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Thrombocytopenia in Systemic Lupus Erythematosus Patients and Its Association with Antiphospholipid Antibodies

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ABSTRACT

Introduction: Systemic lupus erythematosus (SLE) is a complex systemic autoimmune disease, characterized by immune-mediated inflammation in different organs. The course of the disease is characterized by relapses and remissions, and the degree of severity of the clinical manifestations is greatly affected by the number and nature of the various organ affection. The death rate in patients with SLE is still significant, and it may be due to lupus activity, when vital organs are affected, the complications of treatment especially infections or long-term complications, such as cardiovascular disorders.

Objective: To detect the relation between thrombocytopenia in SLE patients and presence antiphospholipid antibodies.

Patients and methods: This study was a cross-sectional study included 100 SLE patients who attended to Sohag University Hospitals. Patients included in this study were classified as SLE patients according to either the 2012 SLICC criteria or the new 2017 ACR/EULAR SLE classification criteria. All of the participants were subjected to the following: Full history, full clinical examination, routine investigations, ANA by immunofluorescence, and ANA profile for the most common 19 autoantibodies by immunoblot. All of the participants were subjected to detection of serum titers of all antiphospholipid antibodies (aPLs) including lupus anticoagulant (LA), anti-cardiolipin (aCL) and anti-beta2-glycoprotein I (ab2GPI).

Results: In this study, we demonstrated that aPLs are strongly associated with increased risk of thrombocytopenia in SLE patients. We identified aPL profiles, especially LA and IgM isotypes, as biomarkers for the risk stratification of thrombocytopenia in SLE patients.

Conclusions: We concluded that aPLs are strongly associated with increased risk of thrombocytopenia in SLE patients.

Keywords: Thrombocytopenia, Systemic lupus erythematosus, Antiphospholipid antibodies.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a heterogeneous systemic autoimmune disease characterized by immune-mediated inflammation in multiple organs. The course of the disease is characterized by exacerbations and remissions, and the severity of the clinical picture is greatly affected by the number of factors and nature of the various organ manifestations [(1)]. The mortality in patients with SLE is still considerable, and it may be due to lupus activity, when vital organs are involved, the complications of treatment, in particular infections or long-term complications, such as cardiovascular disorders [(2)]. Typically, patients with SLE produce numerous autoantibodies. Some of the SLE-related autoantibodies, e.g., anti-dsDNA, correlate with disease activity, while others appear to be markers of specific disease subsets (e.g., anti-Ro/SSA). Moreover, the presence of antiphospholipid antibodies (aPLs) is definitely pathogenic. aPLs positivity itself predisposes to accelerated atherosclerosis and to an increased thromboembolic risk [(2)].

Antiphospholipid syndrome (APS) is characterized by arterial and venous thromboembolic events and pregnancy morbidity (mainly recurrent fetal losses), in the presence of antiphospholipid antibodies (aPLs). APS can occur in individuals without an underlying systemic autoimmune disease (primary APS) or in the context of other systemic autoimmune diseases, with systemic lupus erythematous (SLE) being the most common (30–50%) [(3)]. The aPLs form a heterogeneous group of autoantibodies, including lupus anticoagulant (LA), anti-cardiolipin (aCL) and anti-beta2-glycoprotein I (ab2GPI). The latter two antibodies can be present in IgG, IgM and IgA isoforms, and are directed against anionic membrane phospholipids and associated proteins, and the IgG isotypes in particular are of clinical significance [(4)].

The aim of this study was to detect the relation between thrombocytopenia in systemic lupus erythematosus patients and presence of antiphospholipid antibodies.

PATIENTS AND METHODS

This study was a cross-sectional study included 100 SLE patients who were attending to Sohag University Hospitals. Patients included in this study was classified as SLE patients according to either the 2012 SLICC criteria or the new 2017 ACR/EULAR SLE classification criteria [(5)]. This study was conducted in May 2019 in Rheumatology Department, Sohag University Hospital.

Inclusion criteria: Patients diagnosed as SLE according to SLICC 2012 or ACR/EULAR 2017 classification criteria, age from 17 to 60 years, and patient with disease duration > 6 months.

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Exclusion criteria: Patients who had active infections, malignancies, hematologic diseases, hepatosplenic diseases, and other autoimmune diseases including rheumatoid arthritis, scleroderma, mixed connective tissue disease and polymyositis.

