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Isolated anti-ribosomal P antibodies are associated with reduced risk of renal and articular involvement in systemic lupus erythematosus patients. An observational study from one center

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Abstract

Introduction: The aim of the study was to compare the specific clinical manifestations of systemic lupus erythematosus (SLE) or laboratory findings between patients with and without anti-ribosomal P (anti-P) antibodies and to investigate possible associations between isolated anti-P antibodies and these features.

Material and methods: Seventy-five SLE patients were enrolled in this study. They were recruited from the Department of Internal Medicine and Department of Rheumatology at the University Hospital of Monastir, Tunisia (January 2008 – December 2022). All patients met at least four American College of Rheumatology criteria or Systemic Lupus Erythematosus International Collaborating Clinics criteria at the time of disease diagnosis. Antibody typing was performed using a commercial line blot technique. Statistical analysis was performed using the χ^2 test, Fisher's test when appropriate, Student's *t*-test, or Mann-Whitney *U* test according to normality of the data distribution.

Results: Thirty patients (40%) were positive for anti-P (anti-P+). The anti-P+ had higher frequency of skin features (26/49 [53.1%] vs. 4/26 [15.4%], $p = 0.003$) and central nervous system (CNS) involvement (10/15 [66.7%] vs. 20/60 [33.3%], $p = 0.018$) than patients without anti-P. Interestingly, anti-P+ showed a lower frequency of SLE/rheumatoid arthritis overlap syndrome (1/11 [9.1%] vs. 29/64 [45.3%], $p = 0.042$). The comparison between groups of patients according to the presence of anti-P, anti-dsDNA, and anti-Sm showed that the group with anti-P lacking anti-dsDNA and anti-Sm had the highest frequency of neuropsychiatric SLE (75%, $p = 0.034$), and the lowest frequency of lupus nephritis (0%, $p = 0.029$) and arthritis (12.5%, $p = 0.039$).

Conclusions: This study supports the association of anti-P antibodies with CNS and cutaneous manifestations. To the best of our knowledge, this is the first study to report a negative association between isolated anti-P antibodies and renal and articular involvement in SLE.

Key words: systemic lupus erythematosus, lupus nephritis, arthritis, anti-ribosomal P protein antibodies.

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with diverse clinical manifestations that can affect multiple organ systems [1]. Its diagnosis and management are related to the immunological profile, particularly the presence of specific antinuclear antibodies (ANA) [2].

Although anti-double-stranded DNA (dsDNA) and anti-Sm antibodies are well-established markers specific to SLE and are included in the classification criteria,

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other antibodies, such as anti-nucleosomes and anti-ribosomal P (anti-P), are still being evaluated for their diagnostic and prognostic significance [3, 4].

Anti-ribosomal antibodies, which are highly specific for SLE, do not have the same diagnostic value as anti-dsDNA or anti-Sm [4]. However, some studies suggest that anti-P may be associated with certain SLE manifestations, such as neuropsychiatric SLE (NPSLE), lupus nephritis (LN), and hepatic involvement [5].

There is a lack of comprehensive data on the prevalence and clinical implications of anti-P antibodies in patients with SLE from African and Arab populations, with only a few studies from Tunisia (2 studies) and Egypt (1 study) providing limited insights [6–8]. Notably, these studies presented controversies that should be clarified in further investigations, and did not explore all specific SLE manifestations in relation to anti-P antibodies. To our knowledge, this study is the first to specifically investigate the clinical implications of isolated anti-P antibodies (anti-P without anti-dsDNA or anti-Sm antibodies) in SLE patients. Thus, this study aimed to compare the clinical manifestations and laboratory findings of SLE patients with and without anti-P antibodies, and to explore the associations between isolated anti-P antibodies and specific SLE features.

