

Primary Antiphospholipid Syndrome

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Abstract. An antiphospholipid antibody (APLA) syndrome has been proposed for those patients with systemic lupus erythematosus (SLE) or with other connective tissue diseases who have APLA and manifestations that seem related to their effect (venous thrombosis, arterial occlusions, thrombocytopenia, hemolytic anemia, recurrent fetal loss, leg ulcers, and livedo reticularis). Occurrence of a primary antiphospholipid syndrome has also been mentioned but not defined. We present 9 young patients who had at least 2 of the clinical manifestations that have been related to high titers of APLA, but had neither SLE nor other recognizable connective tissue disease. We propose criteria for diagnosis of such a primary antiphospholipid syndrome and discuss the possible mechanisms whereby a single autoantibody can cause systemic disease. (*J Rheumatol* 1989;16:482-488)

Key Indexing Terms:

ANTIPHOSPHOLIPID SYNDROME, PRIMARY
ANTIPHOSPHOLIPID ANTIBODIES
LUPUS ANTICOAGULANT

THROMBOSIS
ANTICARDIOLIPIN ANTIBODIES

In the last few years the notion has evolved that some of the manifestations of systemic lupus erythematosus (SLE) may be related to the presence of antibodies to phospholipids¹. These antibodies may react with phospholipids that participate in coagulation processes, as well as with those on cell walls and, thereby, cause arterial occlusion, venous thrombosis², thrombocytopenia³ and/or hemolytic anemia⁴.

Arterial or venous occlusions can lead to diverse manifestations including recurrent fetal loss, possibly through thrombosis of placental vessels⁵. Hughes and his coworkers⁶ have postulated that an antiphospholipid syndrome may exist that yields these manifestations within the clinical spectrum of SLE but that could also occur, seemingly due to the presence of the antibody, in diseases other than SLE or perhaps, as a primary condition. Although the occurrence of this primary antiphospholipid syndrome has been considered by these authors, it has not yet been clearly defined.

In an ongoing prospective study of 500 patients with SLE we found a strong significant positive association of venous thrombosis, particularly when recurrent, thrombocytopenia, hemolytic anemia, leg ulcers and recurrent fetal loss with presence of antiphospholipid antibodies (APLA) (Alarcón-Segovia, *et al* unpublished observations). A significant, but somewhat less strong, positive association was found between APLA and arterial occlusions, livedo reticularis, and transverse myelitis. We also found that the odds ratio of having APLA at high titers increased markedly with 2 or more of these manifestations in the same patient.

We therefore defined as an antiphospholipid syndrome the occurrence, in the presence of APLA, of at least 2 of the aforementioned manifestations that we found to associate significantly with APLA.

We describe 9 patients who having fulfilled our definition of the antiphospholipid syndrome did not have other manifestations of either SLE or other connective tissue disease. Such patients were considered as having primary antiphospholipid syndrome.

MATERIALS AND METHODS

APLA. These were determined in serum by a solid phase immunoenzymatic assay (ELISA) with cardiolipin as antigen (Sigma Chemicals, St. Louis, MO) as described by Loizou, *et al*⁷ and modified by Gharavi, *et al*⁸ with minor modifications of our own⁹. Known positive and negative sera were kindly provided by Drs. E.N. Harris and G.R.V. Hughes, London, for standardization. Normal values were established by studying 100 clinically healthy individuals. Only 4 of these 100 control sera gave an absorbance higher than 2 standard deviations (SD) above their mean with either IgG or IgM isotypes. None had an absorbance of more than 5 SD above their mean. The mean \pm 2 SD corresponds to 1.9 arbitrary units for IgG, and 2.4 for IgM immunoglobulin isotypes of the APLA. These units were determined as the ratio between the optic density of each sample and the optic density of a pool of 30 sera from normal individuals used as a reference standard.

