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Full Length Research Paper

Association of anti-MCV autoantibodies with SLE (Systemic Lupus Erythematosus) overlapping with various syndromes

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Rheumatoid arthritis (RA) and Systemic Lupus Erythematosus (SLE) both are the systemic autoimmune diseases. Their etiology is still unknown but it is believed that genetic, immunological and environmental factors are involved in the pathogenesis of these diseases. A total of 61 SLE patients were included in the study. This study is purely related to SLE patients. Here, anti-mutated citrullinated vimentin (MCV) (Orgentec, Mainz, Germany) is detected in SLE patients by an ELISA at a cut-off value 20 U/ml. Of these 61 SLE patients, 19 had SLE overlapping with rheumatoid arthritis, 1 had SLE with Budd-Chiari syndrome, 2 had SLE with scleroderma while 20 were the total cases of lupus nephritis. Lupus nephritis patients were further subdivided into two groups: one group included 14 SLE patients with lupus nephritis alone and the second group included 6 SLE patients overlapping with Lupus nephritis (LN) and Rheumatoid arthritis. Of the 19 SLE patients with rheumatoid arthritis, 6 were also suffering from lupus nephritis. These results suggest high specificity and sensitivity of anti-MCV for SLE patients with rheumatoid arthritis.

Key words: Rheumatoid arthritis, Budd-Chiari syndrome, systemic lupus erythematosus, mutated citrullinated vimentin.

INTRODUCTION

The co-existence of rheumatoid arthritis and SLE in patients is rare but SLE is common in families with rheumatoid arthritis than it is in the general population. Rheumatoid arthritis is a systemic autoimmune disease characterized by chronic synovial membrane inflammation that leads to progressive joint damage, chronic pain and impaired mobility.

Citrullination is a physiological process during keratinization, inflammation, and apoptosis. The normal, uninflammed synovium does not contain high amounts of citrullinated proteins. A specific enrichment of citrullinated vimentin could be the result of a less effective clearing of apoptotic cells. Vimentin is selectively citrullinated in macrophages undergoing apoptosis, these activated macrophages secrete fragments of vimentin. Similarly, neutorphils undergoing spontaneous apoptosis express fragments of the C-terminal tail of vimentin on their surface (Bang et al., 2007).

Several citrullinated proteins have been proposed as physiological targets for antibodies to citrullinated protein antigens specificity and one of them is vimentin. The anti-MCV ELISA detects autoantibodies against mutated citrullinated vimentin (MCV). It is an efficient and reliable serological test for rheumatoid arthritis as it detects the disease at a very early stage, even in patients who test negative for rheumatoid factor, and to some degree even before the appearance of specific clinical symptoms. Anti-MCV had 9% higher sensitivity than anti-cyclic citrullinated peptide (anti-CCP) and 4% higher sensitivity than IgM rheumatoid factor. MCV autoantibodies are an indicator of advanced injury to the joints and aggressive progression of the disease. In contrast to the detection of antibodies against synthetic cyclic citrullinated peptides, changes in the anti-MCV concentration correspond to changes of clinical parameters (Dejaco et al., 2006).

MATERIALS AND METHODS

The human studies reported in this manuscript were approved by

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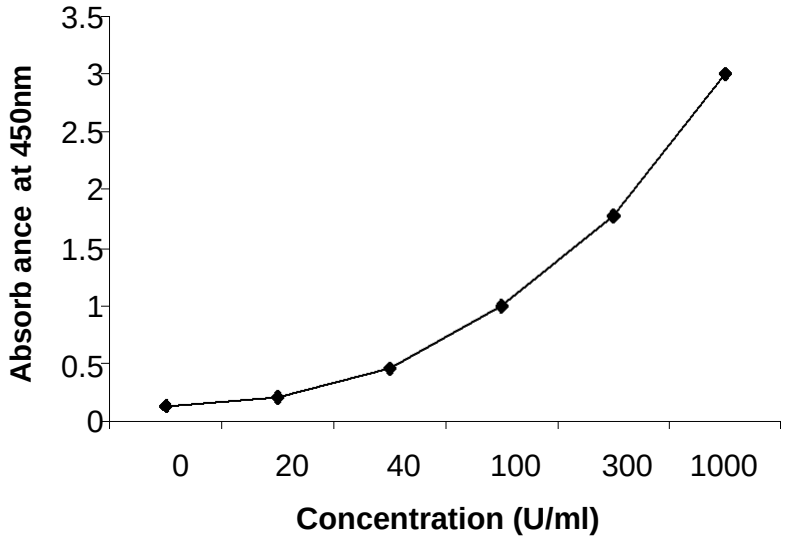

Figure 1. Standard curve for the estimation of serum anti- mutated citrullinated vimentin (anti-MCV) by ELISA.

