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Anti-cyclic citrullinated peptide antibodies in ulcerative colitis, and its relation with disease activity

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Abstract

Background: Ulcerative colitis an inflammatory bowel disease (IBD) and chronically idiopathic immune related that associates with extraintestinal manifestations such as arthritis. Despite of the highly specificity of anti-cyclic citrullinated peptide (CCP) antibodies for rheumatoid arthritis, their role in IBD remains unclear. There are only a few studies on the prevalence of anti-CCP antibodies in patients with IBD. This study aimed to assess the prevalence of anti- CCP antibodies in ulcerative colitis and to investigate possible associations with their clinical and laboratory characteristics.

Methods: In this cross-sectional study, 93 consecutive patients with ulcerative colitis referred to gastroenterology clinics in Razi referral hospital of Rasht, Iran, from September 2010 to September 2011. Rheumatologic examination, demographic data and clinical presentation of patients were recorded on specially prepared data sheets. Blood sample was collected for assessment of anti-CCP and other laboratory tests. Data were analyzed by the Chi square test, Fisher Exact test and student t test, using the SPSS 20 software for Windows, and P value less than 0.05 was considered significant.

Results: Of 93 patients, anti-CCP antibodies detected in 10.8% of cases (CI 95%: 4.5-17.1%). There were a significant relation between the prevalence of anti CCP positivity and aphthous ulcers and ocular manifestations whereas other parameters were not significantly related.

Conclusion: Anti CCP may have a possible role in some ulcerative colitis manifestations but there was no association between the presence of these antibodies and activity or extension of inflammatory colitis. We suggest other studies especially molecular studies to investigate other aspects of these antibodies in IBD patients

Keywords: Anti-CCP, Inflammatory bowel disease, Ulcerative colitis, Extra-intestinal manifestation.

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Introduction

The inflammatory bowel diseases (IBD), Crohn's disease (CD) and ulcerative colitis (UC), are chronic disorders of immune system that affect gastrointestinal tract in genetically susceptible patients (1).

Twenty five percent of patients with this condition also develop several extraintestinal manifestations and 6–46% of these, complicate with musculoskeletal involvements as the most common ex traintestinal manifestations including articular, periarticular, and muscular involvement, osteoporosis and fibromyalgia. IBD related arthropathy, develop joint destruction that classified as an inflammatory arthritis (2,3).

On the other hand, historically we know that anti-CCP antibody titers, first intro-

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duced in 1998, have a prognostic value in destruction of joint in RA (4-5). (With sensitivity of 80% and a specificity of 98%) and studies show that radiographic damages in rheumatoid arthritis (RA) patients with positive anti-CCP antibodies are severe than other anti-CCP-negative ones. Moreover recently several studies demonstrated the association between this autoantibodis and arthropathies in other inflammatory conditions such as psoriatic arthritis (PsA), juvenile idiopathic arthritis and palindromic rheumatism (6-8).

Martinez et al showed that anti-CCP antibodies are associated with erosive arthritis in SLE(9)and Gottenberg and colleagues found that 7.5% of patients with primary Sjögren syndrome were positive for anti-CCP antibodies. (10)

Prediction of which IBD patient will develop the arthritis and discrimination of IBD-related arthritis from other anti-CCP positive arthritides could be an important point in treatment and prevention from late musculoskeletal sequels. Nevertheless there are only a few studies on the prevalence of anti-CCP antibodies in patients with IBD.

The aims of this study were to assess the prevalence of anti- CCP antibodies in ulcerative colitis cases and to investigate any associations with their clinical and laboratory characteristics.

Methods

In this cross sectional study, 93 consecutive patients with UC referred to gastroenterology clinics in Razi referral hospital of Rasht, Iran, from September 2010 to September 2011, were enrolled. The diagnosis was established by classic criteria at least 6 months before study entry (11-12).

Patients with established or suspected diagnosis of RA and other rheumatologic diseases were excluded. Disease activity was classified based on Truelove & Witts Criteria in these patients. Colonoscopy was done at this time for endoscopic and pathologic findings.

