

# Ulcerative colitis and rheumatoid arthritis: a rare association – case report

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## ABSTRACT

Ulcerative colitis is an autoimmune disorder of unknown etiology. Although the large intestine is the major focus of autoimmunity, resulting in chronic diarrhea, that is actually a systemic disease, with numerous extraintestinal manifestations, such as articular involvement. The frequent association of a number of autoimmune diseases in the same patient has been described. However, the coexistence of ulcerative colitis and rheumatoid arthritis is rare. The authors report a case of ulcerative colitis associated with rheumatoid arthritis, in which colitis occurred 12 years before the onset of inflammatory arthropathy.

**Keywords:** rheumatoid arthritis, ulcerative colitis, spondyloarthritis.

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## INTRODUCTION

Ulcerative colitis (UC) is a systemic inflammatory disease of unknown etiology and essentially autoimmune nature, affecting predominantly the colon and rectum, and resulting in chronic diarrhea. Although the association between autoimmune diseases is known, the coexistence of colitis and rheumatoid arthritis (RA) is rare.<sup>1</sup>

Joint involvement occurs in both UC and Crohn's disease, being observed in up to 30% of the cases. Two patterns of joint involvement have been described: the spondylitic and the peripheral forms. Both can precede the intestinal disorders, although arthropathy usually manifests after colitis.<sup>2</sup>

The spondylitic form is clinically and radiologically similar to ankylosing spondylitis. Peripheral arthropathy usually presents as an asymmetric oligoarthritis, affecting mainly the lower limbs. Compared with RA, its course is usually more acute and non-erosive, and, in general, controlling the intestinal

inflammation induces remission. However, it can be chronic and erosive in 10% of the patients. Norton et al.<sup>3</sup> have described patients with atypical arthropathy, erosions, destruction and deformities associated with Crohn's disease. Most patients are seronegative, although low titles of rheumatoid factor (RF) can occur. Association with anti-cyclic citrullinated peptide antibody (anti-CCP) has not been described. Arthritis of the small joints of the hands and wrists is rare. Such involvement requires the differential diagnosis with RA, especially in the presence of positive RF.<sup>2-4</sup>

The differential diagnosis between arthropathy secondary to inflammatory bowel disease, also called enteropathic arthropathy, and the occurrence of joint manifestations related to other pathologies concomitant with UC is sometimes challenging.

The authors report one case of the association between UC and RA, in which colitis occurred 12 years before the onset of inflammatory arthropathy.

Received on 02/07/2011. Approved on 05/08/2012. The authors declare no conflict of interest.

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## CASE REPORT

The patient is a female from the city of Santana, state of Bahia, who sought the Rheumatology Outpatient Clinic in May 2005 complaining of pain and edema in the second, third and fourth proximal interphalangeal (PIP) joints of hands and wrists, accompanied by morning stiffness lasting 1 hour and 30 minutes. She reported symptom onset in 2001. She denied other joint manifestations, sicca syndrome, photosensitivity, orogenital ulcers, cutaneous rash and Raynaud's phenomenon. She reported chronic diarrhea and treatment with a coloproctologist, being diagnosed with UC in 1989. On the occasion, she had liquid diarrhea with mucus, pus and blood for six months, and the colonoscopy evidenced pancolitis, longitudinal ulcers and pseudopolyps. The biopsy then showed intense infiltration of polymorphonuclear cells in the mucosa and crypt abscesses. The patient was using sulfasalazine (2 g/day) regularly.

On physical examination, the patient had arthritis of the second, third and fourth PIP of her hands and wrists, and no other abnormalities. Her complementary exams were as follows: normal red blood count; erythrocyte sedimentation rate, 60 mm; positive C-reactive protein; normal renal and hepatic functions; RF, 451 UI/mL; anti-CCP, 439.5 UI/mL; antinuclear antibody, 1:40, nuclear fine speckled pattern; negative ANCA. The radiograph of her hands showed a marked reduction in the joint space of the carpal joints and marginal erosions in the ulnar styloid process, bilaterally (Figure 1). The diagnosis was RA associated with UC. The prescription of methotrexate (15 mg/week) improved the joint findings. In December 2009, the intestinal and joint manifestations relapsed. Her



**Figure 1**  
Symmetrical reduction in the joint spaces of the wrists with bilateral erosions in the ulnar styloid process.

management was reassessed, and anti-TNF therapy was started, with significant improvement of both joint and intestinal symptoms.

