolysaccharide in synovial cells from patients with reactive arthritis. Lancet 1990;335:685–688.
2. Chun P, Kim Jin Y, Mi Han Y, Mi Kim Y. A case of reactive arthritis after Salmonella enteritis in in a 12-year-old boy. Korean J Pe-

diatr 2011; 54: 313–315.
3. Colmegna I, Cuchacovich R, Espinoza LR. HLA-B27-associated reactive arthritis: pathogenetic and clinical considerations. Clin Microbiol Rev 2004;17:348–369.
4. de Vlam K, Mielants H, Cuvelier C, De Keyser F, Veys EM, De Vos M. Spondyloarthropathy is underestimated in inflammatory bowel disease: prevalence and HLA association. J Rheumatol 2000; 27:2860
5. Rudwaleit M, Baeten D. Ankylosing spondylitis and bowel disease. Best Pract Res Clin Rheumatol 2006; 20:451.
6. Schur P. Arthritis associated with gastrointestinal disease. www.uptodate.com.
7. Leirisalo-Repo M. Reactive arthritis. Scand J Rheumatol 2005;34:251–259.
8. Willkens RF, Arnett FC, Bitter T, et al. Reiter's syndrome. Evaluation of preliminary criteria for definite disease. Arthritis Rheum 1981;24:844–849
9. Colmegna I, Cuchacovich R, Espinoza LR. HLA-B27-associated reactive arthritis: pathogenetic and clinical considerations. Clin Microbiol Rev 2004;17:348–369.
10. Bremer V, Leitmeyer K, Jensen E, et al. Outbreak of Salmonella goldcoast infections linked to consumption of fermented sausage. Epidemiol Infect 2004, 132, 881–887.
11. European Centre for Disease Prevention and Control. Annual Threat Report 2009. Stockholm: ECDC; 2010.
12. Coia J, Cormican M, Ethelberg S, Fisher I, Pezzi G,Hjertqvist M. Outbreak of Salmonella goldcoast affecting tourists exposed in Majorca from the UK, Ireland, Sweden, Norway and Denmark. Euro surveillance: bulletin europeen sur les maladies transmissibles. Nov 2005; 10(10):E051027.3.
13. Scientific Committee On Veterinary Measures Relating To Public Health On Salmonellae In Foodstuffs. European Commission. Health & Consumer Protection. Directorate C - Scientific Opinions. 2003; 13-29.
14. Wordsworth P. Arthritis and inflammatory bowel disease. Curr Rheumatol Rep 2000;2:87.
15. Weiner, SR, Clarke, J, Taggart, N, Utsinger, PD. Rheumatic manifestations of inflammatory bowel disease. Semin Arthritis Rheum 1991; 20:353.
16. Clegg DO, Reda DJ, Weisman MH, et al. Comparison of sulfasalazine and placebo in the treatment of reactive arthritis (Reiter's syndrome). A Department of Veterans Affairs Cooperative Study. Arthritis & Rheumatism 1996; 39:2021-2027.
17. Chen J. Is methotrexate effective for the treatment of ankylosing spondylitis? Nature Clinical Practice in Rheumatology 2007; 3: 490-491
18. Van Denderen JC, Van der Paardt M, Nurmohamed MT, De Ryck YM, Dijkmans BA, Van der Horst-Bruinsma IE. Double-blind. randomised, placebo-controlled study of leflunomide in the treatment of active ankylosing spondylitis. Annals of the Rheumatic Diseases 2005; 64:1761-1764
19. Braun J, Brandt J, Listing J, et al. Treatment of active ankylosing spondylitis with infliximab: a randomised controlled multicenter trial. Lancet 2002; 359:1187-1193
20. De Keyser F, Baeten D, Van den BF, Kruithof E, Mielants H, Veys EM. Infliximab in patients who have spondyloarthropathy: clinical efficacy, safety, and biological immunomodulation. Rheumatic Disease Clinics of North America; 2003. 29:463-479
21. Antoni CE, Kavanaugh A, Kirkham B, et al. Sustained benefits of infliximab therapy for dermatologic and articular manifestations of psoriatic arthritis: results from the infliximab multinational psoriatic arthritis controlled trial (IMPACT). Arthritis & Rheumatism 2005;52:1227-1236
22. Kvien TK, Gaston JS, Bardin T, et al. Three month treatment of reactive arthritis with azithromycin: a EULAR double blind, placebo controlled study. Ann Rheum Dis 2004; 63:1113–1119
23. Hannu T, Inman R, Granfors K, Leirisalo-Repo M. Reactive arthritis or post-infectious arthritis? Best Pract Res Clin Rheumatol 2006; 20:419.
24. Leirisalo-Repo M, Suoranta H. Ten-year follow-up study of patients with Yersinia arthritis. Arthritis Rheum 1988; 31:533.
25. Hart HH, McGuigan LE, Gow PJ, Grigor RR. Reiter's syndrome: chronicity of symptoms and employment. Aust N Z J Med 1986; 16:452.