All the participants were subjected to the following:

1. Full history (demographic data and personal history, detailed history of general health condition and chronic or current diseases).
2. Full clinical examination including general examination and vital signs and complete rheumatologic examination.
3. Routine investigations (complete blood picture, erythrocyte sedimentat
4. ion rate, liver functions and renal functions)
5. ANA by immunofluorescence.
6. ANA profile for the most common 19 autoantibodies by immunoblot.
7. All of the participants were subjected to detection of serum titers of all antiphospholipid antibodies (aPLs) including lupus anticoagulant (LA), anti-cardiolipin (aCL) and anti-beta2-glycoprotein I (ab2GPI) using commercial ELIZA kits.

Ethical approval:

An approval of the study was obtained from Sohag University Academic and Ethical Committee. Every patient signed an informed written consent for acceptance of the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis:

The collected data were coded, processed and analyzed using the SPSS (Statistical Package for Social Sciences) version 22 for Windows® (IBM SPSS Inc, Chicago, IL, USA). Data were tested for normal distribution using the Shapiro Walk test. Qualitative data were represented as frequencies and relative percentages. Chi square test (χ^2) to calculate difference between two or more groups of qualitative variables. Quantitative data were expressed as mean ± SD (Standard deviation). Independent samples t-test was used to compare between two independent groups of normally distributed variables (parametric data). P value ≤ 0.05 was considered significant.

RESULTS

Our study population included 100 patients diagnosed SLE, mean age of them was 33.38 ± 9.36 years with range from 18 to 60 years. Majority of patients in this study were females (90%) (Table 1). Mean of disease duration was 3.47 ± 2.72 years with range from 3 to 15 years. As regards family history, we found that only 2 patients had positive family history and 17/100 (17%) patients had positive gestation history (Table 1).

Table (1): Demographic data of the study patients

	No. (100)	%
Age: (years)		
Mean ± SD (Range)	33.38 ± 9.36 (18.0-60.0)	
Sex:		
Male	10	10
Female	90	90
Duration of disease: (years)		
Mean ± SD (Range)	3.47 ± 2.72 (3.0-15.0)	
Family history		
Positive	2	2
Negative	98	98
Gestation history		
Positive	17	17
Negative	83	83

Clinical manifestations: Figures (1-3)

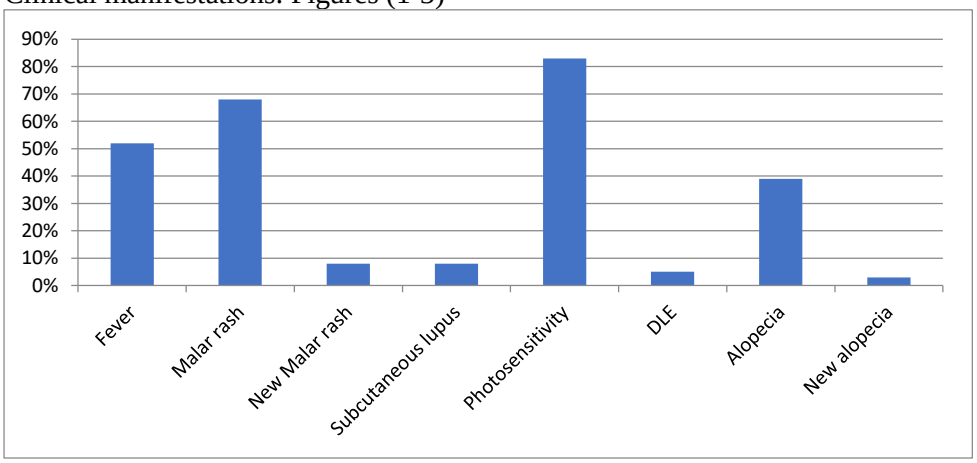

Figure (1): Clinical Manifestation.

