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ORIGINAL ARTICLE

A retrospective review of antiphospholipid syndrome from a South Asian country

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ABSTRACT

Objectives: This study aims to investigate clinical presentations, antiphospholipid antibody patterns and their levels, therapeutic regimens, and outcomes in patients with antiphospholipid syndrome (APS) admitted to a tertiary care hospital of a South Asian country.

Patients and methods: Between January 2009 and December 2019, a total of 216 patients with APS (8 males, 208 females; median age: 35.7±6.9 years; range, 20 to 76 years) who either fulfilled the modified Sydney criteria or those who satisfied only clinical criteria along with positive antiphospholipid antibody on at least one occasion (probable APS) were retrospectively analyzed.

Results: The majority of the patients (n=183, 84.7%) had obstetric complications, followed by venous thrombosis in 23 (10.8%) patients. Recurrent early abortions in 126 (58.6%) and deep venous thrombosis in 16 (7.4%) patients were the most prevalent obstetrical and venous events, respectively, whereas limb gangrene in seven (3.3%) and ischemic stroke in seven (3.3%) were the most common arterial events. A total of 190 (88%) patients had primary APS, while 26 (12%) had secondary APS. Systemic lupus erythematosus was the frequent association with secondary APS found in 19 (73%) patients. Immunoglobulin M (IgM) anticardiolipin antibody was present in 173 (65.0%) patients, being the most commonly reported antibody. Probable catastrophic APS was found in four (1.9%) patients. Majority of the patients (n=190, 87.9%) were treated with a combination of acetylsalicylic acid and low-molecular-weight heparin. Single mortality was observed in our study population due to complications related to catastrophic APS.

Conclusion: Antiphospholipid syndrome has a wide range of thrombotic and obstetrical manifestations with important variations in different regions of the world. There is a significant morbidity and mortality related to APS, despite treatment with anticoagulation and; therefore, describing prognostic markers and optimal therapeutic interventions is pivotal to prevent complications.

Keywords: Antiphospholipid antibodies, antiphospholipid syndrome, Pakistan, pregnancy outcome.

Antiphospholipid syndrome (APS) is a systemic autoimmune illness characterized by venous or arterial thrombosis, recurrent pregnancy losses, or preterm delivery due to preeclampsia, eclampsia or placental insufficiency in the presence of antiphospholipid antibodies (aPLs) which include anticardiolipin (aCL) immunoglobulin (Ig) G and IgM, lupus anticoagulant (LAC) or beta (β)-2 glycoprotein-I.[1,2] Annual incidence of APS is 5/100,000 population, while the prevalence is estimated to be around 40 to 50 cases per 100,000 population.[1] Antiphospholipid syndrome is divided into primary APS (in the absence of underlying connective tissue disorder) and secondary APS (associated with connective tissue disorders such as systemic lupus erythematosus [SLE], rheumatoid arthritis and systemic sclerosis.[3] In addition, APS can manifest in the form of

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neurological presentations such as stroke, seizures, dementia, chorea, psychosis, and demyelinating diseases.[4]

The formation of thrombi both in arteries and veins is the major cause of mortality and morbidity associated with APS.[5] Antiphospholipid syndrome is an autoimmune procoagulant state mediated by aPLs, but a trigger is needed to precipitate thrombosis. This trigger can be in the form of infection, endothelial injury and surgery, leading to immobility or oral contraceptives.[6] Euro-Phospholipid Project reported deep venous thrombosis (DVT) as the main thrombotic event (38.9%) in a cohort of 1,000 patients, followed by stroke in 19.8%.[7]

Antiphospholipid antibodies (aPLs) play a pivotal role in the pathogenesis of APS and is the main culprit behind early and late pregnancy complications. Women having positive LAC or those having triple positive autoantibodies, i.e., the presence of aCL IgG and IgM, LAC, and β-2 glycoprotein-I are associated with poor prognosis.[8] Women having positive aPL have 80% risk of recurrent miscarriages and preterm births.[9] Moreover, a retrospective cohort study reported that 26.7% women with recurrent miscarriages in the first trimester had aPL positivity.[10] The aPL in pregnant women is associated with severe preeclampsia and stillbirth.[11]

Catastrophic APS (CAPS), which is usually precipitated by infection, is defined as wide spread thrombosis in at least three different organs, leading to multi-organ dysfunction in the presence of aPL and histopathological evidence of multiple thrombi. It is a life-threatening manifestation of the disease which has been linked to poor outcomes.[12]

Management with anticoagulation during pregnancy improves maternal and fetal outcomes.[13] The mainstay of treatment is long-term anticoagulation with vitamin K antagonist. In addition, acetylsalicylic acid and low-molecular-weight heparin is the standard of care in pregnancy to improve obstetrics outcomes.[14,15]

Being an uncommon entity, there is a limited number of data regarding clinical manifestations of APS, aPL patterns, and its outcomes, not only in South Asia, but throughout the world. Moreover, various clinical features between different ethnicities have been demonstrated in existing studies of APS in Asian population.[16-18] In this study, we aimed to report a 10-year retrospective analysis on the clinical presentations, patterns of laboratory parameters, treatment options, and outcomes of APS patients in a cohort of Pakistani population.

