Medical conditions associated with a positive anti-double-stranded deoxyribonucleic acid

Suzan M. Attar, FRCPC, FACP, *Emad A. Koshak,* FRCPC, FACAI.

ABSTRACT

الأهداف: لاستكشاف الأمراض المرتبطة بوجود أضداد الحمض النووي مزدوج الخيط ds(DNA) خلاف الذئبة الحمراء (SLE)، ودراسة أي رابط بين مستويات هذه الأجسام والأسباب الأخرى.

الطريقة: أجريت دراسة استرجاعية ذات أثر رجعي لكل المرضى المطلوب لهم تحليل الأجسام المضادة ومعاينة أسباب النتائج الإيجابية (أكثر من 200 وحدة لتر/مليلتر) خلال الفترة من يناير حتى ديسمبر 2007م في مستشفى جامعة الملك عبد العزيز، جدة، المملكة العربية السعودية.

النتائج: قمنا باختبار 212 مريض باختبار الجسم المضاد المعادي للحمض النووي مزدوج الخيط ds(DNA). بعد المعاينة كان 124 مريض (58.5%) مصاب بمرض الذئبة الحمراء، بينما 88 مريض (41.5%) لديهم أمراض أخرى، وتمثل أمراض روماتيزمية 29 مريض (33%)، والتهابات في 11 مريض (12%)، وأورام في 6 مريض (7%). ظهرت نتائج إيجابية عالية (أكثر من 800 وحدة لتر/مليلتر) في 8 مريض فقط (4%)، وتشمل التشخيص التالي، متلازمة الأجسام المضادة للشحوم الفسفورية، وأمراض السل، والتهاب العظام، والأورام، والساركويد، والتهاب الكبد الذاتي المناعة في مريضين. كان هناك ارتباط هامّ بين اختبار الحمض النووي مزدوج الخيط ds(DNA) والأمراض الروماتيزمية.

خاتمة: بالرغم من أن اختبار أضداد الحمض النووي مزدوج الخيط ds(DNA) كان إيجابي بنسبة عالية في مرضى الذئبة الحمراء (SLE)، يجب أن يؤخذ بنظر الاعتبار الأمراض الأخرى عندما تكون المعايير السريرية التشخيصية ليست لمصلحة الذئبة الحمراء.

Objectives: To explore the associated diseases with positive anti-double stranded (ds) DNA other than systemic lupus erythematosus (SLE), and to determine an association if any, between its level in non-SLE causes.

Methods: This is a retrospective review of all patients with positive anti-dsDNA assay (more than 200 IU/ml) tested for any underlying etiology from January to December 2007 at the King Abdul-Aziz University Hospital, Jeddah, Kingdom of Saudi Arabia.

Results: Two hundred and twelve patients with anti-dsDNA antibody testing were evaluated. Of these, 124 patients had SLE (58.5%), while 88 patients (41.5%) had other diseases. Representing non-SLE diseases were: rheumatological disorders in 29 patients (33%), infections in 11 (12%), and malignancy in 6 patients (7%). Strong positive results (>800 IU/ml) were found in only 8 patients (4%) with diagnoses of antiphospholipid antibody syndrome, tuberculosis, osteomylitis, thymoma, lymphoma, sarcoidosis, and 2 autoimmune hepatitis patients. There was a statistically significant association between highly positive anti-dsDNA testing and rheumatological disorders.

Conclusion: Although positive anti-dsDNA test is common in SLE patients, other diseases should be considered when the anti-dsDNA level is equivocal, and the clinical criteria are not in favor of SLE .

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From the Department of Internal Medicine, King Abdul-Aziz University Hospital, Jeddah, Kingdom of Saudi Arabia.

