CASE REPORT

Rheumatoid Arthritis Associated with Ulcerative Colitis

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ABSTRACT

Introduction: **Extra-intestinal mainly articular features of inflammatory bowel disease (IBD) are common and may precede the IBD. Several well-documented reports have revealed that axial manifestations are the most frequent type of inflammatory arthritis which develops in patients with IBD. The frequent association of a number of autoimmune diseases in the same patient has also been described. However, RA associated with IBD is rare and the underlying mechanism remains unknown.**

Case Presentation: **This report describes a 53-year-old woman with ulcerative colitis (UC) and who was diagnosed 14 years after the onset of IBD with RA, based on clinical, radiological and immunologic findings.**

Conclusion: **Because of the paucity of data in this field, we reviewed the cases of overlap RA-IBD and we discussed in this article its treatment stemming from few reports.**

KEY WORDS

inflammatory bowel disease, rheumatoid arthritis, ulcerative colitis, non steroidal anti-inflammatory drug, Salazosulfapyridine, Methotrexate

INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic relapsing inflammatory disease of the gastrointestinal tract which manifests as two distinct clinical entities, Crohn's disease (CD) and ulcerative colitis (UC). Due to the systemic nature of IBD, a large number of patients present also with extra intestinal manifestations involving most commonly joints[1,2]. Rheumatoid arthritis (RA) associated with IBD is scarce; hence the underlying mechanisms of this association remain not obvious. Few cases have been reported in the literature[3-6]. Then, we report a case of RA in a patient with a long-standing ulcerative colitis, we review the cases reported in literature and we discuss the treatment.

CASE PRESENTATION

A 53 year-old woman with a 14 year history of distal ulcerative colitis was admitted to our internal department. The diagnosis of distal ulcerative colitis was established on 1997 when the patient was admitted to the gastroenterology department with an acute abdominal pain, diarrhea with blood-stained stool and weight loss. Barium enema showed lack of haustrations in the sigmoid colon and spiculation from the rectum to the sigmoid colon. Pancolonoscopy revealed friability and localized ulcerative lesion in the rectum, and biopsy specimens showed inflammatory changes compatible with ulcerative colitis. There had been no extra-intestinal manifestations. She was treated with drugs including Salazosulfapyridine and corticosteroid enema 14 years earlier.

On admission to the hospital, she complained of joint pains affecting the elbows, wrists, metacarpophalangeal and proximal interphalangeal joints which lasted for two years with morning stiffness of 2 hours. She was afebrile. The abdomen was minimally tender. Examination of the joints revealed pain and swelling of the second and fourth proximal interphalangeal and metacarpophalangeal joints, both wrists, synovitis of the second and third proximal interphalangeal joints likewise a range of motion restriction and pain of both elbows. Furthermore, other joints showed no tenderness or swelling. She did not experience low back or sacroiliac joint pain. She was in complete remission with normal stool frequency and no rectal bleeding.

The laboratory tests showed a hemoglobin at 13.7 g/dl, white leukocyte count at 5.37 x 10^3/mm^3, platelets at 160 x 10^3/mm^3, C- reactive protein at 4.2 mg/L and erythrocyte sedimentation rate at 25 mm/hour. Blood urea, electrolytes and urine analysis were within the normal range.

Rheumatoid factor was positive at 63 U/ml (normal less than 14 IU/ml), anti-cyclic citrullinated peptide antibodies were positive at 75.33 U/ml (normal less than 5 IU/ml) and antinuclear antibodies were negative.

Skeletal radiographs showed typical small geodes in numerous joints of the hands (figure 1) and foots (figure 2) and skeletal X-ray study showed no abnormalities in cervical and lumbar spine and hip joints.

Other than Salazosulfapyridine 2000 mg/day, the patient was initiated on non steroidal anti-inflammatory drug (NSAID) 75 mg/day and Methotrexate 10 mg/week leading to prompt and complete resolution of all articular features. There was no exacerbation of intestinal lesions without any recurrence over the following year. The patient is currently well and seen regularly in the outpatient department. She is maintained on Salazosulfapyridine at 2000 mg/day, Methotrexate 10 mg/day and NSAID 75 mg/day.