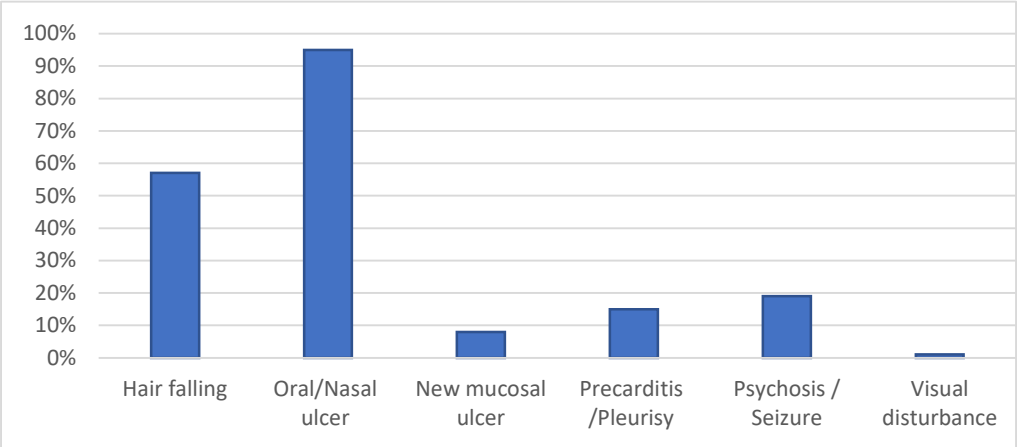

Figure (2): Clinical Manifestation.

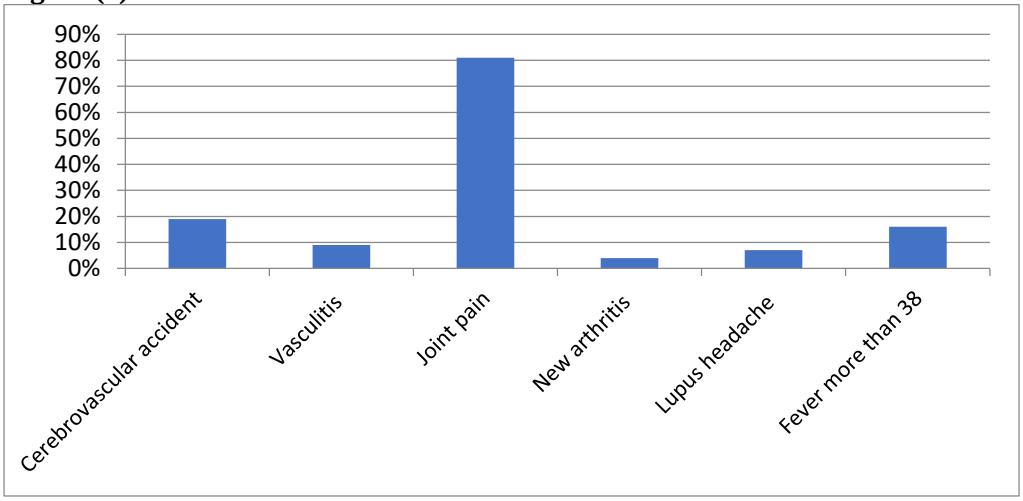

Figure (3): Clinical Manifestation.

In this study, most common clinical manifestations of SLE was cutaneous as oral/nasal ulcer, which observed in 95 (95%) patients, but new ulcers observed in only 8 patients, this was followed by photosensitivity, which was observed in 83% of patients.

Then, malar rash, which was found in 68% of patients, however new malar rash was observed in only 8/100 patients. Besides, hair falling was reported by 57% of patients. On the other hand, alopecia was found in 39% of patients and new alopecia in only 3 patients. DLE was found in only 5/100 patients. Fever was observed in 53% of patients and it was more than 38 in 16% of them.

Regarding neurological manifestations, psychosis/Seizure was found in 19% of patients, cerebrovascular accident was observed in 17%, lupus headache was observed in 6% of patients, and visual disturbance was found in only 1 patient. As regards sororities, pericarditis /pleurisy were found in 15% of patients. Vasculitis was found in only 8 patients. Musculoskeletal manifestations was observed as follows: arthralgia reported by 82% of patients, new arthritis observed in only 4 patients but myositis not found in any patient.

Laboratory investigations:

Mean of ESR was 53.05 ± 28.90. Low c3/c4 was found in 19% of patients. As regards kidney function tests, mean of s. creatinine was 0.849 ± 0.438, albumin in urine was found in 39% of patients, casts, RBCs, and pus (20-25) were found in only 4 patients. As regards liver enzymes, mean of ALT was 26.14 ± 21.30 and mean of AST was 33.95 ± 33.52.

In current study, 99% of SLE patients had positive ANA, it was speckled in 59%, homogenous in 40% and both speckled and homogenous observed in only 1 patient (Table 2).

Table (2): ANA profile

	No. (100)	**%**
ANA positivity		
Positive	99	99
Negative	1	1
Type		
Speckled	59	59
Homogenous	40	40
Both	1	1

Table (3) showed that antiphospholipid antibodies was observed in thrombocytopenic patients as, lupus anticoagulant in 23% of patients, B2 glycoproteins IgM in 22% of patients, anticardiolipin IgM in 14%, B2 glycoproteins IgG in 13%, and anticardiolipin IgG in 11%.