Other laboratory studies. Antinuclear antibodies (ANA) were determined by indirect immunofluorescence on mouse kidney section and HEp-2 cells. Anti-DNA antibodies were determined by Farr assay⁹, the upper limit of uptake in our laboratory being 36%. Complement components (C3 and C4) were determined by nephelometry. Sera were tested with the Venereal Disease Research Laboratory (VDRL) standard slide flocculation test with FTA absorption test. An abnormal activated partial thromboplastin time (PTT) was considered if it was prolonged more than 5 s above the control and failed to correct with a mixture of normal plasma. The kaolin clotting time as described by Exner, *et al*¹⁰ was used for establishing the presence of lupus anticoagulant.

Definition of terms. The criteria for antiphospholipid antibody syndrome have been defined as follows: venous thrombosis, any episode of deep venous thrombosis occurring without other apparent cause, with a convincing clinical picture and diagnosed as such by a physician, preferably with confirmation

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by means of venogram and/or isotopic studies. Pulmonary embolism is included as venous thrombosis but counts as a distinct episode only if not associated with overt thrombophlebitis at the time. Because we have found that the strength of the association of APLA is much higher with repeated venous thromboses than with single episodes in our group of patients with SLE (Alarcón-Segovia, *et al* unpublished observations) we give particular importance to them as well as to thromboocclusive pulmonary hypertension which we have also found to associate with APLA in patients with SLE. Thrombocytopenia was diagnosed with platelet counts below $100 \times 10^9/l$ on 2 separate occasions. Hemolytic anemia was considered only when there had been a fall in blood hemoglobin of at least 3 g/dl coincident both with a rise in unconjugated bilirubin of at least 0.6 mg/dl and a reticulocyte count above 5% when corrected for hemoglobin levels. Leg ulcers, when occurring coincident with a disease exacerbation and not the result of either trauma or venous stasis. Recurrent fetal loss was considered in women who had had 3 or more spontaneous abortions or intrauterine deaths or 2 if these represented 50% or more of their pregnancies. Abortions were considered only if pregnancy had lasted 2 or more months or had been confirmed by tests. Arterial occlusions were considered only if of named arteries or causing a well defined infarction. Arteriographic, ultrasonographic, roentgenographic or radionuclide confirmation was necessary. Livedo reticularis was considered only if it had appeared coincident with the disease, had not been noticed since childhood, and did not tend to appear only upon exposure to cold. Cutis marmorata is infrequent in the Mexican mestizo population, but should be excluded. Although transverse myelitis is infrequent in SLE we found it to associate with APLA in our study. We have subsequently extended our observations by culling patients from other hospitals and have confirmed the association in most patients (Lavallo C, *et al* unpublished observations). This criterion was determined solely on clinical grounds including examination by a neurologist.

Selected Case Studies

Patient 1. This 26-year-old woman miscarried her last 3 pregnancies. After her 3rd (of 5) pregnancy that resulted in a stillbirth, she developed left hemiplegia. A carotid angiogram showed thrombosis of the right middle cerebral artery. She was given oral anticoagulants which she took only briefly. Soon afterwards she had a left sural thrombophlebitis (Figure 1). In 1986 she developed anemia, with positive Coombs' test, metrorrhagia, and purpura. She was given 70 mg of prednisone with improvement. She then consulted us. She had also complained of migraines. She was found to have livedo reticularis and left hemiparesis. One sister had died elsewhere with a diagnosis of SLE. There was no other data suggestive of SLE.

Laboratory studies showed a prolonged activated PTT of 47.1 s (control < 42 s) and thrombocytopenia ($96 \times 10^9/l$). She had negative LE cells, VDRL and anti-DNA antibodies (10.5% uptake) but positive APLA: IgG:3.7 units, IgM:0.7 units. She has continued having migraine, has stopped prednisone and refuses to continue anticoagulant therapy.