the Ethical Committee of the School of Biological Sciences, University of the Punjab, Lahore, Pakistan. A total of 61 SLE patients fulfilling American College of Rheumatology (ACR) criteria and 61 controls were enrolled in this study. Sample number is low because SLE is a quite rare disease in Pakistan. Rheumatology and Nephrology department of different hospitals of Lahore were chosen because most of the patients were referred to these departments for the diagnosis of lupus. Of the 61, fifty-five (90.16%) were females and six (9.83%) were males. The female versus male ratio was 9.16:1 indicating that SLE is quite common in females. Mean age at diagnosis was 30.35 ± 1.687 years and the range was 12 to 68 years. Mucocutaneous involvement was found in lupus patients such as malar rash 6 (9.84%), discoid rash 11 (18.03%), photosensitivity 11 (18.03%). Various syndromes were overlapping SLE and the most common one was rheumatoid arthritis (19 patients: 31.14%) but cases of Sjogren's syndrome (10 patients: 16.39%), Scleroderma (2 patients: 3.27%), Secondary Antiphospholipid syndrome (2 patients: 3.27%), and of Budd-Chiari syndrome (1 patients: 1.63%) were also found along with SLE. Renal involvement was found in 20 patients: 32.78%) patients characterized by proteinuria and red cell cast. SLE patients were diagnosed by performing various ELISA techniques for the detection of autoantibodies like ANA, dsDNA, Sm, Ro, La, Rib-P. In the present study, anti-MCV ELISA was used to detect autoantibodies against mutated citrullinated vimentin in SLE patients overlapping with various syndromes.

Several citrullinated proteins have been proposed as physiological targets for antibodies to citrullinated protein/peptide antigens specificity and one of them is vimentin. The anti-MCV ELISA detects autoantibodies against mutated citrullinated vimentin (MCV). It is an efficient and reliable serological test for rheumatoid arthritis as it detects the disease at a very early stage, even in patients who test negative for rheumatoid factor, and to some degree even before the appearance of specific clinical symptoms. Thus, anti-MCV ELISA makes it possible to monitor therapeutic progress (Smith and Shmerling, 1999).

This study is purely related to SLE patients, here anti-MCV (Orgentec, Mainz, Germany) is detected by an ELISA at a cut-off value 20 U/ml. ORGENTEC uses the complete sequence of the citrullinated, mutated protein, which equates 100% homology of the natural type. The anti-MCV concentration of the samples was determined from the standard curve. Statistical analysis was done by using SPSSver13.

RESULTS

This study was purely related to SLE patients, a total of 61 SLE patients were included in the study. Here anti-MCV (Orgentec, Mainz, Germany) was detected by an ELISA at a cut-off value 20 U/ml. Of the 61 SLE patients, 38% were positive for anti-MCV while 62% were negative for anti-MCV (Figure 2). The minimum concentration of anti-MCV was 1 U/ml and the maximum was 780 U/ml (Figure 3). The mean concentration of anti-MCV antibodies in SLE patients was 89.836 ± 24.33 (Table 1). The concentrations of anti-MCV autoantibodies are summarized in the Figure 2. One sample t-test was applied (Table 2). The p value is less than 0.05, so it was found to be significantly associated with SLE. Of the 23 anti-MCV positive SLE patients, 82.6% were the cases of SLE with rheumatoid arthritis, 4.34% had Budd-Chiari syndrome while 4.91% were the patients of lupus nephritis alone (Figure 4).

Variable concentrations of anti-MCV autoantibodies were seen in SLE patients with rheumatoid arthritis, Budd-Chiari syndrome, lupus nephritis and scleroderma. It is evident from the Figure 5 that all SLE patients with rheumatoid arthritis and of Budd Chiari syndrome showed high level of anti-MCV autoantibodies. Similarly, 3 SLE patients with lupus nephritis and 6 SLE patients with lupus nephritis as well as with rheumatoid arthritis showed high concentration of anti-MCV but SLE patients with Scleroderma had very low level of anti-MCV.

Table 1. MCV frequencies.

Anti-MCV autoantibodies in SLE patients (n = 61)	
Mean	89.836
Standard deviation	190
Standard error of mean	24.33

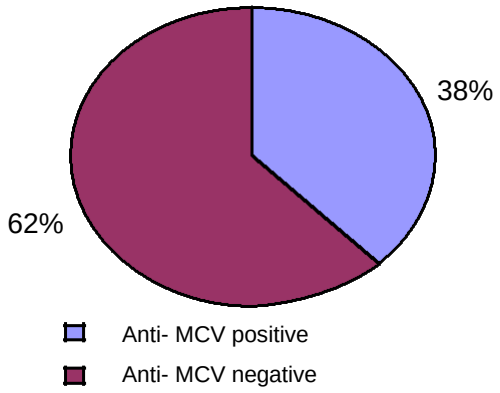

Figure 2. Percentage of anti-MCV in SLE patients.

