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Anti-cyclic citrullinated peptide antibodies in ulcerative colitis with and without joint involvement

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Anti-cyclic citrullinated peptide antibodies in ulcerative colitis with and without joint involvement

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Abstract

Background

Joint affection is the most common extraintestinal manifestation of ulcerative colitis (UC). Despite the high specificity of anti-cyclic citrullinated peptide (CCP) antibodies for rheumatoid arthritis, their role in UC remains unclear.

Aim

The aims of this study were to assess the prevalence of anti-CCP antibodies in patients with UC and to investigate any association with joint affection.

Patients and methods

A total of 60 patients with UC were studied. Demographic data were collected, careful history was taken, and clinical examination including rheumatologic examination was done. A blood sample was collected for assessment of anti-CCP and other laboratory tests. Colonoscopy was done for assessment of severity and extension of UC.

Results

Joint affection was found in 28.33% of patients. Anti-CCP antibody was positive in 8.33% of patients. There were no statistically significant differences between patients with positive and negative anti-CCP antibody regarding joint affection or UC activity or extension.

Conclusion

The prevalence of anti-CCP antibodies in patients with UC was 8.33%, but there was no association between the presence of these antibodies and the joint affection or disease activity or extension.

Keywords: Cyclic citrullinated peptide antibodies, joint, ulcerative colitis

INTRODUCTION

Ulcerative colitis (UC) is a chronic idiopathic inflammatory condition causing continuous mucosal inflammation of the colon without granulomas on biopsy, affecting the rectum and a variable extent of the colon in continuity, which is characterized by a relapsing and remitting course. It is characterized by rectal bleeding, diarrhea, abdominal pain, weight loss, and fever. UC is a chronic disorder of immune system that affects gastrointestinal tract in genetically susceptible patients [1].

Extraintestinal manifestations occur in 25% of patients with this condition, and the most common extraintestinal manifestations are musculoskeletal involvements, including

articular, periarticular, and muscular involvement. UC-related arthropathy develops as joint destruction and is classified as an inflammatory arthritis [2,3].

Anti-cyclic citrullinated peptide (anti-CCP) antibody titers were introduced firstly to have important prognostic and diagnostic values for patients with rheumatoid arthritis (RA) [4] (with sensitivity of 80% and a specificity of 98%), and studies identified that patients with anti-CCP positive RA had more severe radiographic damage than other anti-CCP negative

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ones [5]. Moreover, recently several studies demonstrated that other inflammatory arthropathies are associated with these autoantibodies, such as juvenile idiopathic arthritis, psoriatic arthritis palindromic rheumatism [6–8], and erosive arthritis in systemic lupus erythematosus [9] and these autoantibodies are also found in 7.5% of patients with primary Sjögren syndrome [10].

Despite the relatively high prevalence of musculoskeletal affection in UC, few studies have evaluated anti-CCP in this disease.

The aims of this study were to assess the prevalence of anti-CCP antibodies in patients with UC and to investigate any association with joint involvement.

PATIENTS AND METHODS

Sixty patients with UC were included in this study and were selected from the GIT Unit and the Internal Medicine Department, at Mataria Teaching Hospital, Cairo, Egypt, from June 2016 to November 2017.

Inclusion criteria are age more than or equal to 17 years and diagnosis of UC at least 3 months prior to inclusion. The diagnosis of UC was established by classic clinical, laboratory, and endoscopic parameters, including histopathology criteria [11,12]. Only patients with a definite diagnosis of UC were included. Patients with established or suspected diagnosis of RA and other rheumatologic diseases were excluded.

All studied patients were subjected to the following:

Demographic data, such as age and sex, were collected.

Careful history taking (clinical presentation and duration of UC, frequency of bowel movement, presence and amount of blood in stool, fever, articular manifestations, erythema, warmth, and motion limitation).

Thorough clinical examination, including pulse, temperature, and a complete rheumatologic examination.

Arthritis was defined as at least one previous or current episode of pain, swelling, and increased skin temperature in one or more joints. Peripheral arthritis diagnosed by clinical examination and peripheral joint disease diagnosed by disease history were recorded separately. Radiography was performed when clinical findings were suggestive of erosive arthritis. Peripheral arthritis associated with UC was considered when other causes of joint diseases were ruled out. Arthralgia was recorded based on patients' self-reporting peripheral joint pain and mobility restriction without any objective sign of active inflammation detected either by the treating physician or by a consulting rheumatologist.