Patient 2. This 32-year-old woman has had hyperthyroidism treated with ^{131}I . Six years before we saw her she had thrombophlebitis of the left lower extremity and may have had pulmonary embolism. In 1985 she was seen elsewhere with heart failure secondary to multiple pulmonary embolisms and pulmonary hypertension. On examination she was also found to have perforation of the nasal septum. She had thrombocytopenia ($83 \times 10^9/l$), prolonged PTT time (39.2 s, control < 29.3), normal antithrombin III and negative ANA. She was sent to us in February, 1987 when she had another bout of hemoptysis with thrombocytopenia ($19.9 \times 10^9/l$). When we saw her she had evidence of left lower postphlebotic syndrome, pulmonary hypertension and absent tendon reflexes in her lower extremities and left arm. Studies showed prolonged prothrombin and PTT time due to the presence of a lupus anticoagulant, negative VDRL 78×10^9 platelets/l, normal DNA uptake (8.6%), multiple cerebral infarcts in a computerized axial tomogram scan and lack of uptake of the left lung with multiple perfusion defects on the right in a perfusion lung scan (Figure 2). APLA were 10.1 units of IgG and 2.5 units of IgM. Subsequent determinations revealed levels of IgG APLA up to 23.0 units. She has remained stable taking oral anticoagulants.

Patient 3. The mother and one cousin of this 25-year-old woman has had thrombosis of the central retinal artery. She has had migraine headaches for the last 4 years and her 2 pregnancies ended in abortion with placental infarcts. In April, 1986 she had an episode of transient cerebral ischemia and in December of that year she had occlusion of her left internal carotid artery with resulting aphasia and right hemiplegia. She was seen in another hospital where a lupus anticoagulant was detected. She was also found to have a functional deficiency of protein C but no antigenic deficiency. She was referred to us. We found positive ANA with a speckled pattern at a titer of 1:20. DNA uptake, C3 and C4 were normal and antibodies to nRNP were negative. Platelets were $128 \times 10^9/l$ and she had APLA IgG 2.3 units and IgM 4.0 units. She was given oral anticoagulants and has had no other ischemic episodes. Subsequent studies showed that the functional deficiency of protein C had reverted to normal (with adjustment for the oral anticoagulation).

Patient 4. The first pregnancy of this woman occurred at age 18 and resulted in a stillbirth and the 2nd, one year later, in abortion. Three months later she developed swelling of her left lower extremity that resolved partially



Fig. 1. Narrowing of left femoral artery in Patient 1 with primary antiphospholipid syndrome (arrow).

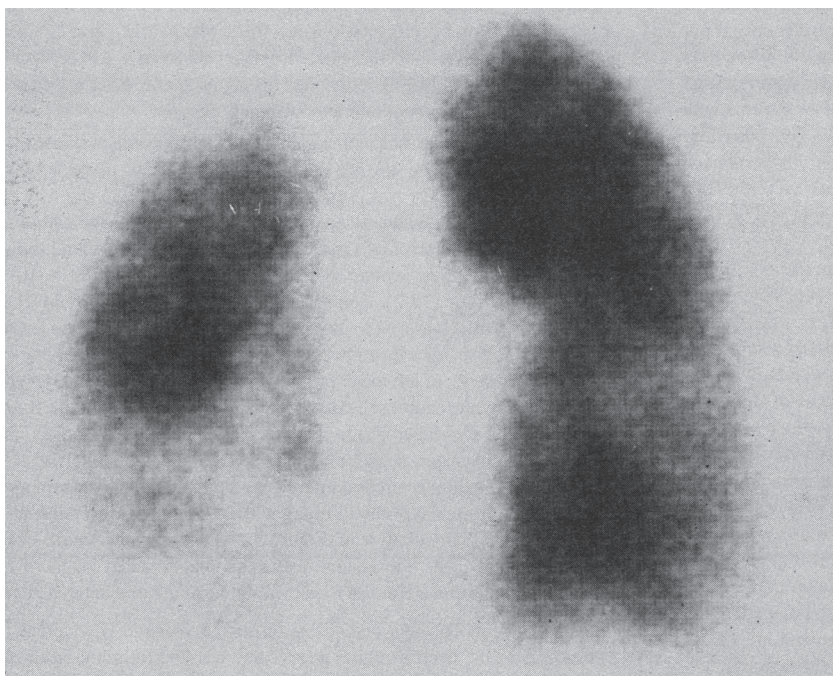


Fig. 2. Pulmonary ^{99m}Tc scans in Patient 3 with evidence of bilateral hypoperfusion indicative of pulmonary infarcts.

