ORIGINAL ARTICLE

Seroprevalence of Anti-Citrullinated Protein Antibodies (ACPA) in Patients with Rheumatic Diseases other than Rheumatoid Arthritis

Renu Saigal[1*], Surendra Singh Bhakal[2], Laxmikant Goyal[3], Akhil D Goel[4]

Abstract

Objective: To evaluate the prevalence of anti- citrullinated protein antibodies (ACPA) in patients with a variety of rheumatic diseases other than rheumatoid arthritis (RA).

Methods: 144 cases of rheumatic diseases other than rheumatoid arthritis (RA) over a period of 1 year were recruited after consenting and followed up for 2 years. Their serum samples were tested for ACPA.

Result: ACPA seropositivity of 9.03% was observed in rheumatic diseases other than RA.

Conclusion: Whether ACPA seropositivity in non-RA rheumatic diseases indicates a false positive result or an overlap RA syndrome is a mystery yet unsolved. Long term follow ups of these patients will be required to understand the course of rheumatic diseases in relation to ACPA.

Introduction

ACPA have demonstrated their usefulness for the diagnosis of RA. However these antibodies have also been found positive in rheumatic diseases other than RA like Systemic Lupus Erythematosus (SLE),[1] Psoriatic arthritis,[2] Juvenile idiopathic arthritis (JIA),[3] Idiopathic Inflammatory myositis (IIM),[4] Systemic sclerosis (SSc),[5] Primary Sjogren's syndrome(PSS) and others.

Very few studies have reported the seroprevalence of ACPA in rheumatic diseases other than RA as incidence of ACPA in other rheumatic diseases is low but needs to be evaluated in further studies.

Aim of our study was to find out seroprevalence of ACPA in rheumatic diseases other than RA.

Material and Methods

All the patients with rheumatic diseases attending the Rheumatology Clinic at a Medical College Hospital in North India from June 2011 to May 2012 were screened and followed up for two year. We categorized patients in different rheumatic diseases according to American College of Rheumatology classification criteria.

Patients with RA at first visit or on follow up were excluded. We, thus, recruited 144 patients of rheumatic diseases other than RA and followed them up for 2 years. Well-informed and written consent was obtained from each recruited patient. Necessary approval was obtained from the ethics committee of institution.

Clinical assessment: Detailed history and physical examination was done thoroughly. *Laboratory Evaluation:* Fasting venous samples of the patients were taken for Glucose, kidney and liver function tests, ESR, C-reactive protein (CRP) and ACPA. Patients were further investigated for any complications indicated clinically or by initial investigations. ESR and CRP were measured using Westergren method and Nephelometry respectively. Serum ACPA levels was measured by an ELISA test system for the quantitative measurement of IgG class ACPA in human serum or plasma with positive cut off value ≥ 20 U/ml.

Results

Out of the 144 patients of rheumatic disease, 90 (62.5%) were females. Systemic Lupus Erythematosus (SLE) 65 (45.1%) cases, 47 (32.6%) cases of Spondyloarthritides (SpA), 10 (6.9%) of SSc, 4 (2.8%) of PSS and 18 (12.5%) patients were of other rheumatic diseases [one case of Antiphospholipid Antibody Syndrome (APS), 1 case of Adult Onset Still Disease (AOSD), 3 cases of Enthesitis- related Arthritis (ERA), 2 cases of Henoch Schonlein Purpura (HSP), 3 cases of Juvenile Idiopathic Arthritis (JIA), 4 cases of Mixed Connective Tissue Disease (MCTD), 3 cases of IIM and 1 case of Relapsing polychondritis] (Figure 1).

Thirteen (9.03%) patients were positive for ACPA and 131 (90.97%) were negative. Out of 13 ACPA positive patients 6 were of SLE, 3 of SpA, 2 of SSc, 1 of PSS and 1 of HSP (Figure 2, Table 1).

Discussion

Enzyme Peptidyl Arginine Deiminase (PAD) converts Arginine to Citrulline on peptide proteins. This is a post-translational modification changing biochemical properties of proteins. Citrullination is predominantly observed in proteins like cytokeratin, filaggrin, vimentin, α and β fibrin, α-enolase, and peptides of collagens I

[1]Professor and Head, Department of Medicine, Jaipur National University IMSRC, Jaipur, Rajasthan, Former Senior Professor and Head, Department of Medicine, Former In-Charge Rheumatology Services, SMS Medical College, Jaipur, Rajasthan; [2]Former Resident; [3]Assistant Professor, Department of Medicine, SMS Medical College, Jaipur, Rajasthan; [4]Senior Resident, Centre for Community Medicine, All India Institute of Medical Sciences, New Delhi; *Corresponding Author
Received: 05.02.2016; Accepted: 21.12.2017