Disease extension was classified as ulcerative proctitis if inflammation limited to the rectum, ulcerative proctosigmoiditis refers to disease limited to the rectum and sigmoid colon, and not involving the descending colon. Left-sided or distal ulcerative colitis is defined as disease that extends beyond the rectum and as far proximally as the splenic flexure. Extensive colitis refers to disease extends beyond the splenic flexure but not as far as the cecum and ultimately pancolitis, when the inflammatory process extends beyond the splenic flexure involving the cecum.

All patients had a complete rheumatologic examination by an expert rheumatologist at the time of IBD diagnosis. At this stage, past and current occurrence of peripheral arthritis was evaluated in all cases. Arthritis was defined as at least one anamnestic 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. X-rays 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.

Demographic data such as age, sex, and clinical presentation including articular manifestations (erythema, warmness and motion limitation), ocular manifestations (episcleritis, uveitis), dermatologic manifestations (erythema nodosum, pyoderma gangrenosum) of patients were recorded on specially prepared data sheet.

Blood sample was collected during routine venepuncture .Laboratory tests including complete blood count, erythrocyte sedimentation rate, C-reactive protein and anti-CCP.

Anti-CCP reactivity was determined using a commercially available citrullinated protein antibodies ELISA kit of first generation (Genesis Diagnostics, UK), in which citrullinated recombinant rat filagrin is used as the antigen for the detection of anticitrullinated protein antibodies. The assay was performed according to the manufacturer's instructions. Anti-CCP antibodies were

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measured in U/mL and were considered to be positive at a cut-off value of≥ 6.25 units/mL. This study was approved by the local ethical committee and informed consent for drawing extra blood at the time of routine venepuncture was obtained from subjects.

Statistical analysis

Results were expressed as mean ± standard deviation (SD) or as number (percentage). Normality of the variables' distribution was tested by using the one sample Kolmogorov-Smirnov test. Analysis was performed by using Chi square test, Fisher Exact test and student T test. All statistical analyses were done by the SPSS 20 software for Windows and p values less than 0.05 considered significant.

Table 1. Demographic, clinical and laboratory characteristics of patients with ulcerative colitis

	Anti-CCP positive (n=10)	Anti-CCP negative (n=83)	p
Male/female	6/4	57/26	NS
Age, mean ± SD (years)	34.55±10.33	35.36± 12.65	NS
Duration of disease(years, mean ± SD)	4.2 ±1.3	4.4 ±1.5	NS
Smokers	3(30%)	23(27.7%)	NS
Treatment modality (Surgical/Medical)	0/10	0/83	NS
Treatment with AZA,6MP	8/10(80%)	54/83(65%)	NS
Disease Extension			NS
Ulcerative proctitis	1	11	
Proctosigmoiditis	0	5	
Left-sided colitis	3	41	
Extensive colitis	0	0	
Disease Presentation			
Bowel movements (per day)			NS
≤4	8	66	
4-6	2	14	
≥6	0	3	
Blood in stool			NS
small	8	64	
Moderate	2	17	
severe	0	2	
Arthralgia	3	12	NS
Arthritis	3	10	NS
Erythema nodosum	0	1	NS
Uveitis	1	0	0.001*
Aphthous ulcer	3	7	0.014*
Fever			NS
<37.5°C mean (<99.5°F)	9	82	
>37.5°C mean (>99.5°F)	1	1	
Pulse rate(mean pulse)			NS
<60	1	11	
60-90	8	70	
>90	1	2	
Endoscopic appearance			NS
Erythema, decreased vascular pattern, fine granularity	3	29	
Marked erythema, coarse granularity, absent vascular markings, contact bleeding, no ulcerations	6	43	
Spontaneous bleeding, ulcerations	1	11	
Laboratory findings			
Hemoglobin (g/dl)			NS
Normal or Mild (Hb>11)	8	88	
Moderate (Hb>10.5-11)	1	5	
Severe(Hb<10.5)	1	0	
CRP(+)	6	76	NS
ESR(>30 mm)	6	74	NS

* p values less than 0.05 were considered significant- NS= not significant

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Results

Patients included in this study, 63(67.7%) male and 30(32.3%) female, with 15–79 years old and the mean age of 35.23±13.68 years.