in one month without treatment. At this time she noticed swelling down the right side of her thigh. When she consulted us she was found to have edema of both lower extremities, as well as livedo reticularis. Laboratory tests revealed 138×10^9 platelets/l, negative ANA, normal DNA uptake, prolonged activated PTT and positive APLA (IgG:4.6, IgM:2.7 units). A percutaneous venogram showed obstruction of the deep venous system bilaterally. She was given oral anticoagulation with coumadin and has been well since.

Patient 5. This 25-year-old woman consulted us because of consecutive fetal loss in 2 pregnancies. Study of the placentae had shown thromboses. She also gave a history of classical migraine for 2 years that had disappeared 2 years before. She had livedo reticularis. She had no other evidence of connective tissue disease and her ANA, LE cells and rheumatoid factor were negative on 3 occasions. DNA binding was 9.2%, VDRL was positive and APLA were IgG:5.0, IgM:2.3 units.

Patient 6. In 1985 this woman was 20 years-old and apparently healthy when she suddenly developed right chest pain, hemoptysis, fever, and dyspnea. She was hospitalized elsewhere and diagnosed as having had a pulmonary embolism on the bases of roentgenologic, scintigraphic and electrocardiographic studies (Figures 3 and 4). After initially receiving heparin she was given oral anticoagulants which she took for one year. A VDRL test had been negative at that time but in January, 1987, when she was tested to obtain a marriage license, she was found to have a positive VDRL with a negative FTA test. In March, 1988 in her 3rd month of pregnancy, she developed left iliofemoral thrombophlebitis for which she was given subcutaneous heparin. One month later she was found to have had intrauterine death. At this time the possibility of APLA was considered and a blood sample sent to us for testing was positive. In July, 1988 she had another episode of pulmonary embolism. She was given oral anticoagulants and referred to us for study. She had had no symptoms suggestive of SLE and on examination livedo reticularis was the only pertinent finding. Laboratory tests revealed a positive VDRL with a negative FTA. Anticardiolipin antibodies (aCL) were IgG:2.0 and IgM:5.2 units. She had 3.9×10^9 leukocytes with 1.1×10^9 lymphocytes/l. Blood platelets were normal. She has continued to take oral anticoagulants.

Patient 7 is reported in detail elsewhere because of a peculiar effect of purified thrombomodulin on his levels of APLA¹¹. Patients 8 and 9 (Figure 5) cor-



Fig. 3. Chest roentgenogram showing pulmonary hypertension secondary to multiple pulmonary embolisms (Patient 6).

respond to Patients 1 and 3 of our report on antiphospholipid arterial vasculopathy¹².

RESULTS

A compendium of clinical and laboratory data in the 9 patients can be seen in Tables 1 and 2. Table 1 shows how they ful-

