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ANTI-NUCLEOSOME ANTIBODIES: DIAGNOSTIC AND CLINICAL IMPLICATIONS IN SYSTEMIC LUPUS ERYTHEMATOSUS PATIENTS

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ABSTRACT

Systemic lupus erythematosus is a chronic , inflammatory autoimmune disease with a wide range of clinical and immunological abnormalities. The presence of varied autoantibodies, immune complex deposition and end organ damage are characteristic of the disease. Among the wide range of anti-nuclear antibodies lined up in the diagnostic armamentarium of SLE presently, antinucleosome antibodies are considered superior to the previously main diagnostic marker anti-dsDNA antibodies. Antinucleosome antibodies have a higher sensitivity and specificity for diagnosis of SLE and SLE disease activity. They are found in active SLE cases and even in ds-DNA negative patients. More ever, they are not found in healthy controls. Thus, antinucleosome antibodies can be utilized as a potential marker for the diagnosis and assessment of SLE disease activity.

KEY WORDS : SLE, Anti-nucleosome Antibodies, Anti-ds DNA Antibodies)

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INTRODUCTION

Systemic lupus erythematosus is a complex, inflammatory autoimmune disease of unknown aetiology. It is a multisystemic disorder of connective tissue, which predominantly involves the skin, joints, kidneys and serosal membranes .SLE patients sera shows the presence of a wide range of different auto antibodies directed against nuclear antigens, cytoplasm and cell surface proteins[1]. The American College of Rheumatology (ACR) established 11 criteria in 1982, which were later revised in 1997, for the purpose to operationalise the definition of SLE in clinical trials, a person has SLE if any 4 out of the 11 symptoms are present simultaneously or serially on two separate occasions (specificity 95% and sensitivity 75%)- Malar rash , Discoid rash, Photosensitivity, Oral ulcers, Arthritis, Serositis , Renal disorder , Neurological disorder, Hematological disorder ,Immunologic disorder & Antinuclear antibody[2]. In at least, 95% of SLE patients, auto antibodies are present[3]. These anti-nuclear antibodies lined up in the diagnostic armamentarium of SLE are Anti-nucleosome antibodies (ANuA), along with specific antibodies against double-stranded DNA (anti ds-DNA), anti-histone antibodies, anti-Smith (anti-Sm) antibodies and Anti-centromere antibodies.The most widely accepted diagnostic tool for SLE includes, a rise in anti ds-DNA antibodies and fall in complement C3. Similarly, anti-histone antibodies are positive in drug induced lupus while, anti-centromere antibodies are pathognomonic markers of (CREST syndrome) of PSS, while antibodies against Scl-70 occur in up to 75% PSS cases[4]. However, the anti ds-DNA antibodies are found only in 60% of SLE patients[3] and may be elevated without any overt renal disease hence, they may not always correlate with disease activity. These anti-nuclear antibodies are also detected in healthy individuals , as chromatic antigens appear to be a common target of auto antibodies. Anti-nuclear antibodies are positive in other connective tissue disorders like, Systemic Sclerosis, Polymyositis, Sjogren's syndrome , Dermatomyositis, etc. thus, they have low specificity for the diagnosis of SLE. The differences in affinity, specificity and subclass of the antibody or it may be the size, conformation and accessory proteins of the antigen, which are the attributing factors for their low specificity in detecting the anti-ds-DNA antibodies[3]. Different tests yield different results, like Farr assay detects relatively high-affinity antibodies, whereas ELISA and immunofluorescence detect low-affinity antibodies. Hence, the hunt for other auto-antibodies which may be useful in the diagnosis of SLE as well as monitoring disease activity in SLE lead to Antinucleosome Antibodies (ANuA).

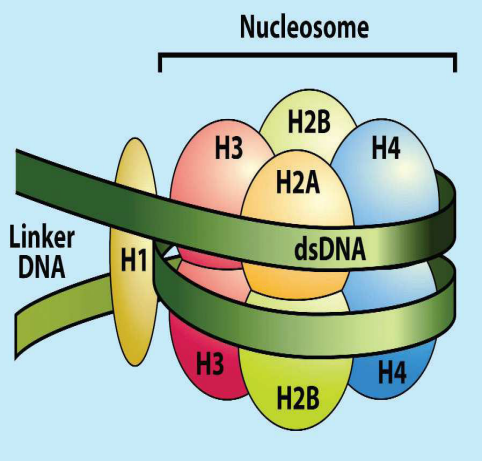
These Antinucleosome Antibodies are produced during the pathogenesis of SLE. It includes tissue damage by auto antibodies produced by the hyper-reactive B cells, leading to immune dysregulation and apoptosis. Presently, defective apoptosis is considered as one of the most accepted mechanism in SLE pathogenesis[5]. During cell apoptosis nucleosomes are generated by the cleavage of chromatin by endonucleases[5]. The term "nucleosome" defines a unit of chromatin consisting of 146 base pairs of DNA wrapped around a protein core. The protein core comprises of two molecules each of the histones H2A,H2B,H3 and H4 constituting the histone octomer . Histone H1 outside the nucleosome core join together neighbouring nucleosomes by linker DNA[6].(Fig-1) . Anti-nucleosome-specific antibodies (ANuA) belong to the nucleosome family as do Anti-dsDNA and anti-histone antibodies. These nucleosomes share several common epitopes with dsDNA and histones. Nucleosome specific antibodies recognise conformational epitopes resulting from interactions between DNA and histone, hence, although they are directed to the native nucleosome particle,but do not react with the individual components of nucleosomes (i.e. DNA and histones)[7]. Nucleosomes are among the most important autoantigens in SLE and high prevalence of ANuA in patients sera is seen [8], still the diagnostic use of this parameter has been greatly limited, as many patients with progressive systemic sclerosis (PSS) also demonstrated significant positive reactions. Hence, it was mistakenly assumed that ANuA were associated with both

