CASE REPORT

Anti-Nuclear Antibody (ANA) Negative Systemic Lupus Erythematosus

*Alnaqdy A.*, *Al Siddiqui M.* and **Elagib E.
Departments of *Microbiology & Immunology and**Medicine, College of Medicine
Sultan Qaboos University, Al Khod, Sultanate of Oman

Abstract:

We report the diagnosis of Systemic Lupus Erythematosus (SLE) in an Omani lady with consistently negative antinuclear antibody (ANA) results and an anti double stranded DNA (dsDNA) titre of 1:640. The presence of a negative ANA with a high titre of dsDNA is very unusual in SLE.

Keywords: SLE, ANA, dsDNA

Introduction:

SLE is characterized by immune dysregulation resulting in the production of autoantibodies such as ANA, generation of circulating immune complexes, and activation of the complement system. A positive ANA result is consistent with SLE and it is extremely rare for them to have a negative ANA. The presence of ANA in SLE patients is both a diagnostic and a prognostic marker. The individual nuclear antigens which ANA are directed against fall into two categories: (a) poorly soluble nucleosomal antigens i.e. DNA and histones and (b) soluble antigens which are easily extractable (in saline) from cell nuclei, the so-called extractable nuclear antigens (ENA).

Antibodies to the various ENA antigens are more useful as diagnostic tools for SLE. For instance, the specificity of anti-Sm for SLE is extremely high although it is found in only 5-30% of SLE cases. Anti-Ro and anti-La are detected in 35% and 15% of SLE patients respectively while 30-40% of SLE patients have anti-RNP. The positive serological correlation between ANA and DNA which has been demonstrated by clinical studies on SLE patients, made it necessary to test for anti dsDNA on sera from patients who are positive for ANA screen. If the test result for anti dsDNA is negative, this doesn’t exclude the possibility of the presence of anti-ENA.

It is well understood that a negative ANA result makes a diagnosis of SLE unlikely but not impossible. Some cases (<5%) of patients with lupus variants, particularly those with a predominance of photosensitive skin disease, display low-level or negative ANA results with positive results for SSA.

In many hospital laboratories, anti dsDNA tests have been performed only on positive ANA SLE cases. The following case report describes an unusual case where the ANA screen was consistently negative throughout.

The Case:

This 31-year-old Omani lady had enjoyed good health all her life until two years prior to presenting to the Accident & Emergency Department at Sultan Qaboos University Hospital (SQUH). She complained of a one-month history of joint pain, which was equally distributed in hands and feet. When she awoke in the morning these joints, in addition to her hip joint, were stiff and eased as the day wore on. She had noticed an increased loss of hair and intolerance to sun exposure especially her eyes and skin. Based on these symptoms, she was referred to the Rheumatology Clinic at SQUH.

On examination, nothing remarkable was found. A blood sample was taken to test for ANA the results of which showed a very weak positive reaction with a titre of 1:40 that was consequently negative when repeated. In view of this result, and taking her complaints into consideration, further tests were performed for antibodies that are characteristically found in SLE. An elevated level of anti dsDNA was measured by the Crithidia luciliae assay and an enzyme-linked immunosorbent assay (ELISA). The titre was greater than 1:640 and 970 units/ml respectively (normal range is < 20 units/ml). Serum IgM class of anti-cardiolipin was positive at a level of 27 MPL (normal range is < 12.5 MPL), whereas the IgG subclass was negative at 15 GPL (normal range is < =15 GPL). Other tests included extracted ENA, complement components C3 and C4, full blood cell counts, erythrocyte sedimentation rate (ERS), urine microscopy, urea and electrolyte, liver function tests, echocardiogram and bone densitometry analysis, which all gave normal results.

The patient was diagnosed as having SLE with predomi-
nantly musculoskeletal manifestations. She was advised to take 200 mg of hydrochloroquinine twice a day and 20 mg of prednisolone once daily. She was seen to be doing fairly well on subsequent follow up and her prednisolone was successfully tapered to a maintenance dose of 5 mg with concurrent hydrochloroquinine. Noticeably, her ANA levels remained negative throughout and she sustained significantly high levels of anti dsDNA.

Discussion:

SLE is the classical systemic autoimmune disorder with the hallmark being the presence of autoantibodies. ANA negative SLE is extremely rare. In a few cases, negative serological tests may become positive at a later date \(^5\). Earlier studies have demonstrated similar cases of ANA negative SLE with antibodies to dsDNA \(^6\). It is well recognised that up to 50% of SLE patients may lack anti dsDNA antibody, especially those with quiescent disease \(^1\). In cases where both ANA and anti dsDNA are negative in SLE, further tests such as ENA can be carried out. SLE cases which are ANA/dsDNA negative with positive ENA have also been reported \(^7\).

ANA negative results may also be seen in discoid lupus, antiphospholipid syndrome and in patients who have been on long-term immunosuppressive therapy that their test becomes negative. Insensitive or bad technique for ANA testing in the laboratory cannot be excluded as a cause of negative results. In the US, 97% of those with SLE, are ANA positive using a Hep-2 substrate. However, in the UK and other countries where other substrates are being used, up to 10% can be ANA negative.

In a similar situation, a total haemolytic complement or CH50 measurement can be useful. A CH50 of zero is consistent with those unusual patients who have a homozygous early complement component deficiency (e.g. Clq, C2, C4), and at risk for developing a SLE-like illness, but are ANA negative.

Anti-Ro and La (SS-A, SS-B), which are associated with Sjogren's syndrome, can be positive in SLE (Ro lupus).

They can also be seen in rare ANA negative SLE cases. This disorder manifests most often by a partially photosensitive skin rash referred to as subacute cutaneous lupus erythematosus.

Antibodies to dsDNA are diagnostic of SLE (specificity >99%) and are found in more than 70 percent of cases. Some studies have shown that levels of anti dsDNA antibodies vary with clinical disease activity and have also been used clinically to monitor disease activity. High titers are associated with the development of nephritis and portend a poorer prognosis. The close association of anti dsDNA with SLE has implied that immune responses to DNA are an exclusive feature of autoimmune disease \(^8\).

In this unusual case, ANA was consistently negative with a high titre of anti dsDNA throughout. The patient had maintained relatively good health and only manifested musculoskeletal symptoms. Negative ANA may indicate good prognosis.

Conclusion:

Patients with SLE can be negative for ANA. When the ANA is negative in patients who satisfy the clinical criteria for SLE, other antibody markers of lupus may be present, such as dsDNA and cardiolipin antibodies.

References: