

The Clinical Significance of Antibody Determination to Cyclic Citrullinated Peptides in Systemic Sclerosis

Bojana Stamenković¹, Aleksandra Stanković¹, Aleksandar Dimić¹, Nemanja Damjanov², Jovan Nedović¹, Sonja Stojanović¹, Vojin Savić³, Dragan Djordjević¹

¹Institute for Treatment and Rehabilitation "Niška Banja", Niška Banja, Serbia;

²Institute for Rheumatology, Belgrade, Serbia;

³Institute for Biomedical Research, School of Medicine, University of Niš, Niš, Serbia

SUMMARY

Introduction Anti-citrullinated peptides antibodies (ACPA) are present in 80% of sera of rheumatoid arthritis (RA) patients with high specificity for diagnosis and prediction for the development of early erosive arthritis. A few studies have reported a low frequency ACPA in systemic sclerosis (SSc) patients with the presence of arthritis.

Objective The aim of our study was to determine the frequency of ACPA in systemic sclerosis (SSc) patients, their correlation with clinical manifestations and radiographic features.

Methods The study included 82 patients with SSc, mean age 54.4 years, 59 with the limited (lSSc) and 23 with the diffuse (dSSc) form of the disease. The control group included 28 healthy age and sex matched subjects. ACPA and rheumatoid factor (RF) were determined in all SSc patients and healthy subjects in whom standard radiography of hands and wrists was also done.

Results The presence of ACPA was detected in 11 (13.4%) of SSc patients. Their level was not increased in any of the controls. Positive RF was found in 15.9% of SSc patients. Arthritis was present in 17.1%, as well as marginal bone erosions. There was a statistically significant association between positive ACPA and arthritis ($p < 0.0001$) and positive ACPA and marginal bone erosions ($p = 0.0002$).

Conclusion The research confirmed the correlation between ACPA with clinical signs of arthritis and radiographic damage of hand joints. ACPA is a useful diagnostic marker in the identification of SSc patients with arthritis and anatomic bone damage enabling the use of adequate therapy in order to prevent joint damage and poor quality of life.

Keywords: anti-citrullinated peptide antibodies; systemic sclerosis; arthritis; erosions

INTRODUCTION

Systemic sclerosis (SSc) is a chronic autoimmune disease of unknown origin, characterized by increased production of matrix proteins by fibroblasts, their precipitation in the walls of blood vessels, skin and internal organs leading to fibrosis of the skin and internal organs, concurrently with the activation of the immune system and significant vascular damage.

The basic classification was defined according to the degree and location of skin thickening: limited disease (lSSc) and diffuse systemic sclerosis (dSSc) with different severity and prognosis [1].

Immunopathogenesis of systemic sclerosis is complex. Cellular immunity has the main role, while the activity of humoral immunity has been observed, which is characterized by the formation of disease-characteristic antibodies. Quantification of total antinuclear antibodies (ANA) and especially specific, anticentromere (ACA) and antibodies to topoisomerase 1 (ATA) is useful in the diagnosis, classification and prognosis of systemic sclerosis [1, 2].

During the evolution of the disease, a large number of patients have arthralgia, myalgia, muscle atrophy, arthritis with or without flexion contracture, which can lead to permanent damage of joint function and disability

[3]. The literature identifies the different frequency of articular manifestations in 24-97% patients [4, 5].

The most serious disorders in the joint damage are flexion contractures of joints that usually occur in later phases of the disease, usually affecting wrist, fingers and elbow joints, followed by the restriction of movements, functional incapacity and limitation of daily activities. There are no clearly defined conclusions on whether the contractures occur due to periarticular fibrosis, synovitis, or as a solid connection between thickened and tough fibrous skin with subcutaneous tissue [6-9].

Articular damage on the hands is usually diagnosed by physical examination and radiography, which can help in the visualization of different bone abnormalities, divided into two groups: extraarticular (subcutaneous calcinosis, digital tuft resorption) and articular (joint space narrowing, juxtaarticular osteoporosis, marginal bone erosions) [6].