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Address correspondence and reprint request to: Assistant Professor Suzan M. Attar, Consultant, Department of Internal Medicine, King Abdul-Aziz University Hospital, PO Box 80215, Jeddah 21589, Kingdom of Saudi Arabia. Tel. +966 (2) 6408243. Fax. +966 (2) 6408315. E-mail: suzan_attar@hotmail.com

Numerous auto-antibodies can target some intracellular antigens of the nucleus and mediates tissue damage.[1] One of these intracellular antigens is double-stranded deoxyribonucleic acid (dsDNA), proven to be the main antigen responsible for the immune mediated cell damage in systemic lupus erythematosus (SLE).[2] Systemic lupus erythematosus is diagnosed based primarily on the presence of 4 criteria out of the 11 classified by the American College of Rheumatology (ACR) in 1982.[3] One of these criteria is the presence of antibodies to dsDNA (anti-dsDNA). First described in the 1950's,[4,5] these antibodies are found in high frequency in SLE patients (60-80%),

and correlates with the disease activity and tissue/organ damage, particularly lupus nephritis.[6,7] Several laboratory techniques are commercially available to measure anti-dsDNA. The most frequently used in routine clinical laboratories are radioimmunoassay (RIA), *Crithidia Luciliae* immunofluorescence test (CLIFT), and enzyme-linked immunosorbent assay (ELISA). The sensitivity and specificity of anti-dsDNA antibodies testing to diagnose SLE is greatly dependent on the method used.[8] Despite the fact that the ELISA anti-dsDNA is highly specific for SLE (91-96%), it has been reported in less than 5% of patients with other conditions in normal individuals, particularly first-degree relatives of patients with lupus.[9] In the literature, among the non-SLE rheumatic diseases associated with positive testing for anti-dsDNA are: rheumatoid arthritis (RA), ankylosing spondylitis (AS), mixed connective tissue disease (MCTD), Sjögren's syndrome, scleroderma, Raynaud's phenomenon, discoid lupus, myositis, uveitis, juvenile rheumatoid arthritis (JRA), and antiphospholipid (APA) syndrome.[10,11] The non-rheumatological diseases that may be associated with positive anti-dsDNA testing are: chronic active hepatitis, infectious mononucleosis, biliary cirrhosis, autoimmune hepatitis, Grave's disease, familial Mediterranean fever, Alzheimer disease, sarcoidosis, lymphoma, and silicon breast implants.[12-15] Furthermore, anti-dsDNA antibodies have also been reported in a subset of patients with drug induced lupus who received minocycline, penicillamine, hydralazine, and biologics such as, etanercept and infliximab.[16,17] Over the past years, many referrals to the rheumatology service have been made concerning a positive anti-dsDNA testing to rule out SLE. On occasions after reviewing the clinical data and detailed laboratory investigations, patient has turned out to have an etiology other than SLE. Hence, the objective of this research was to determine the clinical utility of positive anti-dsDNA antibody testing at a tertiary center, with focus on associated non-SLE causes.

Methods. This study was carried out at the King Abdulaziz University Hospital (KAUH), Jeddah, Kingdom of Saudi Arabia. The KAUH is a teaching hospital, and a major tertiary referral center providing healthcare to patients from different nationalities and ethnic backgrounds. This study is a simple, cross-sectional retrospective design with no involvement of patient interaction. Data were collected and anonymously arranged for statistical analyses. Approval from the Medical Research Ethics Committee of KAUH had been obtained for conducting this study.

