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Research Article

Clinical Features and Pattern of Antiphospholipid Antibodies in Patients of Antiphospholipid Syndrome (APS) with Systemic Lupus Erythematosus (SLE)

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ABSTRACT

Background: Evaluation of antiphospholipid antibodies (aPL) profile in Systemic lupus erythematosus (SLE) patients with obstetric and thrombotic complications and to see the association of different anti phospholipid antibodies in different clinical features of Antiphospholipid syndrome (APS) in SLE patients.

Materials and methods: Cross sectional prospective interdisciplinary study was conducted between July 2019 to January 2021 at the Section of Chemical Pathology and Department of Rheumatology, Fatima Memorial Hospital Lahore.

After taking IRB approval, diagnosed cases of APS with SLE presenting with thrombosis and pregnancy complication were studied. After informed consent, performa was filled by patient including age, gender and clinical symptoms. Blood sample were taken for Anti-beta-2-glycoprotein 1(anti-b2GPI), anticardiolipin (aCL) analyze on Alegria based on ELISA.

Results: Total of 60 diagnosed patients of SLE, presenting with thrombosis or pregnancy complications were included in the study. Mean age of patients was 31.3 ± 5.3 years. There were 56 (93.3%) female and 4 (6.7%) male patients.

Non-thrombotic lupus manifestations in decreasing orders were; cutaneous features in 40 (66.7%), oral ulcers in 33 (58.3%), arthritis and nephritis each in 23 (38.3%), neuropsychiatric manifestation in 7 (11.6%), and serositis in 4 (6.7%) patients.

Among thrombotic manifestations; pregnancy loss was reported in 30 (50%) with 22 (36%) in first trimester and 8 (14%) in 2nd trimester, deep venous thrombosis of extremities was noted in 14 (23.3%), thromboembolic stroke in 11 (18.3%), arterial thrombosis in 5 (8.3%), and pre-eclampsia was reported in 4 (7.1%) patients.

Out of 60 patients with SLE, 18 (30%) were positive with single APLS antibody, 28 (46.7%) were positive with double –antibodies and 14 (23.3%) were positive with triple positive APLS. Person who had five thrombotic events was triple ELISA positive as compared to person who had 1 or two thrombotic events were double ELISA positive.

Conclusion: aPLS antibodies of any type and number leads to cumulative obstetric and thrombotic complication in SLE, which is higher in high risk antibody profiles.

Keywords: ELISA; Antibodies; Systemic lupus erythematosus

INTRODUCTION

Antiphospholipid syndrome (APS) is characterized by presence of specific antiphospholipid antibodies (aPL) with history of thrombosis and/or pregnancy morbidity [1].

APS can arise without an underlying systemic autoimmune disease (primary APS) or with other systemic autoimmune diseases, like SLE [2]. Anti-phospholipid antibodies (aPL) is a comprehensive antibody profile which includes lupus anticoagulant [LA], anticardiolipin antibodies [aCL], and/or anti-β2-glycoprotein-I antibodies [aβ2GPI]). The prevalence of a "clinically significant" aPL profile in lupus patients is approximately 20%-30%. These antibodies may affect the clinical presentation, outcome, treatment and prognosis of SLE patients [3]. A comprehensive antibody

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profile is needed for both diagnosis and classification of patients with APS, most significantly for the risk assessment of both pregnancy morbidity and thrombosis [4].

Among individuals with persistent aPLs, only about one-third will experience a thrombotic event. Approximately half of APL positive patients with thrombosis have coincident non-aPL risk factors at the time of thrombosis [5].

Patients may have different combinations of antibody positivity; the pattern of APL antibodies is useful in clinical practice when determining the appropriate therapy. Isolated LA (LA, aβ2GPI) shows an inconsistent pattern of antiphospholipid antibodies and has low thrombotic risk [6].