Material and methods

Patients

We reviewed the medical records of 75 (7 men, 68 women) SLE patients who were recruited from the departments of internal medicine (n = 40) and rheumatology (n = 35) at the University Hospital of Monastir, Tunisia, between January 2008 and December 2022. All patients fulfilled the updated 1997 American College of Rheumatology (ACR) criteria [9] or Systemic Lupus Erythematosus International Collaborating Clinics (SLICC) criteria for the classification of SLE [10]. The clinical manifestations and blood samples were collected at the time of diagnosis. Neuropsychiatric SLE was defined using the 1999 ACR recommendations for NPSLE syndrome [11]. The diagnosis of LN, which was made at the time of SLE diagnosis, was histologically confirmed by renal puncture biopsy. Systemic lupus erythematosus disease activity was evaluated at the time of diagnosis according to the SLE Disease Score Index 2000 (SLEDAI) [12]. We excluded patients who were likely to have SLE but exhibited some, but not all, ACR 1997 or SLICC 2012 criteria for SLE at the time of evaluation [13]. These patients could be included in the study only if they presented again (throughout the study period) with features fulfilling the classification criteria. We also excluded patients who were positive for anti-dsDNA antibodies by ELISA but negative for *Crithidia luciliae* immunofluorescence test (CLIF). This is because of the high frequency of false-positive anti-dsDNA results owing to the high sensitivity of ELISA. This is in line with the latest guidelines that recommend the use of CLIF for the identification of anti-dsDNA antibodies [14].

Antinuclear antibody testing

Screening of ANA was performed by an indirect immunofluorescence (IIF) assay using *HEp-2* cells (Euroimmun, Lübeck, Germany: ANA cutoff ≥ 1 : 180). Anti-dsDNA antibodies were quantified by ELISA (Biosystems S.A., Barcelona, Spain) and confirmed by IIF assay using CLIF (cutoff > 1 : 20). Anti-nucleosomes, anti-histones, anti-Sm, anti-Sm/RNP, anti-SSA/Ro (Ro60/Ro52), anti-SSB/La were analyzed by the Euroline ANA-profile (Euroimmun, Lübeck, Germany).

Anti-ribosomal P evaluation

Line blot assay, a semi-quantitative platform capable of detecting multiple autoantibody specificities, is a reliable and validated diagnostic tool [15–17]. The detection of anti-P using this sensitive and specific technique avoids the low sensitivity of IIF for screening these antibodies [18, 19].

Anti-P antibodies were assessed by a specific line blot assay (Euroimmun, Lübeck, Germany) using a purified ribosomal P protein from a native source as an antigen. In this immunoenzymatic semi-quantitative assay, the strips were incubated with 1/100 diluted patient sera. After washing, the strips were incubated with alkaline phosphatase (ALP)-labeled anti-human IgG, and subsequently with 5-bromo-4-chloro-3′-indolylphosphate p-toluidine salt (BCIP)/nitro blue tetrazolium chloride (NBT) substrate for color development. The results were evaluated and interpreted using the EUROLINE Scan software. Line blots are automatically identified, quantified, and registered, and a complete results report is obtained.

Statistical analysis

The comparison between qualitative parameters was performed using the χ^2 test or Fisher's exact test when appropriate. The distribution of quantitative variables was determined using the Kolmogorov-Smirnov test. Normally distributed variables are summarized as mean ± standard deviation, and their means were compared using Student's t-test. Non-normally distributed variables were summarized as median plus interquartile range, and they were compared using the Mann-Whitney U non-parametric test. All statistical evaluations were performed using SPSS Statistics for Windows (version 21; IBM Corp., USA). A p-value (asymptotic sig-

nificance [2-sided]) < 0.05 was used to define statistical significance.

Bioethical standards

The study was conducted according to the guidelines of the Declaration of Helsinki. The Ethics Committee of the University Hospital of Monastir, Tunisia confirmed that in this retrospective data analysis no ethical approval is required. Written informed consent was obtained from all patients for anonymous publication of the details of their medical cases.

Results

The mean age at the time of diagnosis of SLE was 39.2 ±16.2 years. Women constituted 90.7% (n = 68) of all the patients, with a sex ratio of men/women = 0.1. In our study, 30 patients (40%) had anti-P. The general features of study subjects are shown in Table I.