We included all patients that underwent anti-dsDNA tests from January to December 2007. Their laboratory results had been retrieved and reviewed from blood samples with request for antinuclear antibody (ANA) testing. We excluded those duplicated orders, errors in registration, ANA titer less than 1:80, and unavailable clinical information. The ANA test was performed using indirect immunofluorescence technique, utilizing human epithelial cells (HEp-2) fixed on glass slides, commercially prepared (ANA HEp-2 [IMMCO Diagnostic Inc, NY, USA). The IIF pattern was recorded and classified into homogenous, speckled, nucleolar, peripheral or rim, centromere, and mixed. According to the American College of Rheumatology (ACR) Guidelines, anti-dsDNA testing is routinely carried out if the ANA test was positive, and particularly if the ANA titer was more than 1:80.[18,19] The anti-dsDNA test is performed using the ELISA technique (Quanta Lite,™ dsDNA Kit, INOVA Diagnostic Inc, CA, USA), and measured in IU/mL according to manufacturers' instruction. Sample results of anti-dsDNA tests were classified as follows: negative - if the level is between 0-200 IU/mL (0-92.6 World Health Organization [WHO] units/ml), equivocal - if the level is between 201-300 IU/mL (92.7-138.9 WHO units/mL), moderately positive - if the level is between 301-800 IU/mL (139-370.4 WHO units/mL), and strongly positive - if the level is >801 IU/mL (>370.5 WHO units/mL) according to the manufacturers' instruction.[20] Medical records of patients with positive anti-dsDNA test results were reviewed retrospectively for demographic variables, age, gender, and nationality (Saudi or non-Saudi). We recorded the diagnoses and classified it into SLE and non-SLE. The SLE was diagnosed by a rheumatologist according to the 1997-revised ACR classification criteria.[3] Non-SLE causes were further divided into rheumatological and non-rheumatological. Rheumatological causes included RA,[21] JRA,[22] AS,[23] MCTD,[24] Sjögren's syndrome,[25] APA,[26] Raynaud's phenomenon,[27] polymyositis and dermatomyositis,[28] and scleroderma, which was divided into systemic sclerosis and CREST (calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia),[29,30] and other causes.

Data were entered in the database and was scrutinized for outliers. Statistical analysis was carried out using Statistical Package for Social Sciences software version 16 (SPSS Inc, Chicago, IL, USA). Descriptive statistics were performed as appropriate including frequency, mean ± standard deviation, and cross tabulations. Frequency distributions were compared using the Chi-square test. Mean values were compared using the t-test. The association between quantitative anti-dsDNA with SLE and non-SLE causes were determined using chi-square test and logistic regression. Statistical significance was set at $p<0.05$ throughout the analysis.

Results. There were 212 samples eligible for inclusion. Females represents 189 (89%) with a mean age of 34 ± 14.8 years, while 23 patients (11%) were males with a mean age of 34.4 ± 17.92 years. The global mean age was 34 years with an age range of 15-75 years. Saudi nationals accounted for 121 patients (57%) compared to non-Saudis. Non-Saudis represent 91 patients (43%) as such: 50 Arabs (24%), 18 Africans (8.4%), 15 Asian-Indians (7%), 5 Asian-others (2.3%), and 3 Europeans (1.4%). The SLE was found in 124 (58.5%), while other diagnoses other than SLE were found in 88 patients (41.5%). Rheumatological disorders occurred in 29 of the 88 patients such as: APA syndrome, RA, CREST, scleroderma and vasculitis, JRA, and MCTD. In the SLE patients, 25 out of 124 (20%) had skin manifestations, in the form of malar rash in 20 patients (16%), and photosensitivity in 12 patients (10%). Non-rheumatological disorders were found in 59 out of 88 patients (67%), sepsis in 2 (0.9%), cellulitis, osteomyelitis, pyrexia of unknown origin, dengue fever, and pyelonephritis in one patient (0.5%) each. Malignancy was found in 6 patients with lymphoma, thymoma, lung, breast, stomach, and cervical cancer. Endocrine disorders were found in 8 patients (3.7%), as Hashimoto's thyroiditis in 3 patients (1.4%), diabetes mellitus (DM) in one patient (0.5%) associated with hypothyroidism, hypothyroidism in one patient (0.5%), hypoparathyroidism in one patient (0.5%), hypopituitarism one patient (0.5%), and Addison's disease in one patient (0.5%). Positive anti-dsDNA testing was recorded in 11 patients (5.1%) only with non-specific complaints. **Table 1** shows the causes of positive dsDNA in the studied group. The distribution of dsDNA level among this group is illustrated in **Tables 2 & 3**. With regards to the ANA immunofluorescence pattern there were: homogenous - 92 patients (43.4%) in which 44 (47%) had strong positive result, speckled - 108 patients (50.9%), nucleolar - 8 patients (3.8%), peripheral - 2 patients (0.9%), centromere and mixed in one patient each (0.5%). In testing the association of SLE presence/absence with ANA pattern using Chi-square test, it was found that no relationship was present. We could not determine the association between the rim pattern and the anti-dsDNA due to the small sample size (2 patients only). The anti-dsDNA had a sensitivity of 86% (95% confidence interval [CI]: 80.4-90.9%), and a specificity of 80% (95% CI: 67-88%), positive predictive value of 89% (95% CI: 83-93%), negative predictive value of 75% (95% CI: 63.6-80%). Based on chi-square testing, a significant positive association (p=0.001) was found between both negative and strongly positive anti-dsDNA results for SLE/non-SLE diagnosis. On logistic regression, a significant positive correlation exist (p=0.02) between strongly positive anti-dsDNA testing (>800 IU/mL), and rheumatological causes (odds ratio [OR]=0.15, 95% CI 0.056-0.98). Regression analyses had shown no correlation between positive anti-dsDNA testing and infections, malignancy, hepatitis, or sarcoidosis .