Laboratory investigations including complete blood count, erythrocyte sedimentation rate, C-reactive protein, and anti-CCP.

Anti-cyclic citrullinated peptide

Anti-CCP was studied using the third-generation assays for anti-CCP 'Quanta Lite CCP3.1 IgG/IgA ELISA'

(Inova Diagnostics, San Diego, California, USA), according to manufacturer protocol. The cut-off level was used for CCP positivity more than or equal to 20 U.

UC activity was classified based on Montréal classification of disease activity in UC [12,13] (Table 1).

Colonoscopy was done for assessment of severity and extension of UC. A video colonoscope Pentax EC-3890LK was used.

The endoscopic features of mild inflammation are erythema, vascular congestion, and at least partial loss of the visible vascular pattern. Moderately active colitis is characterized by a complete loss of vascular pattern, blood adherent to the surface of the mucosa, and erosions, often with a coarse granular appearance and mucosal friability (bleeding to light touch). Severe colitis is characterized by spontaneous bleeding and ulceration [14].

Disease extension was classified according to the Montréal classification as 'proctitis': if inflammation limited to the rectum, 'left-sided' refers to disease limited to the proportion of the colon distal to the splenic flexure, and 'extensive' refers to disease extends proximal to the splenic flexure, including pancolitis [13].

This study was approved by the local ethical committee, and informed consent was obtained from every patient.

Statistical analysis

Statistical analysis was performed using SPP Inc., Chicago, Illinois, USA. Data were expressed as the mean \pm SD or as number (percentage) for numerical variables.

The *P* value more than 0.05 indicates no significance (NS), and *P* value less than or equal to 0.05 is considered to be statistically significant.

RESULTS

Sixty patients with UC were included in this study, comprising 30 (50%) male and 30 (50%) female, with 23–46 years old, and the mean age of 32.73 ± 5.34 years.

The duration of the UC ranged from 6 months to 10 years, with mean duration of 2.17 ± 1.78 years.

Regarding the extension of UC, 'proctitis' was found in 19 patients, 'left-sided' colitis in 29 patients, and 'extensive' in 12 patients.

Table 1: Disease activity in ulcerative colitis (Montréal classification)

	Mild	Moderate	Severe
Stools/day	<4	4 or more if	≥ 6 and
Blood in stool	Small	Moderate	Severe
Pulse (bpm)	<90	≤ 90	>90 or
Temperature (°C)	<37.5	≤ 37.8	>37.8 or
Hemoglobin (g/dl)	>11.5	≥ 10.51	<10.5 or
ESR (mm/h)	<20	≤ 30	>30 or
CRP (mg/l)	Normal	≤ 30	>30

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

The endoscopic appearance was mild in 19 patients, moderate in 26 patients, and severe in 15 patients, whereas the disease activity was mild in 31 patients, moderate in 15 patients, and severe in 14 patients.

Joint affection was found in 17 (28.33%) patients. Eight patients had arthralgia, two patients had arthritis, five patients had low back pain, one patient with both arthralgia and low back pain, and one patient had sacroiliitis.

The anti-CCP antibody was positive in five (8.33%) patients.

Demographic, clinical, laboratory, and endoscopic characteristics of patients with positive and negative anti-CCP antibody are summarized in Table 2.

There were no statistically significant differences between patients with positive and negative anti-CCP antibody results regarding age, sex, duration of UC, extension of UC, endoscopic appearance of UC, disease activity of UC, or joint affection.

Demographic, clinical, laboratory, and endoscopic characteristics of patients with UC with and without joint affection are summarized in Table 3.

There were no statistically significant differences between patients with UC with and without joint affection regarding age, sex, duration of UC, extension of UC, endoscopic appearance of UC, disease activity of UC, and presence of anti-CCP antibody.

DISCUSSION

In our study, joint affection was found in 17 (28.3%) patients. Two (3.3%) patients had arthritis, whereas one (1.6%) patient has sacroiliitis. Fourteen (23.3%) patients had noninflammatory joint complaints in the form of arthralgia in eight patients, low back pain in five patients, and both arthralgia and low back pain in one patient.

This finding is consistent with a previously reported study.

In a recent study at 2017, Malaty *et al.* [15], studied 357 patients with UC and found that 17% of patients with UC had at least one type of joint pain.

A retrospective study from Italy reported that of the 160 patients with UC, 53 patients (33.15) had experienced at least one musculoskeletal manifestation [16].