PATIENTS AND METHODS

This retrospective, cross-sectional study was conducted at Department of Medicine, The Aga Khan University Hospital, Karachi-Pakistan, which is a Joint Commission International Accreditation (JCIA) accredited medical institute in South Asia, between January 2009 and December 2019. A total of 216 patients with APS (8 males, 208 females; median age: 35.7±6.9 years; range, 20 to 76 years) who either fulfilled the modified Sydney criteria[19] or those who satisfied only clinical criteria along with positive antiphospholipid antibody on at least one occasion (probable APS) were retrospectively analyzed. Patients whose clinical manifestations were explained by other causes including protein C or S deficiency, homocysteinemia or Factor V Leiden mutation were excluded. The study protocol was approved by the Ethical Review Committee of the Aga Khan University Hospital, Karachi (ERC 2019-1366-3563). The study was conducted in accordance with the principles of the Declaration of Helsinki.

The patients were recognized using the 10th version of the International Statistical Classification of Disease (ICD-10) coding and medical records were manually reviewed to confirm the presence of APS. The aPL and their levels were confirmed using online database for laboratory tests.

Serum aCL was tested using the enzyme-linked immunosorbent assay (ELISA). The aCL IgG and IgM were labeled as positive, when titers were above 14.4 GPL-U/mL (G PhosphoLipid Unit) and 7.2 MPL-U/mL (M PhosphoLipid Unit), respectively. The LAC was tested in patients' plasma using diluted Russell Viper Venom test (DRVVT) including screening and confirmation steps as per standard guidelines.[20] The normalized ratio was determined and laboratory cut off

value of >1.2 was considered positive dRVVT. The β-2 glycoprotein was tested using the ELISA on patients' sera and laboratory cut-off value (97% percentile of healthy subjects) for males was above 2,286 ng/mL and for females was above 2,454 ng/mL. Activated thromboplastin time (aPTT) levels above 34.5 sec were labelled as prolonged.

Data including patients' demographics, clinical presentations, types of aPL and their levels, aPTT levels, presence of underlying connective tissue disorder (SLE, mixed connective tissue disease, and others), obstetrical history, radiological investigations, treatment, length of hospital stay and mortality were retrieved from medical records and entered on a predesigned proforma.

Statistical analysis

Statistical analysis was performed using the SPSS version 22.0 software (IBM Corp., Armonk, NY, USA). Continuous variables were presented in mean ± standard deviation (SD) or median (min-max), while categorical variables were presented in number and frequency. Association between clinical presentation and number of positive antibodies was analyzed using the chi-square test, while the Student t-test was used to analyze the association between the length of stay and type of complication. A *p* value of <0.05 was considered statistically significant.

RESULTS

The most common clinical presentation was related to obstetric complications of APS in 183 (84.7%) patients, followed by venous thrombosis in 23 (10.8%) patients. Recurrent early abortions in 126 (58.6%) and DVT in 16 (7.4%) were the prevalent obstetrical and venous events respectively, whereas limb gangrene in seven (3.3%) and ischemic stroke in seven (3.3%) were the most common arterial events (Table 1). The most common diagnostic test found to be positive was aCL IgM antibody, detected in 173 (65.0%) patients (Supplementary Table 1). If these values are mean, please add their SD values. If not, give these values as median (min-max). In addition, aPTT was prolonged only in eight (3.7%) patients with a median value of 69.7 sec. Of note, 37 (17.1%) patients had more than two clinical manifestations on presentation; i.e., three or more unexplained abortions before the 10th week of gestation, as well as late fetal loss in 13 (6%) patients. Combined venous and arterial thrombosis was recorded in two (0.9%) patients (Table 2).