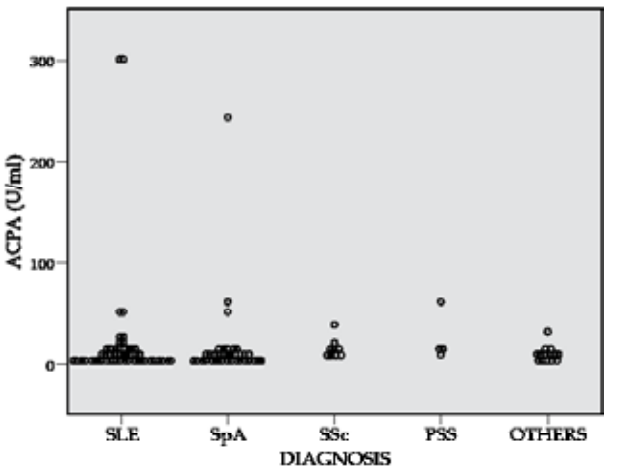

Fig. 1: Distrbutin of 144 patients of Non-RA rheumatic diseases

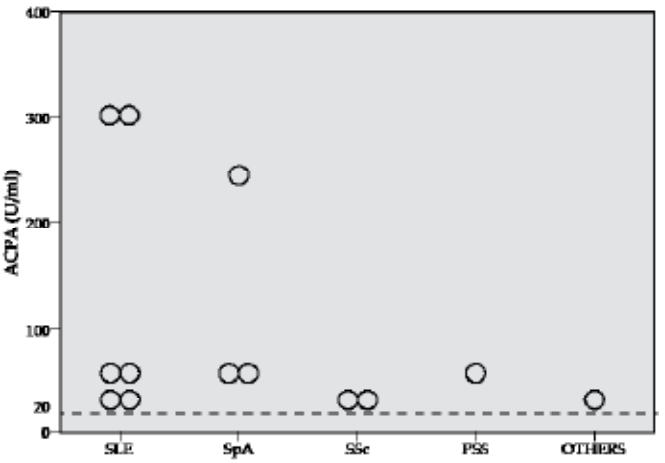

Fig. 2: Distribution of 13 ACPA positive patients and ACPA levels

Table 1: Distribution of rheumatic disease patients other than rheumatoid arthritis

	ACPA positive (n=13)	ACPA negative (n=131)	P value
Sex, Female	10 (76.9)	80 (61.1)	0.37
Age, Mean ± SD	27.4 ± 10.1	29.6 ± 10.0	0.44
Diagnosis			
SLE	06 (46.2)	59 (45.0)	
SpA	03 (23.1)	44 (33.6)	
SSc	02 (15.4)	8 (6.1)	-
PSS	01 (7.7)	3 (2.3)	
Others	01 (7.7)	17 (13.0)	
CRP positive	11 (84.6)	96 (73.3)	0.372

*P value calculated using Fischer Exact Test. All values in parentheses are column-wise percentages.

and II.[7] Antibodies recognizing these citrullinated peptides are known as anti-citrullinated protein antibodies (ACPAs).[8] ACPAs are locally produced by synovial B cells and therefore contribute to the inflammatory and destructive processes in the RA.[9] ACPAs are present early in the course of the RA and may precede the clinical onset.[10]

ACPA has 95% specificity and 75% sensitivity for RA.[7] RA should be differentiated from other rheumatic diseases as early initiation of treatment leads to better prognosis. Such high specificity should be evaluated in patients with suspected rheumatic diseases. In our study, patients with inflammatory rheumatic diseases excluding RA, were taken as study population.

We observed a seroprevalence of 9.03% of ACPA in rheumatic disease other than RA. This is in concordance with the few studies where seroprevalence was 9.8% and 10% respectively.[3,11] We found prevalence of ACPA in SLE 9.23% which was higher than one study[1] of 7% but lower than another study[12] of 17%.

Among ACPA positive SLE patients one patient with titre >300 U/ml presented with symmetric polyarthralgia for 1 year along with characteristic SLE manifestations. Another patient with titre >300 U/ml presented with SLE class 4 nephritis and vasculitis without arthralgia. One more patient with titres of ACPA equal to 51.6 U/ml was diagnosed as cutaneous lupus with inflammatory bowel disease (celiac disease) on routine follow up this patient developed symmetric polyarthritis however, patient was RF negative and on routine follow up did not show any radiological erosions.

In our study we observed a seroprevalence of 6.38% of ACPA in SpA. One patient of undifferentiated SpA had titre of 49.2 U/ml while 2 other ACPA positive patients one was diagnosed as Ankylosing Spondylitis and other patient with chronic ReA and they had ACPA titers of 243.6 u/ml and 58.71 u/ml respectively but in both these patients there was no hand joint involvement. We observed a seropositivity of 20% of ACPA in Systemic Sclerosis (SSc), which is higher than the other studies.[5,11] This can be explained by small number of SSc patients in our study. Y. Morita et al[5] recommended that ACPA titres should be measured in SSc patients suffering from joint involvement so that SSc-RA overlap patients may be diagnosed early. So ACPA may play important role to differentiate SSc from SSc –RA overlap.

One patient of PSS which was ACPA positive was 41 years female present with bilateral parotid enlargement, dry eyes and dry mouth with background history of Raynaud's phenomenon (RP) and arthralgia for 1 year. She had high titre ACPA positive (62.90 u/ml) as well as high titer anti Ro/SSA antibody positive (99.92 u/ml). In our study ACPA positive patient had RP while G J Tobo´n et al[13] found that 2 out of 5 ACPA positive patients had RP. It is possible that marked B-lymphocyte hyper-reactivity which is a characteristic of primary Sjogren's syndrome may explain the presence of ACPA.[14]

The possibility that patients with ACPA positivity could be prone to develop RA in future cannot be ruled out, warranting regular follow up. We followed our patients for 2 years. All the ACPA positive patients on follow up were found to have no erosions and these were fitting in the diagnostic criteria of that particular rheumatic disease. One of the 13 ACPA positive patients in our study developed symmetric polyarthritis resembling RA on routine follow-up but she did not have radiological erosions. So the term "false positive" cannot be applied in this patient and these patients need continuous follow up for development of erosions when these patients may be put under overlap syndromes or pure RA.[15]

Conclusion

In our study 13 patients were ACPA positive among 144 patients with inflammatory rheumatic diseases other

than RA. So prevalence of ACPA was 9.03 %. Out of these 13 seropositive patients, one developed symmetric polyarthritis resembling RA on routine follow-up of 2 years. Term "false positive" cannot be strictly applied to these patients of non-RA rheumatic diseases, as ACPA is known to antedate RA by many years and these patients need follow up.

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