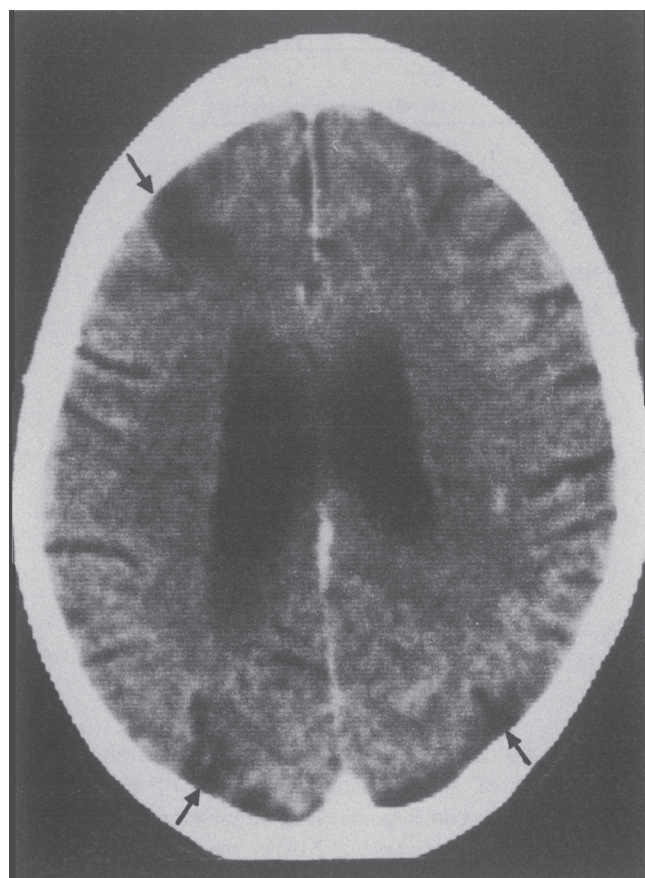


Fig. 4. Cerebral infarcts (arrows) in CAT scan of Patient 6 with primary antiphospholipid syndrome.

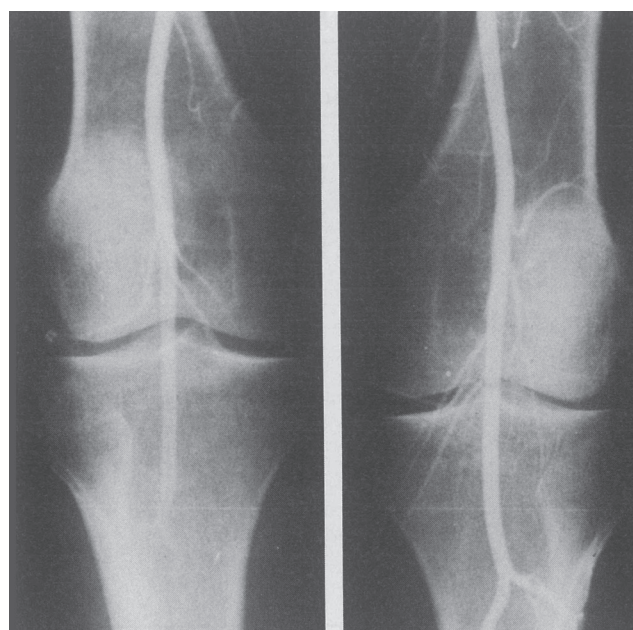


Fig. 5. Right popliteal arterial occlusion in Patient 9.

filled the proposed criteria for antiphospholipid syndrome as well as other clinical data. Table 2 show data on laboratory manifestations. All patients had 2 or more years of followup and none fulfilled criteria for SLE. All had negative DNA uptake, and only one had lymphopenia and one had low titer ANA.

Table 1. *Primary antiphospholipid syndrome. Summary of clinical data*

PT	Age	Sex	Manifestations Associated with APLA*								Other Clinical Features	Family History
			VT	TCP	HA	RFL	LU	AO	LR	TM		
1	26	F	+	+		+		+	+		+ Coombs	SLE
2	32	F	+	+		NR		+			Pulmonary hypertension, perforation nasal septum	
3	25	F				+		+			Placental infarction, migraine	Retinal vein thrombosis
4	19	F	+			+			+			
5	25	F				+			+		Placental thrombosis, migraine	
6	22	F	+			NR			+			
7	16	M	+	+		NR					Pulmonary hypertension	
8	43	F				NR		+	+		Cutaneous vasculitis	
9	23	F	+	+		NR	+	+				SLE

Abbreviations: VT = venous thrombosis; TCP = thrombocytopenia; HA = hemolytic anemia; RFL = recurrent fetal loss; LU = leg ulcers; AO = arterial occlusions; LR = livedo reticularis; TM = transverse myelitis; NR = not at risk.