## DISCUSSION

The coexistence of RA and other autoimmune diseases, such as autoimmune thyroiditis, vitiligo, and systemic lupus erythematosus, is common. The major association reported is with the Sjögren syndrome, which occurs in as much as 30% of the cases. Association with inflammatory bowel disease is rarely observed.<sup>2,5</sup>

The association of RA and UC has been rarely reported in the literature. Aoyangi et al.,<sup>6</sup> in a prospective cohort conducted between 1980 and 1989 with patients with UC, have not observed any case of overlapping with RA. Utsunomiya<sup>7</sup> has reported a 0.4% prevalence of RA in 5,833 patients with UC. Sawada<sup>8</sup> has reported the same prevalence in a smaller study with 1,433 patients. Snook et al.<sup>9</sup> have reported only seven cases of RA in 858 patients with UC. In most reports, UC complicated the course of established RA.<sup>5-9</sup>

Regarding our patient, the insidious disease onset, the involvement of the small joints of her hands and wrists, the radiographic findings, and the positive RF and anti-CCP support the hypothesis of the coexistence of RA and UC. Anti-CCP is rarely present in other rheumatic diseases, such as psoriatic arthritis. It seems to be directly related to smoking, which amplifies the process of citrullination of autoantigens. Up to 1% of healthy controls and 2%–5% of sick controls react to anti-CCP, usually at low titers, with a mean level of 39 UI/mL. High concentrations of anti-CCP are almost exclusively associated with RA.<sup>10</sup>

The relationship between RA and UC has not been clearly defined. Certain genes might predispose to both conditions simultaneously. So far, however, no genetic risk factor has been identified. Studies carried out in patients with UC and controls have suggested that HLA-DR4 act as a protective factor against colitis. This could justify the rare association, because that antigen of the class II major histocompatibility complex plays an important role in the pathogenesis of RA.<sup>11</sup>

The use of immunosuppressive drugs for treating UC can also play a relevant role in the low frequency of the association with RA. Drugs, such as sulfasalazine and corticosteroids, inhibit the systemic inflammatory response, justifying the lower incidence of other autoimmune pathologies concomitantly with inflammatory bowel disease.

Abnormal immune response to intestinal bacteria has been demonstrated in different types of arthritis. Some studies in

animal models have reported that fragments of the bacterial cell wall, mainly the polysaccharide complexes, can trigger both synovitis and colitis via T cell activation. However, the gastrointestinal tract infection might play a relevant role in both UC and RA.<sup>12,13</sup> Asada et al.<sup>2</sup> have described a case of UC occurring during the course of RA, accompanied by selective IgA deficiency, which favors the breaking of the barrier against the intestinal flora, widening the exposure of the immune cells of the mucosa to bacterial antigens.<sup>2</sup>

Confirmation of the increased expression of interleukin 15 in the intestinal mucosa, similarly to that which happens in rheumatoid synovia, and the weak evidence of Th2 response predominance in UC support the link between both entities. However, those findings are still insufficient to totally explain the mechanisms involved in the coexistence of both diseases.<sup>12,13</sup>

Recently, Amezcua et al.<sup>14</sup> have described UC in a patient with RA after using abatacept. It is speculated that the use of that drug would modify the balance of pro-inflammatory mediators and the lymphocytic profile, favoring the

occurrence of a new autoimmune disease. The blockade to co-stimulation could interfere with the maintenance and development of regulatory T cells, which control intestinal inflammation.<sup>14</sup>

Colitis can complicate the RA course. In this case, the presence of the following should be considered: rheumatoid vasculitis; drug-induced colitis; secondary amyloidosis; and infectious colitis (pseudomembranous and cytomegalovirus colitis).<sup>13,14</sup>

When RA occurs in the course of established UC, the major differential diagnosis is arthropathy secondary to inflammatory intestinal disease itself.<sup>13</sup>

In the presence of peripheral arthritis in patients with inflammatory intestinal disease, the diagnosis of enteropathic arthropathy should be carefully considered. Although up to 30% of the patients can have that systemic manifestation, differential diagnoses, such as overlapping with RA, should not be neglected. Further studies are required to enhance the understanding of the pathogenic mechanisms determining that rare association.

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