Table (3): Antiphospholipid antibodies in thrombocytopenic patients

	No. (100)	%
Lupus anticoagulant		
Positive	23	23
Negative	77	77
Anticardiolipin IgM		
Positive	14	14
Negative	86	86
Anticardiolipin IgG		
Positive	11	11
Negative	89	89
B2 glycoproteins IgM		
Positive	22	22
Negative	78	78
B2 glycoproteins IgG		
Positive	13	13
Negative	87	87

Disease activity:

Mean of SLEDAI in this study was 7.78 ± 6.12 with range from 0 to 28. We found that there was positive and non-significant correlation between PLTs count and SLEDAI score as shown in table (4). There was non-significant difference between positive and negative all APS patients regarding SLEDAI.

Table (4): Correlation between thrombocytopenia and SLEDAI score

	SLEDAI
r	0.01
p value	0.924

r = person correlation

Table (5) showed that there was negative and significant correlation between platelet count and both anticardiolipin IgM titer and B2glycoprotein IgM titer (p= 0.01, 0.05 respectively). There was negative high significant correlation between platelet count and both lupus titer and anticardiolipin IgG titer. Platelet count also was negatively but non-significantly correlated with B2glycoprotein IgG titer (p= 0.195). There was non-significant correlation between SLEDAI and antiphospholipid antibodies.

Table (5): Correlation between Thrombocytopenia and AP antibodies

		PLTs
Lupus titer	Pearson Correlation	-.663-**
	p	**<0.001**
Anticardiolipin IgM titer	Pearson Correlation	-.338-*
	p	**.011**
Anticardiolipin IgG titer	Pearson Correlation	-.629-**
	p	**<0.001**
B2glycoprotein IgM titre	Pearson Correlation	-.258-
	p	**.055**
B2glycoprotein IgG titer	Pearson Correlation	-.176-
	p	.195

DISCUSSION

Our study population included 100 patients diagnosed SLE who had thrombocytopenia, mean age of them was 33.38 ± 9.36 years with range from 18 to 60 years. Majority of patients in this study were females (90%). Mean of disease duration was 3.47 ± 2.72 years with range 3 to 15 years. As regards family history, we found that only 2 patients had positive family history and 17/100 (17%) of patients had positive gestation history. Also, **Yang *et al.*** [6] reported that the mean age was 48 years (range, 18 to 79), and 45 patients (64.3%) were female which is similar to our results.

In this study, most common clinical manifestations of SLE were cutaneous as oral/nasal ulcers, which were observed in 95 (95%) of patients, but new mucosal ulcers were observed in only 8 patients. This was followed by photosensitivity, which was observed in 83% of patients, then malar rash, which was found in 68% of patients, however new malar rash was observed in only 8/100 of patients. Hair falling was reported by 57% of patients. On the other hand, alopecia was found in 39% of patients and new alopecia in only 3 patients.

DLE was found in only 5/100 patients. Fever was observed in 53% of patients and it was more than 38 in 16% of them. Regarding neurological manifestations, psychosis/seizure was found in 19% of patients and cerebrovascular accident in 17%. Additionally, lupus headache was observed in 6% of patients, and visual disturbance was found in only 1 patient. As regards serositis and pericarditis/pleurisy were found in 15% of patients. Vasculitis was found in only 8 patients. Musculoskeletal manifestations was observed as follows: arthralgia reported by 82% of patients, new arthritis observed in only 4 patients, but myositis not found in any patient.

In this study, mean WBCs was 5.87 ± 4.27. WBC less 3,000 was observed in 14% of patients. Mean Hb was 10.10 ± 1.87, mean MCV was 79.49 ± 11.26 and mean PLTs was 101.90 ± 34.08. PLTs < 100.000 was observed in 32% of patients. Our results about PLTs were lower than **Pontara *et al.*** [7] as mean platelet count was 119 and in high-risk APS patients, it was 210 ± 72. Percentage incidence of the platelet count less than 100,000/ml was 7%-30% in SLE patients in study of **Wallace *et al.*** [8], which is lower than our percentage. In a 1990 systematic review by **Love *et al.*** [9], SLE patients with either LA or aCL were, on average, three times more likely to have moderate to severe thrombocytopenia than aPL-negative patients.