Table 2. Primary antiphospholipid syndrome. Summary of laboratory findings

Patient	APLA, IgG	Units IgM	VDRL	PTT (control)	Lupus Anticoagulant
1	3.7	0.7	Neg.	50.9 (24.5 – 42.0)	+
2	23.0	2.5	Neg.	105.6 (24.5 – 42.0)	+
3	2.7	6.6	ND	53.4	+
4	4.6	2.7	ND	88.6 (40.1)	ND
5	5.0	2.3	+	ND	ND
6	2.0	5.2	+	51.3 (24.5 – 42.0)	ND
7	17.7	2.2	+	70.5 (24.5 – 42.0)	ND
8	29.5	7.6	+	106.1 (24.5 – 42.0)	+
9	19.0	9.6	+	86 (24.5 – 42.0)	+

Abbreviations: PTT = activated partial thromboplastin time; ND = not done.

With a mean age of 25.5 years in our group of patients it seems that primary antiphospholipid occurs primarily in young people, particularly, but not exclusively, in women, and it may have a genetic background as suggested by family histories of thromboses or SLE in 3 of our 9 patients. The levels of APLA in these patients were extremely high, some of them above 25 SD over the mean of normal controls. All but one patient (Case 6) had elevation of the IgG isotype of the APLA. Five also had elevated IgM APLA but in only 2 of these was the IgM isotype of APLA higher than the IgG isotype. In addition 5 patients had positive VDRL, 8 had prolonged activated PTT, and all 5 who were specifically studied had a lupus anticoagulant.

DISCUSSION

All 9 patients had 2 or more of the manifestations related to the presence of APLA that we have found significantly associated with the presence of APLA in a large group of patients with SLE. These included thrombophlebitis and/or pulmonary embolism, arterial occlusions, recurrent fetal loss, leg ulcers, livedo reticularis and thrombocytopenia. Although one patient had a positive Coombs' test, hemolytic anemia that has also been found associated to APLA in patients with SLE¹³, was not encountered in this group of patients with primary antiphospholipid syndrome. This could be due to the association of hemolytic anemia with APLA of the IgM isotype rather than with that of the IgG class¹³ which was the main isotype of APLA found elevated in our patients with primary antiphospholipid syndrome.

By requiring 2 of the clinical criteria for classification and diagnosis of this syndrome, we might be leaving out patients with only one manifestation who could have it. However,

because we have previously found that the strength of the association of APLA with 2 or more of the increases markedly (Alarcón-Segovia, *et al* unpublished observations) we decided to require at least 2. Also, the inclusion of patients with a single clinical criterion might lend itself to selecting mainly women with recurrent fetal loss or including patients with venous thrombosis who happened to have APLA. This should be avoided for the time being. However, these criteria should be considered preliminary and subject to modification as new knowledge becomes available.

Venous and arterial occlusions have different clinical meanings. An arterial occlusion in a young person calls for extensive investigation, whereas a venous occlusion in a young woman could be considered less ominous and is explainable by labor or bed rest. We therefore considered each as an independent criterion. We have also found that arterial lesions, occurring in patients with APLA, may involve more than a simple thrombosis¹². These criterion could be also applied to the classification of patients with antiphospholipid syndrome secondary to SLE or other connective tissue diseases.

With a followup of 2–8 years (mean 5.5 years) we can be reasonably certain that these 9 patients do not have SLE. Thus, in none have we found high titers of ANA and none (of 6 studied) had LE cells. As opposed to patients with SLE, most of whom have lymphopenia in the course of their disease¹⁴, only one of these patients has had it. One of our patients had been found to have synovitis and another one has had arthralgia. We doubt that this is an indicator of their having a primary rheumatic condition. Rather, it could be that APLA could occasionally cause arthritis, perhaps by

means of immune complexes of APLA-phospholipids that have also been postulated to occur¹⁵. The possibility of ANA negative SLE is also untenable. No patient had subacute SLE and, because we tested for ANA with HEp-2 cells, we can also rule out the presence of cytoplasmic antibodies¹⁶.

No patient fulfilled the criteria for the classification of SLE in either of the 2 versions^{17,18}. Nor did any patients have alternate manifestations, other than those associated with APLA, that are not included in the SLE criteria because of their lower frequency. None had evidence of Sjögren's syndrome that has recently been found associated with livedo reticularis and APLA¹⁹.