The mean age of patients with anti-P (anti-P+) was lower than that of patients without anti-P (anti-P–) (33 ±15.3 years vs. 43.3 ±15.6 years, p = 0.006). Anti-P+, compared to anti-P–, presented with a higher prevalence of skin features (26/49 [53.1%] vs. 4/26 [15.4%], p = 0.003), malar rash (18/28 [64.3%] vs. 12/47 [25.5%], $p \leq 0.001$), central neurological features (10/15 [66.7%] vs. 20/60 [33.3%], p = 0.01), anemia (26/57 [48.1%] vs. 4/21 [19.0%], p = 0.03), and anti-SSA antibodies (19/33 [57.6%] vs. 11/42 [26.2%], p = 0.006). Interestingly, anti-P+ had a lower presence of SLE/rheumatoid arthritis overlap syndrome (SLE/RA OS) (1/11 [9.1%] vs. 29/64 [45.3%], p = 0.04) (Table II).

Table III shows that anti-P+ had higher levels of erythrocyte sedimentation rate (ESR: 86.4 ±47.5 mm/1st hour vs. 61.2 ±38.5 mm/1st hour, p = 0.021) and IgM-anti-cardiolipin antibodies (IgM-aCL: 18.2 ±23.3 MPL/ml vs. 0.7 ± 2.9 MPL/ml, p = 0.004).

Comparison of clinical features between patients with isolated anti-ribosomal P antibodies and patients with other lupus markers (Table IV) shows that patients with isolated anti-P had the highest frequency of NPSLE (6/8 [75.0%] vs. 6/22 [27.3%], p = 0.034), and the lowest frequency of LN (0/8 [0%] vs. 9/22 [40.9%], p = 0.029] and arthritis (1/8 [12.5%] vs. 12/22 [54.5%], p = 0.039). In addition, we compared anti-P+ with anti-SSA/Ro and/or anti-SSB/La antibodies and anti-P+ lacking anti-SSA/Ro and anti-SSB/La antibodies. No significant differences were observed between the 2 groups.

Table I. Clinical, biological and therapeutic features and disease activity of the 75 studied systemic lupus erythematosus patients

Features	Data summary
Age [years], mean ±SD	39.2 ±16.2
Sex ratio (men/women)	0.1 (7/68)
Clinical manifestations [*n* (%)]	
Familial SLE	5 (6.7)
Associated AIDs	20 (26.7)
Cutaneous features	49 (65.3)
Photosensitivity	33 (44)
Pleural effusion	11 (14.7)
Pericarditis	7 (9.3)
Lupus nephritis	18 (24)
Arthritis	34 (45.3)
NPSLE	25 (33.3)
Autoantibodies [*n* (%)]	
ANA	73 (97.3)
Anti-ds DNA	41 (54.7)
Anti-Sm	19 (25.3)
Anti-P	30 (40)
SLEDAI, mean ±SD	10 ±6.2
Treatment [*n* (%)]	
GCs therapy	62 (82.7)
High doses (> 1 mg/kg)	17 (22.6)
Bolus	32 (42.6)
Antimalarics* [mg/kg]	65 (86.7)
Immunosuppressive	20 (26.7)
Methotrexate [mg/week]	14 (18.6)
Cyclophosphamide [mg/m^2]	14 (18.6)
Azathioprine [mg/kg]	8 (10.6)
Mycophenolate mofetil [g/day]	7 (9.3)
Anti-TNF-α** [mg/kg]	2 (2.6)

** Ten SLE patients who had not received antimalarics drugs presented with contraindications to this medication, such as visual problems approved by an ophthalmic examination (retinopathy), severe cardiac problems, or severe hepatic biological abnormalities. ** Infliximab.*
AIDs – autoimmune diseases, ANA – anti-nuclear antibodies, anti-P – anti-ribosomal P, ds – double stranded, GCs – glucocorticosteroids, NPSLE – neuropsychiatric SLE, SD – standard deviation, SLE – systemic lupus erythematosus, SLEDAI – Systemic Lupus Erythematosus Disease Activity Index, TNF – tumor necrosis factor.