DISCUSSION

Circulating autoantibodies are a characteristic phenomenon of autoimmunity but the mechanisms underlying the production of autoantibodies are unknown. SLE is the autoimmune disease with the largest number of detectable autoantibodies. Their production could be antigen-driven, the result of polyclonal B cell activation, impaired apoptotic pathways, or the outcome of idiotypic network dysregulation (Mathsson et al., 2008). MCV is mainly related with RA but this was the first study representing the levels of anti-MCV autoantibodies in SLE patients especially those overlapping with rheumatoid arthritis, lupus nephritis, scleroderma, Budd-Chiari syndrome.

At present, two types of serological markers are used in the early diagnosis of rheumatoid arthritis (RA): antibodies to the Fc part of human IgG (rheumatoid factor) and antibodies to citrullinated protein/peptide antigens. Rheumatoid factor is not specific to RA, because it is present in patients suffering from other autoimmune. Early reliable diagnosis is a prerequisite for successful therapy that prevents the permanent damage. Clinical parameters, modern imaging techniques and the sensitivity detection of specific autoantibodies to citullinated proteins serve as a valuable tool for the diagnosis of rheumatoid arthritis. Antibodies against vimentin are used for the diagnosis of rheumatoid arthritis because of its high specificity. The specificity is 98% whereas the sensitivity is 82% depending on the method used (Remmers et al., 2007).

The specificity of antibodies against citrullinated protein "vimentin" for rheumatoid arthritis was first described in 1994. A Canadian patient with RA revealed an antibody population which was identified as highly specific for RA and was later described as Sa antibody. After 10 years, it was found that the Sa antigen is vimentin. With the help of modern techniques such as proteome analysis and epitope characterization have shown that vimentin possess many more possible antigenic determinants caused by citrullination. Beside these citrullinated variations, different isoforms were identified exhibiting mutations additional to the conversion from arginine to citrulline. Mutated Citrullinated vimentin (MCV) is the identified isoform specific for rheumatoid arthritis and it has a sensitivity of up to 98%. In this study we have used this type of isoform because different studies have reported that in comparison with anti-CCP, anti-MCV is able to surpass all expectations of sensitivity and specificity. This sensitivity advantage is the result of the natural form of the human protein compared to the synthetically produced fragments (El-Gabalawy and Wilkins, 2004).

It was found that anti-MCV alone is a much better prognostic marker for rheumatoid arthritis than the test combination of anti-CCP and rheumatoid factor. Anti-MCV ELISA and anti-CCP ELISA was performed on the samples of rheumatoid arthritis and the comparison of these two ELISA showed that anti-MCV has a sensitivity of 82% and specificity of 98% while anti-CCP has a sensitivity of 72% and specificity of 96%. Furthermore a good correlation of anti-MCV and disease activity was shown with the disease activity score (DAS) score, whereas the DAS-score on anti-CCP did not show any correlation (Song et al., 2008). These results demonstrate the superiority of the naturally occurring mutated citrullinated vimentin compared to the synthetic fragment. All these factors explained that why we have preferred anti-MCV ELISA in this study.

In 2008, Poulsom and Charles detected antibodies to MCV in the sera of 74% rheumatoid arthritis, 2% SLE, 14% Sjogren's syndrome and 2% Scleroderma patients (Poulsom and Charles, 2008). In this study, anti-MCV autoantibodies were assayed in the sera of SLE patients that were further subcategorized as SLE overlapping with Rheumatoid arthritis, Budd-Chiari syndrome, Lupus nephritis and Scleroderma. It was found that anti-MCV was 100% positive in SLE patients with RA representing the significant association of anti-MCV with SLE as well as with RA, but SLE patients with scleroderma were totally negative for this type of autoantibody. Apart from this, SLE patients with Lupus nephritis also showed positivity for anti-MCV and by applying Fisher's exact test we have found a significant association of anti-MCV with Lupus nephritis. Sera of an SLE patient with Budd-Chiari syndrome showed higher level of anti-MCV, but we cannot conclude anything from one patient, however it raises a significant point for the future researchers. High levels of anti-MCV autoantibody were seen in SLE