The analysis of acute phase reactants of inflammation (C reactive protein, rheumatoid factor, sedimentation rate, antinuclear antibodies) in joint damage assessment is useful but insufficient. During the last ten years an important role of antibodies to cyclic citrullinated peptide was proven. It is an important diagnostic marker for rheumatoid arthritis (RA)

Correspondence to:

Bojana STAMENKOVIĆ
Jug Bogdanova 26a, 18000 Niš
Serbia
bojanastm@yahoo.com

with the frequency of about 80% of patients with extreme specificity. It is now believed that ACPA could be a possible predictor for the occurrence of severe, destructive and erosive form of the disease [10, 11].

Recently, the presence of ACPA has been proven in a small number of SSc patients with limited and diffuse forms of systemic sclerosis with some joint manifestations, which leads to a conclusion that a high titer of these antibodies can predict patients with overlap syndrome – SSc and RA. However, we still do not have data about the significance of ACPA in predicting joint damage in SSc [12, 13, 14].

OBJECTIVE

The aim of this study was to determine the frequency of ACPA in systemic sclerosis and its relationship with clinical manifestations and radiographic features of the disease.

METHODS

The study included 82 patients that fulfilled the ACR (American College of Rheumatology) criteria for the diagnosis of systemic sclerosis [15]. Fifty-nine patients had lSSc and 23 dSSc, according to the classification of Le Roy and associates [16]. The control group included 28 healthy age and sex matched controls.

All the patients underwent a physical examination, laboratory testing, standard radiography of hands and were evaluated by clinical manifestations of the disease. Damage to internal organs was defined by the above criteria [17]. Pulmonary involvement was defined by the presence of bibasilar fibrosis on standard radiography of the heart and lungs and/or high-resolution computed tomography (HRCT), pulmonary function tests (FVC, DLCO/VA) and/or the presence of pulmonary arterial hypertension detected by colour Doppler echocardiography.

Esophagus involvement was defined in the case of hypomotility shown by barium radiography. Cardiac involvement was defined by the presence of pericarditis, complex arrhythmias, conduction disturbances, diastolic dysfunction and the presence of reduced left ventricular ejection fraction. Renal involvement was defined by the occurrence of renal hypertension, renal crisis in the history of the disease, proteinuria and/or a rapid decline of renal function.

Joint involvement was defined by the detection of arthralgias, arthritis and/or flexion contracture, and skin involvement was assessed by the modified Rodnan skin thickness score [18].

The presence of ACPA was determined by enzyme-linked immunosorbent assay (ELISA) method using the first generation anti-CCP ELISA kit, Imtec, Immunodiagnosics, Berlin, Germany. The samples were classified as positive if the value was >25 U/ml.

Antinuclear (ANA) and anticentromere antibodies (ACA) were determined by indirect immunofluorescence

on HEP-2 cells (Immunoconcepts, Sacramento, California, USA). As a borderline, ANA titer (cut off titer, i.e., the titer of which the lowest value is accepted as a positive test result) was taken, i.e., a titer of 1:40, the titer which in practice is recommended for screening. Antitopoisomerase I antibodies (ATA) were determined by CIE (counter immunoelectrophoresis), Imtec, Immunodiagnosics, Berlin, Germany.

Standard radiography of the hands and wrists was performed in all patients. The changes were evaluated by radiologist without access to clinical and serological data of patients. The presence of extraarticular changes (digital tuft resorption, subcutaneous calcinosis) or articular manifestations (juxta-articular osteoporosis and marginal bone erosions) was recorded.

The data were statistically analyzed using SPSS 10.0 for Windows. The frequency of categories of described characteristics was tested by Pearson χ^2 -test or Fisher exact probability test when some of the expected frequencies were less than 5.

RESULTS

The study included 77 women and 5 men with SSc, mean age 54.4 ± 12.6 years (range from 26-75 years). Fifty-nine patients had lSSc and 23 dSSc (Table 1). The control group included 28 healthy age and sex matched controls.

Pulmonary arterial hypertension was found in 17 (20.7%) and pulmonary fibrosis in 42 (51.2%) SSc patients. Restrictive disorders of pulmonary ventilation (FVC<75%) was demonstrated in 15 (20.5%) and reduced transfer factor for carbon monoxide (DLco/VA <75%) in 27 (37%) SSc patients.