Discussion

Anti-P antibodies are directed against 3 ribosomal phosphoproteins: P0, P1, and P2 [4]. In this study, we found that anti-P antibodies were significantly associated with central nervous system (CNS) and cutaneous manifestations, hematological abnormalities, and high ESR in patients with SLE. In addition, isolated anti-P antibodies (without anti-dsDNA and anti-Sm antibodies)

Table II. Clinical, biological and therapeutic features and disease activity of SLE patients with or without anti-ribosomal P antibodies

Features	Patients with anti-P (*n* = 30)	Patients without anti-P (*n* = 45)	*p*	OR, 95% CI
Age [years], mean ±SD	33.03 ±15.3	43.3 ±15.6	**0.006**	
Cutaneous features [*n* (%)]	26 (86.6)	23 (51.1)	**0.003**	6.2, 1.8–20.7
Malar rash	18 (60)	10 (22.2)	≤ **0.001**	5.2, 1.9–14.4
Discoid lupus*	5 (16.6)	3(6.6)	0.169	
Ulcerations*	1 (3.3)	6 (13.3)	0.232	
Photosensitivity	15 (50)	18 (40)	0.393	
Alopecia	5 (16.6)	9 (20)	0.717	
Serositis[a] [*n* (%)]	5 (16.6)	7 (15.5)	0.898	
Pleural effusion	5 (16.6)	6 (13.3)	0.689	
Pericarditis*	4 (13.3)	3 (6.6)	0.427	
Arthritis [*n* (%)]	14 (46.6)	20 (44.4)	0.85	
Lupus nephritis [*n* (%)]	10 (33.3)	8 (17.7)	0.122	
Neurological features [*n* (%)]	11 (36.6)	8 (17.7)	0.06	
Central	10 (33.3)	5 (11.1)	**0.018**	4.0, 1.2–13.2
Headache	6 (20)	4 (8.8)		
Seizures	3 (10)	0		
Acute confusional state	1 (3.3)	3 (6.6)		
Myelopathy	0	1 (2.2)		
Peripheral	2 (6.6)	3 (6.6)	1	
Psychiatric features* [*n* (%)]	4 (13.3)	5 (11.1)	1	
Depression	1 (3.3)	5 (11.1)		
Delirium	3 (10)	0 (0)		
NPSLE features [*n* (%)]	12 (40)	13 (28.8)	0.317	
Central	11 (36.6)	9 (20)	0.090	
Rhupus syndrome* [*n* (%)]	1 (3.3)	10 (22.2)	**0.042**	0.1, 0.015–0.9
Hematological disorders[b] [*n* (%)]	27 (90)	33 (73.3)	0.139	
Anemia	26 (86.6)	28 (62.2)	**0.034**	3.9, 1.1–13.2
Leucopenia	13 (43.3)	11 (24.4)	0.086	
Lymphopenia	15 (50)	14 (31.1)	0.100	
Thrombopenia*	3 (10)	8 (17.7)	0.509	
ANA [*n* (%)]	29 (96.6)	44 (97.7)	1	
Anti-ds-DNA	20 (66.6)	21 (46.6)	0.088	
Anti-Sm	10 (33.3)	9 (20)	0.193	
Anti-Sm/RNP	11 (36.6)	13 (28.8)	0.479	
Anti-SSA/Ro	19 (63.3)	14 (31.1)	**0.006**	3.8, 1.4–10.1
Anti-SSB/La	9 (30)	10 (22.2)	0.448	
Anti-histones	11 (36.6)	11 (24.4)	0.255	
Disease activity status[c]				
Weak	5 (16.6)	12 (26.6)		
Mild	12 (40%)	13 (28.8)	0.322	
Strong	12 (40%)	17 (37.7)		

[a] *Serositis – pleural effusion and/or pericarditis.*
[b] *Hematological disorders – anemia and/or leucopenia and/or lymphopenia and/or thrombopenia.*
[c] *Weak [1–5]; mild [6–10]; strong > 10.*
** Fisher's exact test.*
ANA – anti-nuclear antibodies, anti-P – anti-ribosomal P, CI – confidence interval, ds – double-stranded, NPSLE – neuropsychiatric systemic lupus erythematosus, OR – odds ratio, SD – standard deviation, SLE – systemic lupus erythematosus.