Double positivity (LA, aβ2GPI or ACL+) and triple positivity (LA, aβ2GPI+, ACL+) may have worse outcome and the patients with double and triple positivity may have recurrent thrombotic events [7]. Patients with 'triple antibody positivity 'or with high IgG aCL/anti-beta2GPI titers are considered at higher risk. The clinical value of IgM aCL/anti-beta2GPI antibodies needs further studies [4]. Testing of 'non-criteria' antibodies such as antiphosphatidylserine and antiphosphatidylserine/prothrombin complex may be helpful in patients with clinical presentation of APS, with negative classical antibodies, so-called seronegative APS. Counting these non-criteria antibodies may result in a better identification of patients with APS [8]. However, the clinical value of these antibodies remains to be established.

Given the relatively high prevalence of aPL in SLE patients, aPL-positive SLE patients, would have a more severe clinical phenotype and worse prognosis than those without aPL.

Early detection of aPL antibodies may avert patients with many complication associated with SLE as well as from major thrombotic events because the detection of aPL in SLE has been proposed as a predictive and specific tool for the diagnosis of APLS in SLE.72 [9]. There is no printed information of aPL antibodies present in SLE patient in Pakistani population and their clinical significance how they relate to thromboembolic events, neuropsychiatric disorders, thrombocytopenia, and fetal loss.

In this study, we evaluated aPL profile in SLE patients with obstetric and thrombotic complications, to see the association of different anti phospholipid antibodies with different clinical features of APLS in SLE patients.

MATERIALS AND METHODS

A cross sectional prospective interdisciplinary study was conducted after July 2019 to January 2021 at the Section of Chemical Pathology, Department of Pathology and Department of Rheumatology, Fatima Memorial Hospital Lahore.

Study was started after taking approval from Institutional review board (IRB) from Fatima Memorial Hospital. Diagnosed cases of SLE presenting with thrombosis and pregnancy complication were studied. Patients were labelled as anti-phospholipid antibodies with one clinical event (i.e. thrombosis or pregnancy complication) and two positive blood test (Lupus anticoagulant, IgM and IgG Anti-beta-2-glycoprotein 1, IgM and IgG anticardiolipin antibodies) results. The study was fully explained to the participants and an informed consent was taken. Descriptive profile including age, gender and clinical symptoms were recorded in the Performa. Blood sample were taken for Lupus anticoagulant, IgM and IgG Anti-beta-2-glycoprotein 1(anti-b2GPI), IgM and IgG anticardiolipin (aCL) and were analyzed on Alegria based on ELISA. Results were analyzed using the SPSS statistical software package (version 19.0 for Windows). Mean ± SD were used to describe the continuous variables, and number (%) for categorical variables. For all analyses a p-value <0.05 were considered statistically significant.

RESULTS

Total of 60 diagnosed patients of SLE, presenting with thrombosis or pregnancy complications were included in the study. Mean age of patients was 31.3 ± 5.3 years. There were 56 (93.3%) female and 4 (6.7%) male patients. Table 1 shows clinical and serological features of studied patients. Non-thrombotic lupus manifestations in decreasing orders were; cutaneous features in 40 (66.7%), oral ulcers in 33 (58.3%), arthritis and nephritis each in 23 (38.3%), neuropsychiatric manifestation in 7 (11.6%), and serositis in 4 (6.7%) patients.

Table 1: Clinical features of studied population.

Clinical manifestations	**n** (%)
Malar rash	40 (66.7)
Discoid rash	11 (18.3)
photosensitivity	17 (28.3)
alopecia	32 (53.3)
Oral ulcers	35 (58.3)
Nasal ulcers	10 (16.7)
Arthritis	23 (38.3)
nephritis	23 (38.3)
Serositis	4 (6.7)
Seizures	4 (6.7)
Psychosis	3 (5)
Thrombotic manifestations	n (%)
Thromboembolic Stroke	11 (18.3)
Deep venous thrombosis	14 (23.3)
Arterial thrombosis	5 (8.3)
Pregnancy Loss	30 (53.6) 22 (36.7)
1st trimester	8 (14%)
2nd trimester	-
Pre-eclampsia	4 (7.1)
Hypertension	3 (5)
Livedo reticularis	2(3.3)

Among thrombotic manifestations; pregnancy loss was reported in 30 (50%) with 22 (36%) in first trimester and 8 (14%) in 2nd trimester, deep venous thrombosis of extremities was noted in 14 (23.3%), thromboembolic stroke in 11 (18.3%), arterial thrombosis in 5 (8.3%), and pre-eclampsia was reported in 4 (7.1%) patients.