Oesophageal involvement was demonstrated in 28 (54%) of 51 SSc patients, who had undergone barium radiography. Cardiac involvement was found in 38 (46.3%) and renal failure in 3 (3.7%) SSc patients.

Clinical findings of changes in the joints showed the presence of arthralgia in 58 (70.7%), arthritis was detected in 14 (17.1%), while 28 (34.1%) SSc patients had flexion contractures of joints. The presence of ACPA was registered in 11 (13.4%), while positive RF was found in 13 (15.9%) SSc patients. The mean value of the modified score-Rodnan skin thickness was 10.91. Table 1 shows the characteristics of the whole SSc group and in different SSc forms.

Radiological changes of hands and wrists are given in Table 2. We found marginal bone erosion in 14 (17.1%) SSc patients, mostly of capitate and lunate carpal bones or MCP 2, 3 joints; digital tuft resorption in 22 (26.8%), radiological demineralization in 24 (29.3%) and calcinosis in 31 (37.8%) SSc patients.

ACPA were present in 11/82 (13.4%) SSc patients. In the control group of healthy subjects, there were no patients with positive findings for anti-CCP. Positive RF was found in 13 (15.9%) SSc patients.

We found a statistically significant association between ACPA positivity and the presence of arthritis, (Fisher's exact test, $p < 0.0001$), and a highly significant association

Table 1. Characteristics of the patients with systemic sclerosis (SSc), limited form (lSSc) and diffuse form (dSSc)

Parameter	SSc (n=82)	lSSc (n=59)	dSSc (n=23)
Sex (F/M)	77/5	58/1	19/4
Age, mean±SD (years)	54.4±12.6	55.5±11.2	51.7±15.6
Pulmonary arterial hypertension	17 (20.7%)	11 (18.6%)	6 (26.1%)
Bibasilar fibrosis	42 (51.2%)	27 (45.8%)	15 (65.2%)
Oesophagus involvement	28/51 (54.9%)	17/33 (51.5%)	11/18 (61.1%)
Cardiac involvement	38 (46.3%)	24 (40.7%)	14 (60.9%)
Renal involvement	3 (3.7%)	1 (1.7%)	2 (8.7%)
Positive antinuclear antibodies	63 (76.9%)	43 (72.9%)	20 (87%)
Anti-Scl-70 antibodies	15 (18.3%)	3 (5.1%)	12 (52.2%)
Anticentromere antibodies	23 (28.1%)	20 (33.9%)	3 (13%)
Rheumatoid factor	13 (15.9%)	9 (15.2%)	4 (17.4%)
Anti-CCP antibodies	11 (13.4%)	4 (6.8%)	7 (30.4%)
Arthralgias	58 (70.7%)	43 (72.9%)	15 (65.2%)
Arthritis	14 (17.1%)	5 (8.5%)	9 (39.1%)
Flexion contractures	28 (34.1%)	16 (27.1%)	12 (59.2%)
Modified Rodnan (skin thickness score)	10.91	8.64	16.74
Decreased FVC*	15/73 (20.5%)	6/51 (11.8%)	9/22 (40.9%)
Decreased DLCO/VA**	27/73 (37%)	15/51 (29.4%)	12/22 (54.5%)

* <75% normal value; ** <75% normal value

Table 2. Radiographic abnormalities of the hands in systemic sclerosis

Radiological abnormalities	SSc (n=82)	lSSc (n=59)	dSSc (n=23)
Marginal bone erosions	14 (17.1%)	5 (8.5%)	9 (39.1%)
Digital tuft resorption	22 (26.8%)	13 (22.0%)	9 (39.1%)
Radiological demineralisation	24 (29.3%)	16 (27.1%)	8 (34.8%)
Calcinosis	31 (37.8%)	23 (39.0%)	8 (34.8%)

Table 3. Relationship between serum anti-citrullinated peptides antibodies (ACPA), arthritis and marginal bone erosions in 82 patients with systemic sclerosis

Parameter	ACPA positive (n=11)	ACPA negative (n=71)	p
With arthritis	8	3	<0.0001
Without arthritis	3	68	-
With marginal bone erosions	7	7	0.0002
Without marginal bone erosions	4	64	-

between ACPA positivity and the presence of marginal bone erosions ($p=0.0002$). We showed the connection between ACPA positivity with arthritis and marginal bone erosions in SSc patients in Table 3.