Received on October 12, 2023 and accepted on November 4, 2023

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Table1: Review of literature of 19 cases of RA associated with IBD

Case	Number cases	Age (years)	Sexe	IBD	Term RA-IBD	Radiographs	RF/anti-CCP/ANA	Treatment	Follow-up
Sugisaki K *et al* [3]	1	29	F	UC	25 years after IBD	NA	-/ NA	Inravenous Prednisolone Mesalazine enema Methotrexate: 8 mg/week	Remission of UC and RA
Asada Y *et al* [4]	1	56	F	UC	29 years after IBD	Stage III	+/ NA	Intravenous Prednisolone Leucocyte pheresis Treatment of RA non mentioned	Remission of UC RA status unchanged
Aydin Y *et al* [5]	1	36	F	UC	1 year before IBD	Stage I	+/ NA	Salazosulfapyridine: 3g/day Mesalazine enema Methotrexate: 7.5 mg/week	Remission of UC and RA
Adachi Y *et al* [6]	7	58	F	UC	16 months before IBD	Stage III	+/NA/+ HLA-DR4	Salazosulfapyridine: 3g/day, Prednisolone: 7.5 mg/day	Remission of UC and RA
		51	M	UC	3 years before IBD	Stage III	NA	NSAID	Remission of UC and RA
		29	F	UC	4 years before IBD	Stage III	NA	Steroids	NA
		37	F	UC	7 years before IBD	Stage III	NA	NSAID, steroids	NA
		43	F	UC	9 years before IBD	Stage IV	Prednisolone, D Penicillamine		NA
		49	F	UC	9 years before IBD		NA	NSAID, Prednisolone, Salazosulfapyridine	NA
		65	M	UC	30 years before IBD	Stage II	NA	Prednisolone	NA
Klausen *et al* [9]	1	50	M	UC	33 years after IBD	Stage III Sacroiliitis	- / NA/+ HLA-B27	Salazosulfapyridine:1.5 g three time /day, Prednisone enema: 10 mg/day Surgamyl, Withdrawal of D-Penicillamine and NSAID	Remission of RA and UC
Andrisani G *et al* [10]	1	54	F	UC	17 years before IBD	Stage III	-/-/NA	Methotrexate: 15 mg/week, Prednisolone: 1 mg/kg/day, Azathioprine:2 mg/kg/day, Withdrawal of NSAID, Adalimumab:40 mg/2 weeks	Remission of UC and RA
Boyer F *et al* [11]	1	36	F	UC	Concomitant	Stage III	NA HLA-DR1	Methotrexate: 15 mg/week Salazosulfapyridine: 3 g/day	Remission of UC and RA
Toussirot E *et al* [12]	2	60	M	CD	NA (CD before RA)	Sacroiliitis	+/ NA HLA-DR1	NA	NA
		65	F	CD	15 years after IBD		+/ NA HLA-DR1	NA	NA
Cruz VA *et al* [13]	1	NA	F	UC	12 years before IBD	Stage II	+/+/+(1/40)	Methotrexate:15 mg/week TNF blockades	Relapsing of RA treated with anti-TNF with improvement of both RA and UC
Amezcua-Guerra LM et al [14]	1	55	M	UC	7 years after IBD	NA	+/ NA	Methotrexate:25 mg/week Salazosulfapyridine:1.5 g/day Mesalazine enema Prednisone:5 mg/day Leflunomide: 20 mg/day	Remission of UC and active RA
Georgiadis AN *et al* [15]	1	46	F	CD	14 years before IBD	Stage IV	+/NA	Methotrexate: 10 mg/week, Cyclosporine A:100 mg/day, Prednisone: 2.5 mg/day	NA
Our case	1	53	F	UC	14 years after IBD	Stage III	+/+/+ (1/320)	Salazosulfapyridine 2000 mg/day, NSAID: 75 mg/day, Methotrexate: 10 mg/week	Remission of UC and RA

IBD: Inflammatory bowel disease; RA: Rheumatoid arthritis; RF: Rheumatoid factor; anti-CCP: anti-citrullin protein; ANA: anti-nuclear anti-bodies; NA: not available; M: male; F: female; UC: ulcerative colitis; CD: Crohn disease; NSAID: Non steroidal anti-inflammatory drug.