Of a total of 216 patients, 190 (88%) had primary APS, while 26 (12%) had secondary APS. Also, SLE was the most frequent association with secondary APS in 19 (73%) patients (Supplementary Table 2). Abortion after the 10th week of gestation was the most common clinical presentation among patients

Table 1. Frequency of presentations in patients with APS (n=216)

Presentation	n	%
Obstetrical		
Recurrent abortion (in less than 10 weeks)	126	58.6
Abortion after 10 weeks	54	25.1
Pre-eclampsia/eclampsia/placental abruption	35	16.3
Premature rupture of membrane	1	0.5
Venous		
Deep venous thrombosis	16	7.4
Pulmonary embolism	3	1.4
Splenic vein thrombosis	1	0.5
Cerebral venous sinus thrombosis	1	0.5
Uterine vein thrombosis	1	0.5
Portal vein thrombosis	1	0.5
Arterial		
Arterial thrombus/limb gangrene	7	3.3
Cerebrovascular accident	7	3.3
Mesenteric ischemia	1	0.5

Supplementary Table 1. Frequency of positive diagnostic tests in patients with APS

Diagnostic tests	n	%
Only anticardiolipin antibodies	181	83.8
Anticardiolipin antibody IgM[1]	173	65.0
Anticardiolipin antibody IgG[2]	50	18.8
Lupus anticoagulant and anticardiolipin antibodies both	33	15.3
Lupus anticoagulant	34	12.8
Raised aPTT[3]	8	3.7
Beta-2-glycoprotein-I antibody	2	0.8
Anticardiolipin antibodies and beta-2-glycoprotein-I antibody both	1	0.5
Lupus anticoagulant, anticardiolipin antibodies and beta-2-glycoprotein-I antibody	1	0.5

APS: Antiphospholipid syndrome; [1] Immunoglobulin M; [2] Immunoglobulin G; [3] Activated thromboplastin time; Ig: Immunoglobulin; aPTT: Activated thromboplastin time.

Table 2. Patients presenting with more than one manifestations of APS

Presentation	n	%
Recurrent abortion in less than 10 weeks + abortion after 10 weeks	13	6
Abortion after 10 weeks + preeclampsia	5	2.3
Recurrent abortion in less than 10 weeks + preeclampsia	5	2.3
Deep venous thrombosis + recurrent abortion in less than 10 weeks	2	0.9
Deep venous thrombosis + preeclampsia	1	0.5
Abortion after 10 weeks + ischemic stroke	1	0.5
Abortion after 10 weeks + premature rupture of membranes	1	0.5
Recurrent abortion + abortion after 10 weeks + preeclampsia	1	0.5
Abortion after 10 weeks + preeclampsia + ischemic stroke	1	0.5
Deep venous thrombosis + pulmonary embolism	2	0.9
Deep venous thrombosis + arterial thrombus	2	0.9
Mesenteric ischemia + portal vein thrombosis	1	0.5
Ischemic stroke + cerebral venous sinus thrombosis	1	0.5
Arterial thrombus + pulmonary embolism	1	0.5

APS: Antiphospholipid syndrome

Supplementary Table 2. Frequency of underlying diseases in patients with secondary APS (n=26)

Diseases	n	%
Systemic lupus erythematosus	19	73.1
Rheumatoid arthritis	2	7.7
Mixed connective tissue disease	2	7.7
ANCA associated vasculitis	1	3.8

APS: antiphospholipid syndrome; ANCA: Antineutrophil cytoplasmic antibody.

Table 3. Clinical characteristic of probable CAPS patients

Probable CAPS	Patient characteristics	Clinical manifestations	Positive antiphospholipid antibodies with titers	Treatment	Complications	Outcomes
CAPS1	42-year-old female	Acute lower limb ischemia + deep venous thrombosis	LAC[1] 68 seconds LA ratio 2.0	Aspirin + steroids + therapeutic anticoagulation	Renal failure + hospital acquire pneumonia	Died
CAPS2	32-year-old female	Left lower acute limb ischemia + deep venous thrombosis (popliteal and femoral vein)	LAC[1] 126 seconds LA ratio 2.3 aCL IgG[2] 15.2 GPL-U/mL	Therapeutic anticoagulation	Left above knee amputation + candidemia	Discharged
CAPS3	25-year-old female	Mesenteric ischemia + portal vein thrombosis + superior mesenteric vein thrombosis	LAC[1] 78 seconds LA ratio 1.8	Steroids + therapeutic anticoagulation	Adrenal insufficiency + candidemia	Discharged
CAPS4	59-year-old female	Acute lower limb ischemia (anterior tibial artery occlusion) + pulmonary embolism	LAC[1] 53 seconds LA ratio 2.5	Aspirin + hydroxychloroquine + therapeutic anticoagulation	Acute kidney injury + candidemia + acinetobacter bacteremia	Discharged

CAPS: Catastrophic antiphospholipid syndrome; LAC: Lupus anticoagulant; LA: Lupus anticoagulant; [1] Lupus anticoagulant; [2] Anticardiolipin immunoglobulin G.