No statistically significant association was found between positive ACPA and internal organ involvement: with pulmonary fibrosis ($p=0.99$); pulmonary hypertension ($p=0.08$); cardiac involvement ($p=0.42$); oesophageal involvement ($p=0.99$).

Clinical, laboratory and radiological characteristics of patients with SSc and positive ACPA are shown in Table 4.

DISCUSSION

The topic of our study was to determine the incidence and role of ACPA in the differential diagnosis of arthritis and other joint damage in SSc.

Table 4. Clinical features of 11 female patients with systemic sclerosis and positive ACPA

Patient	Age	SSs subtype	Abs	CCP	RF	Radiographic abnormalities			Clinical features						
						Erosions	Osteoporosis	Calcinosis	Arthralgias	Arthritis	Flexion contractures	Lung fibrosis	Cardiac	Renal	Oesophageal
1	68	lSSc	ACA	138	neg	+	+	-	+	+	+	+	+	-	-
2	75	lSSc	ANA	200	384	+	+	-	+	+	+	+	+	-	+
3	28	dSSc	Scl-70	28	neg	-	-	+	-	-	-	-	-	-	+
4	67	dSSc	ANA	26	48	+	-	-	+	+	+	+	+	-	+
5	18	dSSc	Scl-70	38	250	+	+	-	-	+	-	-	-	-	-
6	54	lSSc	ANA	28	neg	+	-	-	-	+	+	-	-	-	-
7	64	dSSc	Scl-70	26	neg	+	-	-	+	+	+	+	+	-	+
8	46	dSSc	Scl-70	28	neg	-	-	-	+	-	-	+	-	-	+
9	54	dSSc	ANA	32	48	-	+	-	+	-	+	+	+	-	+
10	72	dSSc	Scl-70	26	neg	+	-	-	-	+	+	+	+	-	+
11	58	dSSc	Scl-70	86	neg	-	-	+	+	+	+	+	+	-	+

ACA – anti-centromere antibodies; ANA – antinuclear antibodies; Scl-70 – anti topoisomerase I antibodies; CCP – cyclic citrullinated peptides; RF – rheumatoid factor

Joint damage in SSc leads to functional disability, which is caused by arthritis, thickening and hardening of the skin, flexion contractures, which is a challenge to the clinician to precisely define it. In addition to the involvement of synovial tissue, which is clinically manifested by arthritis, SSc patients are quite often discussed in regard to generalized arthralgia and stiffness [7, 9, 19]. Joint pain, researched by numerous authors, was found in 24-97% SSc patients [7, 8, 20, 21]. It could be due to synovial fibrosis, without prior synovitis in the later stages of the disease.

High incidence of joint involvement was found in our research of SSc, which is in agreement with other authors [4, 5, 8, 21]. 70,7% of our SSc patients suffered joint pain and joint stiffness, arthritis was found in 17.1% and 34.1% SSc patients had flexion contracture.

Recently published results of ultrasound and MRI examination of the hands and wrists showed the importance of these tests in the precise diagnosis of hand and wrist synovitis in patients with SSc [22, 23, 24]. The presence of arthritis may be associated with overlapping SSc and RA, or, more likely, in the primary erosive arthropathy specific for SSc [25]. Results of the study of 120 patients with SSc showed radiographic presence of erosive arthritis in 18% of patients [8]. Only 2 patients in this study met the ACR criteria for classical RA. These results are supported by findings of antibodies to cyclic citrullinated in 1.5-10.6% scleroderma patients, which are highly specific for RA [12, 13, 14].