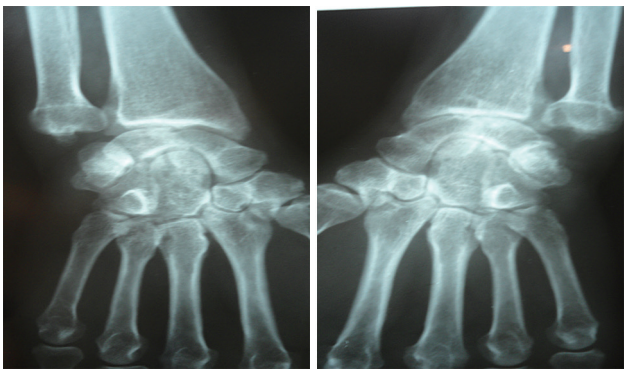

Figure 1: Multiple geodes of the wrist.

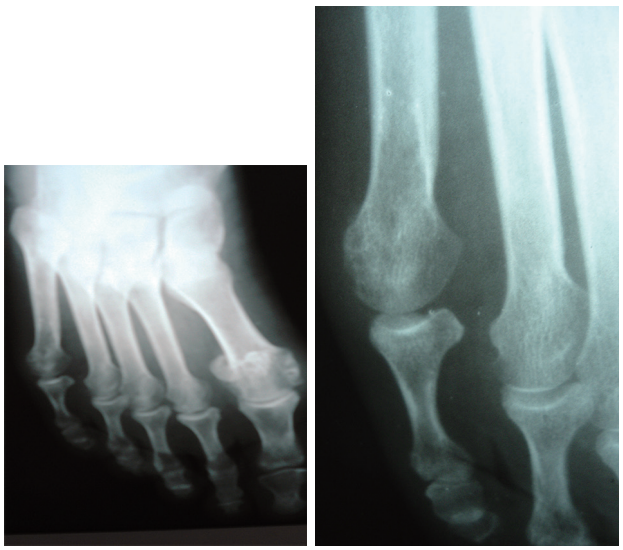

Figure 2: Geodes of the 5th metatarsal of the right foot

DISCUSSION

Joint involvement is present in almost 30% of patients with IBD[1] and includes peripheral and especially axial involvement[1,2] The prevalence of axial involvement in patients with IBD is between 5 and 30%[1,2] and peripheral arthropathy between 10 and 20%[1,2]. Indeed, peripheral arthropathy has been classified into two patterns[2]. Type I arthropathy (5%)[2]; a pauciarticular arthritis typically affects fewer than five often large joints, predominantly those of the lower limbs and is generally migratory, transient and assymetric but recurrent[2]. Type II arthropathy (3-4%) is a polyarthritis mainly affecting the small joints and usually runs a course independent of IBD. It rarely precedes the diagnosis of IBD[6]. Its main differential diagnosis is RA that may hardly overlap with IBD and requires radiographic and immunologic correlation[2].

To our knowledge, there are 26 case reports in the literature describing the association of RA and IBD (Table 1), though sometimes seronegative RA[3,7]. Data missed in 7 cases reported by Snook *et al*[8]. The median age at diagnosis of associated RA-UC in those cases was 48 years old (29-65 years old), and the male/female ratio was 0.36 (5 men and 14 women). The epidemiological data suggest that this association tends to occur in older population of IDB patients. The most commonly associated IBD was UC in 16 cases like our patient, CD was only reported in 3 cases (Table 1).