Mean ESR was 53.05 ± 28.90 mm/hour with range of 7.0-150. Low c3/c4 was found in 19% of patients. As regards kidney function tests, mean of s. creatinine was 0.849 ± 0.438 with range of 0.30-2.9 and albumin in urine was found in 39% of patients. Cast, RBCs, and pus (20-25) were found in only 4 patients. As regards liver enzymes, mean ALT was 26.14 ± 21.30 with range of 2.0-133.0 and mean AST was 33.95 ± 33.52 with range of 6.0-304.0.

In current study, 99% of SLE patients had positive ANA, it was speckled in 59%, homogenous in 40% and both speckled and homogenous was observed in only 1 patient. Anti dsDNA and anti-nucleosome were common antibodies detected (56% & 50%) followed by anti sm and anti RNP (41%), then anti histone that were detected in 19% of our patients, anti RO 60 was detected in 40% of our patients.

SLE patients with either LA or aCL were, on average, three times more likely to have moderate to severe thrombocytopenia than aPL-negative patients. Antiphospholipid antibodies was observed in thrombocytopenic patients in current study as, lupus anticoagulant was found in 23% of patients, B2 glycoproteins IgM in 22% of patients, anticardiolipin IgM in 14%, B2 glycoproteins IgG in 13%, and anticardiolipin IgG in 11%. While, various studies reported an incidence of Antiphospholipid antibodies of 14% to 76% in patients with SLE [10, 11]**.** But **Dayama *et al.*** [12] obtained an incidence of 12% for occurrence of any APLA in patients with SLE, which is lower than our incidence. Also other studies showed an incidence that was lower than that seen in the studies by **Harris *et al.*** [13] (31.3%) and **Yang *et al.*** [6] (28.5%). However, it was almost similar to the incidence documented in the study by **Dasanu and Codreanu** [14] (14%). On the other hand, **Yang *et al.*** [6] detected aCL alone in 15 (75%) patients, **Bidot *et al.*** [15] in 66.7% and **El-Bostany *et al.*** [16] in 76.1%, which is higher than our incidence. They also detected aCL and LA in two (10%), and LA alone in three (15%) which is lower than our incidence.

We observed in thrombocytopenic patients that lupus anticoagulant was in 23% of SLE patients, while in study of **Unlu and Erkan** [17] 38% of SLE patients with LA had thrombocytopenia in comparison with 10% without LA. Also, in a recent meta-analysis by **Chock *et al.*** [18] including 11,877 SLE patients, the prevalence of thrombocytopenia in aPL-positive and aPL-negative SLE patients was 31% (n=1,261/4,128) and 15% (n=1,138/7,749) respectively. Antiphospholipid antibody positivity was associated with a two- to four-fold increased risk of thrombocytopenia in SLE patients and the risk was the highest for the LA test [18]**.** The risk of thrombocytopenia was also significantly increased in SLE patients with IgG or IgM aCL and IgG or IgM aβ2GPI [19].

Mean of SLEDAI in this study was 7.78 ± 6.12 with range from 0 to 28. We found that there was positive and non-significant correlation between PLTs count and SLEDAI score. There was non-significant difference between positive and negative all antiphospholipid antibodies patients regarding SLEDAI. In line with our findings, **Parodis *et al.*** [20] found no correlation between serum aPLs levels and activity or chronicity index scores in renal biopsies, SLEDAI-2K.

We found in our study that there was negative and significant correlation between platelet count and both of anticardiolipin IgM titer and B2glycoprotein IgM titre (p= 0.01, 0.05 respectively). There was negative high significant correlation between platelet count and both lupus titer and anticardiolipin IgG titer. Platelet count also was negatively but non-significantly correlated with B2 glycoprotein IgG titer (p= 0.195). This is similar to results obtained by **Chock *et al.*** [18] who found that thrombocytopenia was significantly associated with LA positivity and IgG aCL and this is in line with previously demonstrated significant associations between serum aPL levels and platelet count [19]. Also, previous studies found no association between aPL and histopathological activity or chronicity features in SLE [22, 23] which is in line with our findings. However, previous studies have consistently demonstrated associations of aCL [24, 25] anti-β2-GPI [26] and LA [27] with APS nephropathy, as well as between APS nephropathy and the development of ESRD [24]**.**

CONCLUSION

We concluded that aPLs are strongly associated with increased risk of thrombocytopenia in SLE

patients. We can use aPLs profiles, especially LA and IgM isotypes, as biomarkers for the risk stratification of thrombocytopenia in SLE patients. Finally, platelet count monitoring should be performed for every aPLs positive patients with SLE, which may guide for early and good clinical management.

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