These young patients have had, almost exclusively, manifestations that can be attributed to their having APLA. These are mainly those related to vascular occlusions that may be venous, arterial, or both and include the placental vessels which possibly explains the recurrent fetal loss they suffer²⁰. The other group of manifestations that associate with APLA are hemocytopenic which, in the group of patients being reported, was only of platelets.

The mechanisms whereby APLA can cause these seemingly disparate manifestations are beginning to be understood²¹. Phospholipids are constituents of cell walls, including those of platelets, erythrocytes and endothelial cells, and participate in various stages of the coagulation process. Although the negatively charged phospholipids (e.g., phosphatidylserine) that cross react immunologically with cardiolipin²², which is not itself a constituent of cell walls, are not located in the outer part of cell membranes, they are expressed on occurrence of cell damage or, in the case of platelets, of activation or aggregation²³⁻²⁵. Thus, they are amenable to reaction with the APLA. This could cause thrombocytopenia, hemolytic anemia and, perhaps initiate endothelial cell damage. In turn, by acting on phospholipids of the platelet wall (platelet factor III) that interact with factor X and factor V in the presence of Ca^{++} ions²⁶, the APLA can cause prolonged prothrombin and PTT that depend on phospholipids. This causes the "lupus" anticoagulant that does not correct with normal plasma because it depends on the presence of the APLA rather than on the lack of a factor. This anticoagulant, however, rarely causes bleeding but has rather long been associated with occurrence of thrombosis^{27,28} probably due to predominance *in vivo* of their effect on other mechanisms where phospholipids participate. An important site of action of APLA could be at the enhancement of thrombomodulin activity by phospholipids²⁹. Interaction of APLA there would cause inhibition of protein C activation on the endothelial cells^{29,30}. It has actually been shown *in vitro* that this inhibition caused by APLA occurs only if endothelial cells are present³⁰. Indeed, one would then expect to have a functional deficiency of protein C with normal antigenic amounts of it²⁹. At least 2 of our patients with primary antiphospholipid syndrome have

been found to have this phenomenon (Ruiz-Argüelles GJ, *et al* Submitted for publication).

Another postulated mechanism of action of APLA is by inhibition of prostacyclin formation, perhaps by interference of arachidonic acid synthesis from phospholipids in the cell membrane³¹⁻³³. It is of interest that one of the patients in whom this possible mechanism was described probably had primary antiphospholipid syndrome³². Other patients with this disorder can be found in the literature describing patients with lupus anticoagulant or APLA³⁴⁻³⁶. Some may be included with patients with SLE or are said to have SLE-like conditions³⁴. We attempt here to contribute to the recognition and understanding of these patients by emphasizing that they do not have SLE and that most, and perhaps even all, of their manifestations may be due to the action of APLA at different sites. We believe that the term lupus-like disease sometimes given to these patients should be avoided since it causes considerable confusion. Recognition of the primary nature of this syndrome may also be important to avoid excessive and, perhaps unnecessary, corticosteroid or immunosuppressive treatment. It would thus far seem that oral anticoagulation would best help solve some of these patients' problems, particularly those related to vascular occlusion. In the case of pregnancy, subcutaneous heparin, corticosteroid treatment and/or plasmapheresis might be considered. Definitive forms of treatment await further study.

This syndrome, however, could be genetically related to SLE, as suggested by at least one of our patients. In a recent study of 46 families with at least one patient with SLE it was found that 22% of their apparently healthy relatives had APLA³⁷. Eight of the 50 relatives with APLA had them at levels akin to those of our patients with primary antiphospholipid syndrome. Difference in complement genotypes were observed between patients with SLE with APLA and their relatives with them. Immunogenetic studies of families of patients with the syndrome may be important to further understand their relationship to SLE and to determine if those SLE patients' relatives who have high titers of APLA are actually at risk of developing primary antiphospholipid syndrome.

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