Our research showed that ACPA may be present in SSc, although their frequency is much lower compared to RA, which can be found in 76% of patients [11]. In our study, these antibodies were detected in 13.4% of SSc patients, and with further analysis of clinical and radiological features we found a significant correlation between ACPA with the presence of arthritis and marginal bone erosions. Data from the literature [11, 12, 13, 25] indicate that the

clinical findings of similar changes in RA on radiography of the hand and wrist (juxtaarticular osteoporosis, erosions) in patients with SSc and high titers of ACPA could be defined as an overlap syndrome of scleroderma and RA.

The prevalence of marginal bone erosions in SSc was estimated to 5-40% in previously published studies [4, 6, 7, 8, 12, 21, 22, 24, 26]. Our results, based on the presence of erosions of the wrists found in 17.1% of SSc patients, are consistent with the above.

By previous research, determined prevalence of overlap syndrome SSc-RA was 4.3% to 5.2% [25, 27]. The published data indicate a higher incidence of RA in SSc than in the general population [27].

Early diagnosis of RA in patients with SSc is difficult, because arthritis can be present in both diseases. Symmetric polyarthritis and joint contractures are often present in both diseases; however, some of the clinical and pathological findings of joint damage are different in these diseases. Radiological findings of joint destruction are usually more difficult in RA than in SSc.

CONCLUSION

Many patients with SSc have musculoskeletal signs and symptoms, such as joint pain, swelling and/or restriction of movement, but according to the skin involvement it is difficult to localize the origin of joint symptoms and to evaluate the role of joint inflammation. This inflammation may be caused by SSc itself or could be a sign of RA associated with scleroderma (overlap syndrome SSc-RA), especially in patients with a high level of ACPA and erosive arthritis. These findings are crucial in the therapy of SSc, because they can provide adequate treatment to prevent further joint damage in patients who already have poor quality of life.

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Клинички значај одређивања антитела на цикличне цитрулисане пептиде у системској склерози

Бојана Стаменковић¹, Александра Станковић¹, Александар Димић¹, Немања Дамјанов², Јован Недовић¹, Соња Стојановић¹, Војин Савић³, Драган Ђорђевић¹

¹Институт за лечење и рехабилитацију „Нишка Бања“, Нишка Бања, Србија;

²Институт за реуматологију, Београд, Србија;

³Институт за биомедицинска истраживања, Медицински факултет, Универзитет у Нишу, Ниш, Србија

КРАТАК САДРЖАЈ

Увод Антитела на циклични цитрулисане пептид (*anti-CCP*) високо су специфична за реуматоидни артритис и важан прогностички маркер за развој ерозивног артритиса. Неке студије су доказале њихову малу учесталост код особа оболелих од системске склерозе (СС) с артритисом.

Циљ рада Циљ рада био је да се утврди учесталост *anti-CCP* антитела код болесника са СС и њихова повезаност с клиничким манифестацијама и радиографским знацима, посебно на зглобовима шака.

Методе рада Испитивање је обухватило 82 болесника са СС (59 са лимитираном СС и 23 са дифузним обликом СС), просечне старости од 54,4 године, и 28 здравих испитаника исте старости, који су чинили контролну групу. Свим испитаницима одређени су *anti-CCP* антитела и реуматоидни фактор (РФ) и начињен радиографски снимак шака с ручним зглобовима.

Резултати *Anti-CCP* антитела су утврђена код 11 болесника (13,4%), док код испитаника контролне групе нису нађена. Позитиван РФ утврђен је код 15,9% болесника. Артритис је дијагностикован код 17,1% болесника, а маргинална ерозије (радиографски) код истог броја болесника. Утврђена је статистички значајна повезаност позитивних *anti-CCP* антитела с артритисом ($p < 0,0001$) и маргиналним ерозијама ($p = 0,0002$). **Закључак** *Anti-CCP* антитела су повезана с клиничким знацима артритиса и радиографским оштећењем зглобова шака. Користан су маркер у препознавању особа оболелих од СС с артритисом и анатомским оштећењем кости, ради примене одговарајућег лечења, чији је циљ превенција оштећења зглобова и лошег квалитета живота болесника.

Кључне речи: антитела на циклични цитрулисане пептид; системска склероза; артритис; ерозије

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