RA was seen concurrently with IBD in one case, preceded the onset of bowel symptoms in 11 cases and occurred, like our case, in 7 patients with longstanding IBD (Table 1). As shown in the most cases, it is sometimes difficult to distinguish by articular manifestations between the two diseases especially which start at the same time. More severe clinical course and a higher incidence of synovitis, and deformities and typical radiologic geodes may obviously advocate the diagnosis of RA, further the presence of rheumatoid factor and HLA-DR[6,16,17]. Rheumatoid factor is absent in most patients with arthropathy due to IBD[2]. Table 1 showed positive RF in 7 cases.

RA associated with IBD was treated with steroids in 11 patients, Salazosulfapyridine in 10, Methotrexate in 8, leukocyte aphresis in one, Azathioprine in one, Cyclosporin A in one, Leflunomide in one. The TNF blockades were prescribed in 2 relapsing cases[18,19]. The combination of Methotrexate and Salazosulfapyridine was noticed in 4 cases. NSAID were withdrawn in only 2 cases. Of note, no patient underwent surgical treatment. Our review suggests that when RA was associated with IBD, the two diseases can be controlled by only medical treatment.

Actually, when colitis appeared in RA patients, drug-induced colitis, infectious, ischemic colitis due to rheumatoid vasculitis[3,7,10] must be first ruled out. Furthermore, few case reports were published reporting flares of IBD during course of NSAID[1,12] treatment and TNF blockades especially Etanercept[1] and Abatacept[9].

In fact, the association RA with IBD may draw the attention to the probable underlying mechanism of the pathogenesis of both diseases[1,4,5]. Coexistence of RA and IBD may be explained by the changes in gut flora caused by treatment for RA especially NSAID[7,11]. In a large, prospective cohort study, Kefalakes H et al found that NSAIDs used with greater weekly doses, and for longer duration were associated with an increased risk of IBD[11]. Moreover, the two diseases may have important mechanisms in common, at least in part through the contribution of T-helper1 / T-helper2 cytokine balance [14/20] by releasing the major pro-inflammatory cytokines TNF-α, IL-1, IL-8, INF-γ, IL-6, IL-12 and IL-2[1,12,14,21].

In our patient, according to the criteria of the American College of Rheumatology, the diagnosis of RA was quite established and the diagnosis of UC was made on the basis of the clinical course, endoscopic findings and histopathological examination.

Since therapy in RA is primarily based on NSAID to improve pain and stiffness, the strategy to minimize adverse effects related to NSAIDs in patients with IBD is to use the lowest effective dose to induce remission in patients with active IBD. There is, therefore, a need for a careful follow-up[12]. The use of the selective COX-2 inhibitors may be safer than NSAIDs[12]. Intra-articular corticosteroid injections and oral corticosteroids can be also associated.

Although several studies assess the efficacy of Methotrexate which may have a steroid-sparing effect in IBD patients, Salazosulfapyridine must often be used as first-line treatment of overlap RA-IBD because it may decrease the risk of colorectal cancer.

Then, it is worth noting in a meta-analysis of nine studies that the use of oral 5-aminosalicylic acid was associated with a lower risk of colorectal cancer (odds ratio [OR]: 0.51; 95% CI: 0.37-0.69)[20]. Given that our patient had already received oral Salazosulfapyridine even at 2000 mg/day with exacerbation of RA, NSAID and Methotrexate were associated leading to promptly and maintained remission.

Since IBD may be regarded as dysregulated immune response, several studies have recently showed the efficacy of TNF blockades (infliximab, adalimumab) in particularly refractory CD and UC with a high capacity to induce clinical remission and mucosal healing as well as for both axial and peripheral arthritis[1,10,13,21]. Thereby, these new agents are promising in management of RA associated with IBD refractory to conventional therapies.

In conclusion, peripheral arthritis is not an uncommon finding in IBD. Though rare, the diagnosis of overlap RA should be raised. This case enhances the intricate pathogenesis of RA and UC as well the tricky task of treatment. Further studies are required to ravel out the mechanism underlying this association and to establish the guidelines of management of overlap RA-IBD.

CONFLICT OF INTEREST

The authors declare they have no competing interests.

ETHICS APPROVAL

The authors obtained the approval of research ethics committee to carry out this study.

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