Table III. Serological parameters and activity index of SLE patients with or without anti-ribosomal P antibodies

Variables	Patients with anti-P (*n* = 30)	Patients without anti-P (*n* = 45)	*p*
ESR [mm/h]	86.4 ±47.5	61.2 ±38.5	**0.021**
CRP [mg/l]*	10.5 (2.5–44.3)	17.9 (3.2–46.9)	0.702
Creatinine [µmol/l]	89.9 ±54.7	64.9 ±18.7	0,069
Proteinuria [g/24 h]*	0.17 (0.05–1.1)	0.24 (0.12–0.62)	0.884
C3 [g/l]	0.9 ±0.3	1.2 ±0.3	0.05
C4 [g/l]*	0.16 (0.1–0.2)	0.24 (0.16–0.3)	0.229
IgM-aCL [MPL/ml]	18.2 ±23.3	0.7 ±2.9	**0.004**
IgG-aCL [GPL/ml]	7.2 ±12.3	3.8 ±13.7	0.415
IgM-aβ2GPI [U/ml]	13.7 ±45.3	0.6 ±2.2	0.266
IgG-aβ2GPI [U/ml]	2.1 ±3.7	0.4 ±1.4	0.111
SLEDAI	11.7 ±7.1	8.8 ±5.3	0.051

** Median interquartile range, Mann-Whitney U test.*
aβ2GPI – anti-β2 glycoprotein I (IgG and IgM cutoff < 8 U/ml), aCL – anti-cardiolipin (IgG cutoff < 10 GPL/ml, IgM cutoff < 7 MPL/ml), CRP – C-reactive protein; C3 (normal range: 0.81–1.57 g/l) and/or C4 (normal range: 0.13–0.39 g/l) fractions, IgG – immunoglobulin G, IgM – immunoglobulin M, ESR – erythrocyte sedimentation rate, SLEDAI – SLE Disease Activity Index.

Table IV. Comparison of clinical and biological features and disease activity between patients with isolated anti-ribosomal P antibodies and patients with other lupus markers

Features	Isolated anti-P* (*n* = 8)	Anti-P with anti-dsDNA, anti-Sm, or both (*n* = 22)	*p*	OR, 95% CI
Age** [years], mean ±SD	40.6 ±15.2	29 ±13.8	0.059	
ESR** [mm/h]	70.5 ±51.4	88.6 ±46.2	0.425	
SLEDAI**	9.1 ±4.4	12.4 ±7.9	0.282	
Arthritis*** [*n* (%)]	1 (12.5)	12 (54.5)	**0.039**	0.1, 0.01–0.95
Lupus nephritis***	0	9 (40.9)	**0.029**	
Neurological features***	6 (75)	5 (22.7)	**0.029**	9.6, 1.45–63.50
Central	5 (62.5)	5 (22.7)	0.083	
Peripheral	2 (25)	0	0.069	
Psychiatric features***	0	4 (18.2)	0.552	
NPSLE***	6 (75)	6 (27.3)	**0.034**	8, 1.25–51.13
Central	5 (62.5)	6 (27.3)	0.197	
Rhupus syndrome***	1 (12.5)	0	0.276	
Anemia***	6 (75)	19 (86.4)	0.3	

** Patients with anti-P lacking anti-dsDNA and anti-Sm antibodies.*
*** Student's t-test.*
**** Fisher's exact test.*
CI – confidence interval, ds – double-stranded, ESR – erythrocyte sedimentation rate, NPSLE – neuropsychiatric systemic lupus erythematosus, OR – odds ratio, SD – standard deviation, SLE – systemic lupus erythematosus, SLEDAI – Systemic Lupus Erythematosus Disease Activity Index.

were associated with a higher frequency of NPSLE features and a lower frequency of renal and articular involvement.