At least 7 (11.7%) females had history of five or more abortions in studied population, 4 (6.7%) presented with the history of 4 abortion, 8 (13.3%) presents with the history of 2 abortions and 11 females (18.3%) had history of 1 abortion.

ANA by ELISA method was positive in 52 (86.7%), while anti ds DNA was positive in 43 (71.5%) patients. Mean hemoglobin was 9.5 ± 4.1 and mean platelet count was 208.3 ± 151.3. Out of 60 patients, 26 (43.3 %) were anemic (Hb<11 gm/dl) and 6 (10%) had thrombocytopenia (platelet count <100 × 1069/L).

Out of 60 patients with SLE, 18 (30%) were positive with single APLS antibody, 28 (46.7%) were positive with double –antibodies and 14 (23.3%) were positive with triple positive APLS. Further patients with double or triple antibody positivity had more clinical features compared to those had single antibody positivity. Person who had five thrombotic events was triple ELISA positive as compared to person who had 1 or two thrombotic events were double ELISA positive.

In descending order, anti-b2gp-IgG was most prevalent anti body in the study population, present in 33 (55%) patients, followed by LAC and Anticardiolipin (aCL) IgG each in 32 (53.3%) patients, while anti-b2gp-IgM was present in 27 (45%) and aCL IgM was the least common 26(43.3%) antibody present. Nine (15%) were single positive with LAC, 8(13%) with b2GP1-IgG and 6 (10%) were positive with aCL-IgG alone (Table 2).

Among thrombotic events, arterial thrombosis was exclusively in double or triple positive. Similarly, Stroke and pregnancy losses were more common in double positive than single positive antibody profile. DVT on other hand was more common in single antibody profile than double or triple positive (Table 3).

Table 2: Clinical and laboratory manifestations of studied population.

Clinical manifestations n (%)	(LAC) N (%)	(aCL) IgM N (%)	(aCL) IgG N (%)	Anti-b2GP1 IgM n (%)	Anti-b2GP1 IgG n (%)
Total	32 (53.3)	26 (43.3)	32 (53.3)	27 (45)	33 (55)
n (%)					
Stroke	6 (10)	4 (6.7)	6 (10)	4 (6.7)	5 (8.3)
11 (18.3%)					
Venous thrombosis 14 (23.3%)	9 (15)	5 (8.3	5 (8.3)	7 (11.7)	10 (16.7)
Arterial thrombosis 5(8.3%)	3 (5)	3 (5)	4 (6.7)	2 (3.3)	4 (6.7)
Pregnancy Loss					
30 (50%)	14 (23.3)	14 (23.3)	17 (28.3)	14 (23.3)	14 (23.3)
1st trimester					
22 (36.66%)	7 (11.7)	10 (16.7)	14 (23.3)	12 (20)	12 (20)
2nd trimester					
8 (13.33)	7 (11.7)	4 (6.7)	3 (5)	2 (3.3)	2 (3.3)

Table 3: Single, double and triple antibody positivity in different thrombotic events of studied population.

	Arterial thrombosis	Stroke	DVT	Pregnancy loss	Total
Single antibody positive	–	4 (36.4)	7 (50)	10 (33.3)	21
Double antibody positive	4 (80)	5 (45.5)	4 (28.6)	13 (43.3)	26
Triple antibody positive	1 (20)	2 (18.2)	3 (21.4)	7 (23.3)	13

DISCUSSION

Presence of Anti phospholipid antibody in any connective tissue disease including lupus increase the morbidity by increasing thromboembolic events [10]. SLE specifically is extended in its manifestations over a wide range in the presence of APL antibodies. We present here our experience with clinical manifestations of lupus associated with aPL antibodies. In our study, aPL antibodies were associated with a wide range of obstetric and thrombotic complications, which was more pronounced in double and triple positive antibody profiles.