Discussion. In this study, we had 3 important observations: firstly, the frequency of positive anti-dsDNA testing in non-SLE patients was high (up to 41%); secondly, anti-dsDNA antibodies were detected in high frequency in other autoimmune diseases, malignancies, infections, AIH, and sarcoidosis. Finally, an association exists between strong positive anti-dsDNA testing, and other rheumatological disorders.

Systemic lupus erythematosus is a chronic systemic autoimmune disease affecting women during childbearing age, and associated with high morbidity

Table 1 - Causes of positive anti-double strand DNA test in 212 patients.

Diseases	N=212	(%)
SLE	124	(58.8)
Non-SLE	88	(41.5)
Rheumatological disease	29	(13.7)
Antiphospholipid antibody syndrome	10	(4.7)
Rheumatoid arthritis	9	(4.2)
CREST	4	(1.9)
Scleroderma	2	(0.9)
Vasculitis	2	(0.9)
Juvenile rheumatoid arthritis	1	(0.5)
Mixed connective tissue disease	1	(0.5)
Malignancy	6	(6.8)
Lymphoma	1	(0.5)
Other cancers	5	(2.4)
Infection	11	(12.5)
Tuberculosis	4	(1.9)
Other infections	7	(3.3)
Endocrine disorders	8	(3.8)
Hepatitis	5	(2.4)
Autoimmune hepatitis	3	(1.4)
Chronic hepatitis B	2	(0.9)
Sarcoidosis	1	(0.5)
Familial Mediterranean fever	1	(0.5)
Other causes	27	(12.7)
Idiopathic thrombocytopenic purpura	2	(0.9)
Rheumatic heart disease	2	(0.9)
Myasthenia Graves' disease	1	(0.5)
End stage renal disease	1	(0.5)
Ulcerative colitis	1	(0.5)
Epilepsy	1	(0.5)
Fibromyalgia	1	(0.5)
Osteochondritis	1	(0.5)
Osteoarthritis	2	(0.9)
Evans syndrome	1	(0.5)
Skin psoriasis	1	(0.5)
Skin rash for investigation	1	(0.5)
Non-specific complaints	11	(5.1)

SLE - sytemic lupus erythrumatosus, CREST - calcinosis, Raynaud's disease, esophageal dysmotility, sclerodactyly, and telangiectasia

Table 2 - Level of anti-double stranded DNA in 212 patients .

Variables	Negative 0-200 IU/mL n=36 (%)	Equivocal 201-300 IU/mL n=45 (%)	Moderate positive 301-800 IU/mL n=66 (%)	Strongly positive >801 IU/mL n=65 (%)
SLE, n=124	9 (4.2)	21 (9.9)	36 (17)	58 (27.4)
Non-SLE, n=88	27 (12.7)	23 (11)	30 (14)	8 (4)
Sensitivity	92	83	71	47
Specificity	61	65	72	92
PPV	65	48	55	89
NPV	75	25	39	55
χ^2	20	3.2	0.6	36
Accuracy	(59)	(60)	(62)	(92)
P-value	0.001*	0.063	0.43	0.001*

SLE - systemic lupus erythematosus, PPV - positive predictive value, NPV - negative predictive value, *significant positive association $p<0.05$ by Chi-square test (χ^2).