Supplementary Table 3. Frequency of presentations in each underlying disease in patients with secondary APS (n=25)

Clinical Presentation	Systemic lupus erythematosus (n=19)	Rheumatoid arthritis (n=2)	Autoimmune hemolytic anemia (n=1)	ANCA associated vasculitis (n=1)	Mixed connective tissue disease (n=2)
Deep venous thrombosis	4	1	0	0	0
Arterial thrombus/ limb gangrene	1	0	0	0	0
Recurrent abortion	5	1	0	0	2
Abortion after 10 weeks	7	0	0	0	0
Pre-eclampsia/eclampsia/ placental abruption	3	0	1	0	0
Cerebrovascular accident	2	0	0	1	0
Immune thrombocytopenic purpura	1	0	0	0	0

APS: Antiphospholipid syndrome; ANCA: Antineutrophil cytoplasmic antibody.

with secondary APS, due to underlying SLE. Regarding aPL in secondary APS, both LAC (n=10, 52.63%) and aCL IgM antibody (n=10, 52.63%) were the most common antibodies found in patients with SLE. Clinical presentations in different underlying diseases are shown in Supplementary Table 3. Probable CAPS was found in four (1.9%) patients (Table 3). Of these patients with CAPS, one succumbed to death due to hospital-acquired pneumonia and acute renal failure.

The majority of the patients (n=190, 87.9%) were treated with a combination of acetylsalicylic acid and low-molecular-weight heparin, while warfarin and novel oral anticoagulants (NOACs) were used in 20 (9.3%) and five (2.3%) patients, respectively. Acetylsalicylic acid alone was

prescribed to five (2.3%) patients. Rivaroxaban was the only NOAC prescribed to our patients. There was no significant difference in clinical manifestations between the patients with single and double positive aPL. The mean length of stay in patients with thrombosis was 6.8±8.1 days compared to those who had obstetric APS (3.5±1.3 days; p<0.001).

DISCUSSION

The present study is one of the largest data of APS from South Asia. It demonstrated important clinical characteristics, patterns of APS investigations, and treatment regimens offered to APS patients at a tertiary care hospital of a low- and middle-income country (LMIC) of South Asia. Antiphospholipid syndrome is accountable for life-threatening manifestations characterized by thrombotic and obstetric events resulting in significant morbidity and mortality. There is paucity of data in the medical literature, particularly in South Asian population regarding clinical features and outcomes of APS, as previous studies have focused primarily on treatment regimens of different manifestations of APS.[21]

In the current study, we observed three or more consecutive unexplained abortions in less than 10 weeks of gestation as the most common obstetric complication, being present in around 60% of the patients. However, Singh et al.,[18] in a study from India, demonstrated recurrent early fetal loss only in one-fifth of their patients. Similarly, studies from Thailand and Japan demonstrated that early fetal loss comprised of around 13% of their study population, which is much less than our finding.[16,17] Moreover, late fetal demise was the commonest obstetric manifestation in the aforementioned studies.

In our cohort, DVT was the major thrombotic event. Similar findings were reported by Singh et al.[18] However, in Japanese and Thai populations, cerebral infarction was observed as the predominant thrombotic complication.[16,17] Pons-Estel et al.[22] reported DVT as the major thrombotic complication in a cohort of 1,000 patients with secondary APS due to SLE. Late fetal loss was the most common outcome reported in our cohort with secondary APS.

Catastrophic APS, a devastating complication of APS usually occurs in less than 1% of patients with APS.[23] Combination regimen in the form of steroids, anticoagulation, plasma exchange with or without intravenous Ig is the standard of care.[24] Probable CAPS (multi-organ thrombosis) was reported in 10% of patients in a study by Jatuworapruk et al.[17] Review of the literature suggests that the incidence of CAPS is higher in individuals who have triple positive aPL.[23] In our study, we had four patients of probable CAPS in our cohort. All four were positive for LAC, while one patient was positive for both LAC and aCL IgG. Candidemia was a common complication in our CAPS patient, being present in three patients. Three patients with probable CAPS were treated successfully with steroids and anticoagulation, whereas one patient died due to multi-organ failure, acute kidney injury, and hospital-acquired pneumonia.