diseases. However, the newer 2nd generation ANuA ELISA technique based on a novel nucleosome preparation, consisting of mononucleosomes free of histone H1, non-histone proteins such as Scl-70, and chromatin DNA fragments, demonstrated that ANuA are highly and specifically associated with SLE but not with PSS[6]. Out of the above three frequently associated autoantibodies tested, as markers of Systemic Lupus Erythematosus (SLE) - ANuA, anti-dsDNA and anti-histone. ANuA yielded the highest individual diagnostic hit rate. . These nucleosome-restricted or specific antibodies are the first to emerge, before the occurrence of the above two antibodies and persist later in the course of the disease, along with the development of anti-dsDnA and antihistone antibodies[9] Antinucleosome (anti-nCS) antibodies are shown to be present in active but also in inactive SLE patients (most of whom are anti-dsDNA negative)[9] . Hence,they could possibly be a sensitive marker of anti-dsDNA negative SLE patients. Additionally, several studies have shown that antinucleosome antibodies titers are more closely correlated, with the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) than anti-dsDNA [10]. However there are indications that a significant fraction of SLE patients have little, if any, anti-dsDNA or anti-histone reactivity but they do have high anti-nucleosome activity. Hence, Anti-nucleosome antibodies are a highly sensitive marker of SLE.

J.A. Simon et al[11], in their study found that, Anti-NCS had a specificity of 97% and sensitivity of 100% for SLE diagnosis. In their, study when SLE and SAD patients were compared [excluding mixed connective tissue disease (MCTD)], the sensitivity of anti-NCS, anti-dsDNA and anti-HST antibodies for SLE diagnosis was found to be 93%, 71% and 40% respectively and the specificity was 97%, 98% and 98%. Anti-chromatin antibodies was found not to be useful in differentiating between SLE and MCTD patients. They found that Anti-NCS antibodies showed highest correlation with disease activity ($r = 0.45$, $P < 0.0001$), especially in patients negative for anti-dsDNA antibodies ($r = 0.58$, $P = 0.001$) and also showed strong association with renal damage .Hence,from their study they concluded that Anti-NCS antibodies could be a useful tool in the diagnosis and assessment of disease activity in SLE patients, especially in patients who are negative for anti-dsDNA antibodies. In contrast, a similar study by Quattrocchi P et al[12], found Anti-nucleosome antibodies in 40 patients with SLE (85.1%), in 10 with RA (45.4%), in 8 with MCTD (42.1%), in 4 with SSc (36.3%), in 1 with SS (10%) and found none of the healthy controls. While, they found Anti-dsDNA antibodies in 23 SLE patients and were absent in other CTD patients and controls. All the patients with SLE and renal involvement were positive both for anti-dsDNA antibodies and anti-nucleosome antibodies. They observed no significant correlation between anti-nucleosome antibodies and disease activity and renal involvement.Thus, they concluded in their study that, Anti-nucleosome antibodies are present in a high percentage SLE patients but they don't seem to be specific markers of the disease. They observed no clear correlation between anti-nucleosome antibodies and disease activity and renal involvement.

The first of its kind, a prospective longitudinal clinical study done to compare levels of anti-nucleosome, anti-dsDNA and anti-α-actinin antibodies in the same patients with SLE.. Jessica J Manson[13] et al, supported the concept that, in the majority of patients, anti-nucleosome antibodies played a major role in pathogenesis of LN, in contrast to anti-α-actinin antibodies A Mumbai based study by,Pradhan VD et al[14], reported no statistical difference, in the presence of these anti-nucleosome antibodies on comparing SLE groups without nephropathy and SLE groups with nephropathy.Thus, they drew the conclusion that anti-nucleosome detection can be useful as an additional disease activity marker to other laboratory tests.In yet another Indian study, Renu Saigal et al, reported that, Anti-nucleosome antibodies showed higher positivity and are more sensitive and specific for the diagnosis of SLE than anti-dsDnA antibodies. But, with SLEDAI cases anti-dsDNA antibodies showed stronger correlation than anti-nucleosome, although both showed positive correlation.

Figure 1
Structure of a nucleosome: dsDNA and histone proteins (H1, H2A, H2B, H3, H4).



CONCLUSION

Antinucleosome antibodies can be used as an additional marker for diagnosis of SLE. They are probably superior to anti-dsDNA antibodies in the diagnosis of SLE, as it has higher sensitivity and specificity. Antinucleosome antibodies are found even in ds-DNA negative patients and they are not found in healthy controls. Hence,it will not be wrong to assume that , till further research and upgrades are available antinucleosome antibodies could be a useful parameter for the diagnosis and assessment of disease activity.

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