Table 3 - Level of anti-double stand DNA in 88 non-SLE patients

Variables	Negative 0-200 IU/mL n=27 (%)	Equivocal 201-300 IU/mL n=23 (%)	Moderate positive 301-800 IU/mL n=30 (%)	Strongly positive >801 IU/mL n=8 (%)	Total n=88 (%)
Rheumatological diseases	8 (30.0)*	9 (39.0)	11 (37.0)	1 (14.3)*	29 (33.0)
APAS	4	3	3	0	
RA	0	4	4	1	
CREST	1	1	2	0	
Scleroderma	1	1	0	0	
Vasculitis	1	0	1	0	
JRA	1	0	0	0	
MCTD	0	0	1	0	
Infection	3 (11.1)	1 (4.4)	5 (17.0)	2 (28.6)	11 (12.0)
Tuberculosis	1	0	2	1*	4
Other infections	2	1	3	1	7
Endocrine disorders	3 (11.1)	4 (17.4)	1 (3.0)	0	8 (9.0)
Malignancy	3 (11.1)*	1 (4.4)	0	2 (28.6)	6 (7.0)
Lymphoma	0	0		1	1
Other cancers	3	1		1	5
Hepatitis	2 (7.4)	0	1 (3.0)	2 (28.6)	5 (6.0)
AIH	0		1	2	3
Chronic hepatitis-B	2		0	0	2
Sarcoidosis	0	0	0	1 (14.3)	1 (1.0)
Familial Mediterranean fever	0	1 (4.4)	0	0	1 (1.0)
Other causes	8 (29.6)	7 (30.4)	12 (40.0)	0	27 (31.0)
ITP	1	1	0	0	2
Rheumatic heart disease	1	0	1	0	2
Myasthenia Graves' disease	0	0	1	0	1
End stage renal disease	1	0	0	0	1
Ulcerative colitis	0	0	1	0	1
Epilepsy	0	0	1	0	1
Fibromyalgia	1	0	0	0	1
Osteochondritis	1	0	0	0	1
Osteoarthritis	0	1	1	0	2
Trigeminal neuralgia	0	0	1	0	1
Evans syndrome	0	1	0	0	1
Skin psoriasis	0	1	0	0	1
Skin rash	0	1	0	0	1
Non-specific complaints	3	2	6	0	11 (5.1)

APAS - antiphospholipid syndrome, RA - rheumatoid arthritis, CREST - calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia, JRA - juvenile rheumatoid arthritis, MCTD - mixed connective tissue disease, AIH - autoimmune hepatitis, ITP -idiopathic thrombocytopenic purpura. *Significant positive association $p<0.05$ by Chi-square test.

and mortality if left untreated.[31] It should be suspected in any young female presenting with symptoms of arthritis, skin rash, stomatitis, renal disease, and pancytopenia.[32] The ACR criteria for defining SLE is more than 90% sensitive and specific.[3] They were used primarily for research purposes as entry criteria, and should be regarded as a guide, rather than a rigid indicator for diagnosis of SLE. In addition, SLE patients may have serological and clinical discordance, such as, being either serologically active or clinically quiescent, or clinically active and serologically quiescent. It is unclear whether such clinical conflicts are reflections of the true native disease states, or false-positive testing.[33] Arbuckle et al[34] observed that positive anti-dsDNA testing is usually present 2.2 years before a clinical diagnosis of SLE could be made. In our study, 0.9% of patients had ITP, others may have autoimmune hemolytic anemia with positive anti ds-DNA, and are not labeled as SLE, yet frequent monitoring is recommended before the development of a full-blown disease picture.