In our cohort, IgM aCL antibodies were the most common aPL detected, followed by IgG aCL and LAC. The β-2 glycoprotein-I antibody was detected in only two of our patients, as this test was introduced at our hospital only a year ago. Similarly, in the Euro-Phospholipid Project of 1,000 patients with primary and secondary APS, aCL antibodies (88%) were the most commonly positive aPL with both IgG and IgM in 32% of patients, while IgG alone was present in 43.6% and IgM alone was present in 12.2% of the patients.[25] In addition, LAC was present in 53.6% of the patients. In a systematic review, LAC was shown to have an odds ratio for thrombosis five to 16 times higher than controls.[26] The PREGNancy in women with ANTiphospholipid Syndrome (PREGNANTS) study which was done in Italy showed aCL antibodies as the principal antibodies present in around two-thirds of 750 obstetric APS patients.[8] Additionally, a study done in the United States in 40 patients of APS revealed that three-fourth of the patients had positive LAC, IgM, or IgG aCL antibodies.[27] Furthermore, in our cohort, prevalent antibodies in secondary APS due to SLE were LAC and IgM aCL antibodies, being present in around half of patients. Only one patient was found to have triple positive APS who had SLE and presented with DVT.

In our study, aPTT was prolonged in only eight patients. All of these patients were found to have positive tests for LAC. This is

consistent with the fact that, in patients with APS positive LAC, aPTT can be prolonged due to the interference with assembly of the prothrombinase complex on phospholipids.[28,29] Of note, aPTT is not always elevated in patients with LAC (being prolonged in only half of the patients) and is less commonly prolonged in patients with aCL antibodies.[30]

The literature suggests that secondary APS due to SLE significantly affects survival and outcomes of these patients. An important cause of death in patients with SLE is thrombosis and presence of aPL adversely affects the prognosis with a significantly higher fatality rate.[22] Pons-Estel et al.[22] demonstrated the eight-year survival of primary APS patients as 83%, while it was 75% in patients who had SLE-associated secondary APS. The Euro-Phospholipid Project illustrated a mortality rate of 9.3% over a follow-up period of 10 years and did not show any significant difference of mortality among secondary APS with SLE and primary APS patients (6.8% *vs*. 7.1%, respectively).[25] In our cohort, only one patient died from CAPS. The reduced mortality in our cohort can be explained due to the fact that many of our patients were lost-to-follow-up and no record was available whether these patients developed further thrombotic events. Moreover, the predominant sample of our cohort comprised of obstetric APS patients who have usually a relatively benign course compared to thrombotic APS.

A substantial number of our patients (90%) were managed with combination of acetylsalicylic acid and low-molecular-weight heparin, while about 9% received warfarin alone. The NOACs were prescribed in only five patients. The role of NOACs in APS is still debatable and ongoing trials may elucidate the efficacy of these agents compared to vitamin K antagonists in thrombotic APS.[31] Results from the Rivaroxaban in Antiphospholipid Syndrome (RAPS) trial indicate that rivaroxaban can be an effective alternative to warfarin in thrombotic APS.[32] Hydroxychloroquine (HCQ) was also shown as an additional treatment option for APS by De Carolis et al.[33] It is unique in being able to reduce binding of aPL to syncytiotrophoblasts along with antithrombotic and anti-inflammatory effects. Hence, HCQ is an effective drug in refractory or triple positive APS.[33]

There are some limitations to this study including retrospective design and relatively sample size. Majority of our patients had probable APS, as antibody testing was done once and not repeated after 12 weeks per predefined criteria. This was probably due to financial burden of cost of these laboratory investigations in a LMIC. It is challenging to establish the diagnosis of APS in an obstetric or a thrombotic patient, as it requires extensive laboratory work-up. In a resource-restricted set-up, ordering all three antibodies and repeating it on 12 weeks plays a crucial role in the patient dropout, before diagnosis is accurately established. The β-2 glycoprotein-I antibody was not done as a part of work-up, as this test was not available at our center during the major portion of study period. The vast majority of our study population exhibited obstetric APS as the major clinical manifestation, while about 15% our patients had a documented thrombosis upon presentation. Moreover, many of our patients lost-to-follow-up and long-term outcomes could not be documented. However, our study is one of the few studies from this part of world addressing manifestations of this rare, but potentially fatal disease and is the only study to investigate clinical presentation, aPL patterns, and treatment regimens offered to APS patients in this part of the world.

In conclusion, there is a remarkable variability of manifestations of APS in different regions of the world. These differences have important implications with respect to diagnosis and management of patients with APS. Furthermore, there is a significant morbidity and mortality related to APS, despite treatment with anticoagulation; therefore, describing prognostic markers and optimal therapeutic interventions is pivotal to prevent complications.

Declaration of conflicting interests

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