In our study, the prevalence of anti-P antibodies was 40%. However, 2 previous Tunisian studies reported frequencies of 22% and 23.5% [6, 7]. Mahler et al. [20] noted differences in anti-P prevalence among populations. This discrepancy between Tunisian studies can be attributed to 2 major factors. First, our line blot method detected all 3 ribosomal P proteins, whereas Yalaoui et al. [6] used an immunodot with the C-terminal 22 amino acid peptide as an antigen, which is described as

less sensitive [3]. Additionally, genetic variability among the Tunisian regions may have influenced these results [21–23]. We also found that the mean age was lower in anti-P+ patients. However, Haddouk et al. [7] and Yalaoui et al. [6] found no association between age and anti-P antibodies. Our study showed a significant association between anti-P antibodies and CNS involvement. However, Haddouk et al. [7] did not find an association between anti-P antibodies and CNS involvement despite the higher neurological involvement in SLE patients with positive anti-P antibodies. Yalaoui et al. [6] also found equal CNS feature distribution in patients with and without anti-P antibodies. These discrepancies may stem from differences in the detection methods and population origins, as explained above. In addition, unlike other studies [24], we used the 1999 ACR classification for NPSLE features. The mechanisms proposed to explain this association between anti-P antibodies and CNS involvement include antigen-directed humoral immunity in the brain, inhibition of protein synthesis, neuronal apoptosis, and inflammatory responses [25–32]. In addition, we found a negative association between anti-P antibodies and SLE/RA OS. To the best of our knowledge, only one study has investigated this relationship; it found that anti-P antibodies were more frequent in SLE patients with RA than in those with SLE alone [33]. Interestingly, our study showed an association between anti-P and IgM-aCL antibodies. Although Yalaoui et al. [6] did not find a statistically significant relationship between these antibodies, Haddouk et al. [7] reported an association between anti-P and IgG-aCL. In fact, in their systematic review and meta-analysis, Shi et al. [34] found an association between anti-P and aCL, without describing a specific mechanism to explain it. Regarding isolated anti-P antibodies, we found that 33.3%, 66.7%, and 26.7% of SLE patients with anti-P antibodies lacked anti-dsDNA, anti-Sm, or both antibodies, respectively. Although we found an association between isolated anti-P antibodies and NPSLE features, a previous meta-analysis [34] and review [35] reported controversial conclusions about the association between anti-P antibodies in general and these features. On the other hand, the association between isolated anti-P and low frequencies of LN and arthritis could be explained by a probable cross-reaction between anti-dsDNA (predictive of LN) and ribosomal P antigens [36, 37] and low expression of P-antigen in fibroblasts, which are the principal cells implicated in arthritis [38, 39].

While our study is limited by its historical design and relatively small sample size, it represents the first comprehensive exploration of specific clinical SLE manifestations in patients with anti-P antibodies from African and Arabic populations. To our knowledge, this is the first study to explore the relationship between isolated anti-P antibodies and SLE features. Using a sensitive and specific detection method (line blot assay) and focusing on patients with SLE at the time of diagnosis have enhanced the study results. The specific features found in SLE patients with isolated anti-P antibodies support the relevance of clustering SLE patients based on specific antinuclear antibodies. Cluster analysis can help identify genetic and environmental factors that contribute to disease development. It can also be used to predict disease progression and tailor treatment plans [40]. In fact, the clinical presentation and management of NPSLE differ if it is an inflammation-induced manifestation due to specific autoantibodies, such as anti-P or thrombotic NPSLE induced by anti-phospholipid antibodies [41].

Conclusions

Our study showed that anti-P antibodies are associated with CNS, cutaneous, and hematological manifestations of SLE. Moreover, isolated anti-P antibodies in patients with SLE are likely associated with a reduced risk of renal and articular involvement. Further studies with larger cohorts are needed to support our findings and explore their pathogenesis.

Disclosures

Conflict of interest: The authors declare no conflict of interest.

Funding: No external funding.

Ethics approval: The study was conducted according to the guidelines of the Declaration of Helsinki. The ethics committee of the hospital confirmed that in this retrospective data analysis no ethical approval is required. Written informed consent was obtained from all patients for anonymous publication of the details of their medical cases.

Data availability: The data that support the findings of this study are available on request from the corresponding author (M.E.).

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