Pregnancy related complications of our study are in concordance with multiple studies previously reported. Ko et al. reported the presence of any type of antiphospholipid antibodies significantly increase the risk of pregnancy loss and premature birth [11]. Similarly, Al Farj et al. reported aPL antibodies to be the strongest predictor of pregnancy loss in SLE followed by disease flare and lupus nephritis [12]. Although, increased number of antibodies presence, high risk profile, is cumulative risk factors for thromboembolism and adverse pregnancy outcomes, as reported by Saleh et al. the effect was not related in our study, with no higher pregnancy loss in double or triple positive profile [13]. This finding highlights, even single positive antibody in SLE patients is sufficiently culprit enough to cause damage.

Preeclampsia and Pregnancy induced hypertension are the other gestational sequelae of aPL in SLE. Although not included in primary diagnostic criteria of aPLS, many authors propose it as a strong pathophysiologic complication of aPLS, and are included as a secondary feature of aPLS in presence of other sequel [14]. At least 7.1% of our study population had associated preeclampsia with aPL profiles. Latino et al reported triple positive aPL profile to be a strong predictor of severe preeclampsia in SLE and primary APL [15].

Strokes in SLE reach a prevalence of up to 20% in the presence of aPLS antibodies [16]. APLS however, is not only confined to stroke in SLE, and other neurologic features are also attributed to positive aPL antibodies in SLE [17,18]. Ligen et al. reported a significant association of aPL antibodies with non CVA neurological manifestations, including, epilepsy, neuropathies, and seizures [19]. Whether a specific antibody type has some association with specific neurological manifestation is debatable. However, high risk profile, such as double or triple positive serology has higher risk of thromboembolic neurological insult due to cumulative insult. Brey et al proposed a predictive role of both anti-cardiolipin antibodies and beta 2-glycoprotein antibodies for future stroke risk [20]. The replication of such findings can be further evaluated in prospective studies.

Deep venous thrombosis and arterial thrombosis are by far the most common thrombotic manifestation of aPL antibodies in SLE. Our study reported at least 19 (31.6%) episodes reported, which were more common in double and triple positive serology, specifically for arterial thrombosis. Multiple authors have directly contributed presence of aPL antibodies to different thrombotic events in SLE independent of disease activity status. Shevchuk et al reported any type of antibody as an independent risk factor for both arterial and venous type of thrombosis in SLE [21]. The risk was reported independent of multiple classical risk factors of hypercoagulation, including hyperhomocystinemia, and dyslipidemia.

High risk aPLS profile is a novel concept dedicated to LAC positivity, high titer ACL or b2gp positive, double or triple positive [22,23]. Such high risk antibody profile not causes increased thromboembolic events but also an increased risk of recurrence and potential of developing in Catastrophic APLS, a fatal complication of both primary and SLE related APLS [24]. Current study showed Arterial thrombosis exclusively in double and triple positive cases only, and the cumulative prevalence of majority of the events were more common in high-risk profiles, a finding well concordant with previous literature [25,26].

The current study should be reviewed in light of certain limitation; including, retrospective data analysis, where we only included patients with established complication, presentation of APLS, so the true prevalence (including asymptomatic cases) could not be evaluated, seronegative APLS is another important group of APLS associated with SLE, that can manifest with similar presentation in the absence of available aPLS antibodies. Lastly, the outcomes of different treatment modalities, and effect of disease activity was not studied, that could have confounded the results.

CONCLUSION

The study concluded that antiphospholipid antibodies, especially IgG anti-β2GPI antibodies, contribute to pregnancy complications and thrombotic events. Triple antibody positivity is directly associated with recurrent thrombotic events. Early recognition of pattern of antibodies is essential to prevent the possibility of recurrent thrombotic events by standard anticoagulation therapy.

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