The ELISA technique for anti-dsDNA immunoglobulin (Ig) G measurement is rapid, semi-quantitative, and reproducible, but requires highly purified antigens.[8] It detects high and low affinity antibodies to the dsDNA. Other isotypes (IgA, IgM) have been observed, IgM and IgA isotypes are associated cutaneous involvement, while IgG isotype are found in patients with lupus nephritis.[35,36] Guidelines in the field of laboratory diagnosis of autoimmune disease issued by the ACR in 2002 recommended that anti-dsDNA testing be reserved for patients who are positive for ANA.[18,19] They stated in agreement with the Italian Society of Laboratory Medicine (regarding the anti-dsDNA testing), which ELISA method to be used as an initial screening followed by the CLIFT for positive sample confirmation.[37] In 2007, a Japanese group suggested performing a highly specific anti-dsDNA testing (as Farr or CLIFT), and if ELISA was used, a positive test result must be subsequently confirmed by the CLIFT method.[38,39] The specificity of anti-dsDNA was lower in our work (80%) compared with other previous studies (91-96%).[9] This could be due to the substrate difference, the isotype detected, problems with standardization and collaboration, or because the test was restricted to ANA-positive samples (titer >1:80). According to our data, we could rely on both negative and strongly positive results ELISA anti-dsDNA in differentiating between SLE and non-SLE. However, equivocal and moderate positive results found in 11 and 14% in our non-SLE patients sera should be re-tested to search for appropriate diagnosis.

Initial Western reports showed that the frequency of elevated levels of anti-DNA antibodies in conditions other than SLE to be low (less than 5% of the patients), and when they are present, are often in low titer and with low avidity.[4] In 1995, a Saudi study showed that anti-dsDNA using ELISA could be positive in 35% of patients with rheumatological disorders, and 4% in normal patients.[40] In Oman, it was found in 23% disease control, 16% in RA patients, and 3% in normal individuals.[41] Therefore, why in Arab countries do we have such a high false-positive anti-dsDNA in the blood in comparison to Western society? This could be explained by the theory of "ultraviolet (UV) light-induced keratinocyte apoptosis." The dsDNA antigen is available in the human skin and most of the Arab countries are subtropical and arid where the climate is >40°C. In patients predisposed to autoimmune diseases, exposure to ultraviolet light (UVA and UVB waves in the sunlight) will damage skin cells (keratinocytes) causing them to die (apoptotic).[42] These cells are not cleared away efficiently, and result in the contents of the dying cells as DNA (the genetic material) being released into the blood stream, causing inflammation, which may generate an immune response. Despite that, our patients had low frequency of skin involvement (20%), which is less than the Western reports (75%), attributed the protective clothing, and inadequate exposure to sunlight, which lead to high prevalence of vitamin D deficiency as well.[43] Other factors that may attribute to the false-positive testing are the auto-antibodies production against various autoantigens.

Malignancies and tuberculosis are associated with false-positive results, and both have been reported to be associated with auto-antibodies (between 3-25%) due to cell apoptosis, or as an immune response to the tumor cell.[12,44,45] High prevalence of latent TB infection is reported in our society (72%) that could be attributed to our findings.[46] Research have been ongoing for more accurate tests, for instance, anti-mitochondrial (m)DNA, which is found on the B-lymphocyte is associated with high specificity in detecting SLE at low ANA titer 1:40.[47] As well, anti-nucleosome antibodies (anti-NCS), which are detected in antidsDNA negative SLE patients correlates with disease activity.[48] Due to the sup-optimal specificity and the incidence false-positive results of anti-DNA in SLE, we recommend that anti-dsDNA be ordered by rheumatologists, as such results may delay the appropriate diagnosis, waste laboratory resources, and increase the burden of labor.

This study is limited due to its retrospective nature, lacks the ability to have control group, and no other test was available for the false-positive, or false-negative results.

In conclusion, this one-year retrospective study showed high prevalence of patients with positive anti-

dsDNA testing associated with other diseases, other than SLE. Positive anti-dsDNA testing was associated mainly with other rheumatological diseases, and to a lesser extent with infection and malignancy. The underlying etiology of false-positive testing in our area remains unclear, whether UV light-induced keratinocyte apoptosis has a role in inducing these antibodies to be investigated. Outside the research setting, ordering anti-dsDNA for the diagnosis of any condition other than SLE is not useful. We recommend a longitudinal study of all patients with positive anti-dsDNA over a 3-year period to observe for any susceptibility towards developing an autoimmune disease, including SLE.

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