Demographic, clinical and laboratory characteristics of patients with and without anti-CCP were listed and summarized separately in Table 1.

Anti-CCP antibodies were detected in 10.8% (95% CI: 4.5-17.1%) of patients. Only one anti-CCP positive patients had ocular manifestations (uveitis) compared to 0 out of 83 anti-CCP negative UC patients.

There were ten patients with aphthous ulcers, in which 30% of them (95% CI: 2-58%) were anti-CCP positive (p=0.014). Other parameters were not significantly different between two groups.

It is considered that the majority (93.5 %) of patient with UC classified as mild. There was no relation between disease activity or disease extension of UC and anti-CCP positivity.

Discussion

Anti-CCP antibodies are important diagnostic and prognostic markers for patient with RA.

These antibodies are directed toward epitopes that pass citrullination process; peptidyl arginine deiminase (PAD) enzymes modify structure and function of proteins by converting arginine residues to citrulline in post translational stage. This modification participates in regulation of immune system by converting the chemokines (13-14).

Inflammation of the joint, subsequent event that leads to citrulination of synovial proteins and developing anti-CCP are known mechanisms occurred in RA (15-16). Unlike RA, IBD does not include a homogenous complications and the role of antibodies against the citrullinated peptide is also not well understood in this condition.

Not many studies have evaluated anti-CCP in IBD despite of relatively high prevalence of musculoskeletal involvement in this disease.

Previous studies have shown that anti-CCP antibodies had a low prevalence in patients with IBD. Papamichael et al found that anti-CCP was positive in only 1 out of 84 patients (1.1%) with CD and 0 out of 50 case of UC.(17) This prevalence was reported 1.8% by Koutroubakis et al and 1.2% for IgA subclass of anti CCP by Haga et al. (18-19).

In the present study, it was found that anti-CCP was detected in 10/93 (10.7%) patients with UC. 13.9% of patients had peripheral arthritis that in 23.07% of them anti CCP detected but in Papamichaels study no clinical evidence of arthritis was seen in anti-CCP-positive patient.

Despite of the higher rate of anti-CCP antibody that was seen in our study, no significant association between the prevalence of anti-CCP positivity and IBD related arthritis was found. This result is similar to studies of Papamichaels and Koutroubakis but in earlier study by Haga et al, significant association between IgA class antibodies and arthritis in patients with IBD was shown (17-19).

Moreover, previous studies suggested highly specificity of these markers for RA, recent literature also have shown that anti-CCP antibodies may also be developed in the other inflammatory conditions such as PsA, juvenile idiopathic arthritis and palindromic rheumatism (6-8).

For example Gupta reported that anti-CCP antibodies were more frequently detectable in the sera of JIA patients with severe manifestations like erosions and deformity and concluded that anti-CCP antibodies could be important markers to predict severe complications of this disease (20) but, in our study no significant relation was found.

This differences suggested that pathogenesis of arthritis and other extraintestinal manifestations in UC may differ from mechanisms occurred in RA. According to the significant association that was seen in recent study by Huga, et al, relation between pathological changes in the intestinal

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mucosa of IBD patients with arthritis, could be considered.(18) We suggest further studies are needed to confirm this relation.

In present study there were significant differences in oral and ocular manifestation between positive and negative anti-CCP IBD patients. The probable reason for association between aphthous ulcers and anti-CCP positivity may be similarity of mouth antigens as a part of gastrointestinal tracts and joint antigens that confirmed by Huga, et al study.

In conclusion, we found a low prevalence of anti-CCP positivity in UC patients but it was greater than previous reports. This study had some limitations including patient's participation for colonoscopic evaluation, poor preparation of colon, overall diagnostic performance of antibody assay especially false positive and negative results, and also treatment effects on antibody positivity and its changes with drugs treatment (especially corticosteroids and immunosuppressive drugs).

Conclusion

Our study has shown that there was no significant relation between UC activities, extension and presence of UC arthritis with anti-CCP positivity .We suggest that more studies are required on IBD patients especially on crohns disease patients and its clinical significance and also molecular studies to investigate other aspects of these antibodies in groups of patients.

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