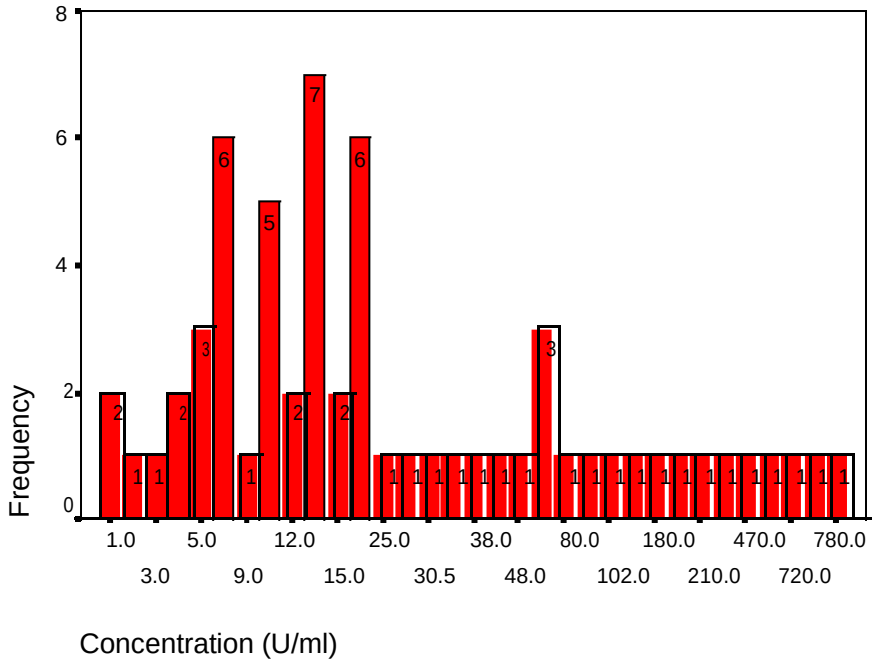

Figure 3. Concentration of anti-MCV autoantibodies in SLE patients (n = 61).

Table 2. One-sample t-test.

Anti-MCV cut-off value = 20	
t	**p**
2.870	0.006

Table 3. Sub-division of lupus nephritis patients.

Parameters	SLE+LN (n = 14)	SLE+LN+RA (n = 6)	Fisher's exact test
Anti-MCV +	3	6	p = 0.002167
Anti-MCV -	11	0	

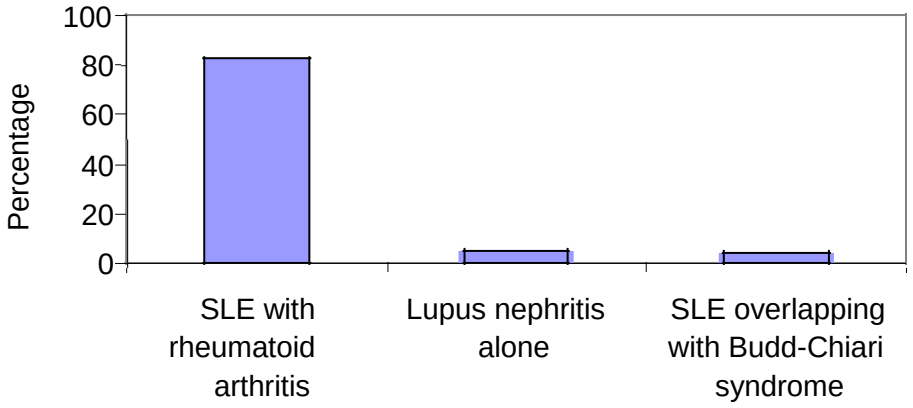

Figure 4. Anti-MCV positive SLE patients (n = 23) associated with rheumatoid arthritis, lupus nephritis, and Budd-Chiari syndrome.

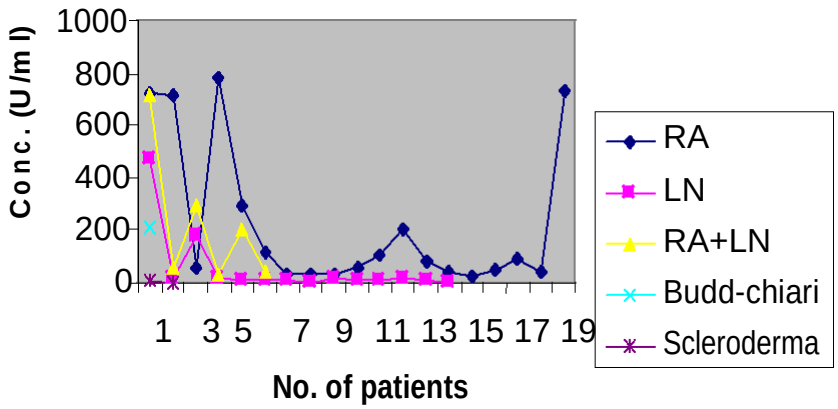

Figure 5. Levels of anti-MCV autoantibodies in SLE patients.

patients, this may be because of the higher inflammatory rate in these patients. Thus one can conclude that anti-MCV autoantibodies are found not only in rheumatoid arthritis but there is a significant association of anti-MCV autoantibodies with SLE overlapping with rheumatoid arthritis, lupus nephritis, and Budd-Chiari syndrome.

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