In another retrospective study from Switzerland, 370 patients with UC with mean age of 42 years were studied. Of these, 21% had joint manifestation [17].

Another study by Ditisheim *et al.* [18] studied 994 with UC and found that inflammatory articular disease axial or peripheral was detected in 35.5% of them.

In other studies, the prevalence of joint affection was much higher. D'Inca *et al.* [19] found that the prevalence of self-reported articular symptoms in inflammatory bowel disease (IBD) exceeded 40%.

Table 2: Demographic, clinical, laboratory, and endoscopic characteristics of patients with ulcerative colitis with and without anti-cyclic citrullinated peptide antibodies

	Anti-CCP positive (n=5)	Anti-CCP negative (n=55)	P
Male/female	3/2	27/28	NS
Age (years)	32.6±4.61	32.74±5.31	NS
Smokers	1 (20)	17 (28.3)	NS
Duration of disease	2.18±1.81	2.2±1.79	NS
Disease extension			
Proctitis	2	17	NS
Left-sided colitis	2	27	
Extensive	1	11	
Disease activity			
Mild	2	29	NS
Moderate	1	14	
Severe	2	12	
Endoscopic appearance			
Mild	2	17	NS
Moderate	1	25	
Severe	2	13	
Joint involvement			
Arthralgia	1	7	NS
Arthritis	0	2	
Low back pain	0	5	
Arthralgia and low back pain	0	1	
Sacroiliitis	1	0	

Anti-CCP, anti-cyclic citrullinated peptide.

Table 3: Demographic, clinical, laboratory, and endoscopic characteristics of patients with ulcerative colitis with and without joint affection

	Patients with joint affection (n=17)	Patients with joint affection (n=43)	P
Male/female	6/11	24/19	NS
Age (years)	32.05±4.72	33±5.43	NS
Smokers	2 (11.7)	16 (37.2)	NS
Duration of disease	1.57±0.88	2.41±1.98	NS
Disease extension			
Proctitis	7	12	NS
Left-sided colitis	5	24	
Extensive	5	7	
Disease activity			
Mild	8	23	NS
Moderate	5	10	
Severe	4	10	
Endoscopic appearance			
Mild	6	13	NS
Moderate	6	20	
Severe	5	10	
Anti-CCP positive	2 (11.76)	3 (6.69)	NS

Anti-CCP, anti-cyclic citrullinated peptide.

In a recent Mexican study that were published in 2017, 52.2% of the patients with UC had joint involvement. The

frequency of peripheral arthralgia was 46.8% and of axial arthropathy was 5.4%. The female sex, elevated erythrocyte sedimentation rate, and disease activity are factors associated with its presentation [20].

In our study, the anti-CCP antibody was positive in five patients (8.33%), and there were no statistically significant differences between patients with positive and negative anti-CCP antibody results regarding age, sex, duration of UC, extension of UC, endoscopic appearance of UC, disease activity of UC, or joint affection.

Shafaghi and colleagues found that anti-CCP was detected in 10/93 (10.7%) patients with UC. Overall, 13.9% of patients had peripheral arthritis, and in 23.07% of them, anti-CCP was detected, but no significant association between the prevalence of anti-CCP positivity and UC-related arthritis was found. In addition, there was no association between the presence of these antibodies and activity or extension of inflammatory colitis [21].

Other studies reported very low prevalence of anti-CCP in patients with UC. Papamichael *et al.* [22] found that anti-CCP was positive in 0 of 50 cases of UC. This prevalence was reported to be 1.8% by Koutroubakis *et al.* [23] and 1.2% for IgA subclass of anti-CCP by Haga *et al.* [24].

In consistent with our results, Al-Jarallah and colleagues from Kuwait studied 125 patients with IBD (mean age, 32.6 ± 12.3 years), where 44 (35.2%) had UC and 81 (64.8%) had Crohn's disease. Forty-four (35.2%) patients with IBD developed arthritic manifestations. Antibody positivity was observed in 24/125 (19.2%) patients with IBD and in 18/81 (22.2%) healthy participants [25], and they concluded that autoantibodies to citrullinated proteins were low in IBD-related arthritis.

In a recent study by Van Erp *et al.* [26], at 2017, no differences were found in positivity of anti-CCP between patients with IBD with and without arthropathies.

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Conflicts of interest

There are no conflicts of interest.

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