Antiphospholipid antibodies and antiphospholipid syndrome in patients presenting with immune thrombocytopenic purpura: a prospective cohort study

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The pathogenetic role and the clinical importance of the presence of antiphospholipid antibodies (APAs) in patients with immune thrombocytopenic purpura (ITP) are not clear. In this study, the prevalence and clinical significance of APAs were investigated in patients with ITP. Eighty-two newly diagnosed ITP patients were prospectively studied. They were evaluated for the presence of lupus anticoagulant (LA) and immunoglobulin G/M anticardiolipin antibodies (ACAs). Thirty-one patients (37.8%) were APA positive at diagnosis. No statistically significant differences were found between the APA-positive and APA-negative groups regarding gender, initial platelet counts, or response to methylprednisolone therapy. After 5 years of follow-up, cumulative thrombosis-free survival of APA-positive (n = 31) and APA-negative (n = 51) ITP patients was 39% and 97.7%, respectively. A significant difference was found between these groups by log-rank test ($P = .0004$). In addition, LA was an important risk marker for the development of thrombosis in ITP patients. After a median follow-up of 38 months, 14 ITP patients (45%) who had APA positivity developed clinical features (thrombosis or fetal losses) of antiphospholipid syndrome (APS). There were no differences between the APA-positive patients with and without APS regarding the initial platelet counts, response to the therapy, or ACA positivity. The positivity rate for LA was significantly higher in those patients with ITP who developed APS (χ^2: $P = .0036$; relative risk 7.15; 95% confidence interval, 1.7-47). In conclusion, this study indicates that a significant proportion of patients initially presenting with ITP and APA positivity developed APS. In patients with ITP, the persistent presence of APAs is an important risk factor for the development of APS. (Blood. 2001;98:1760-1764)

Introduction

Immune (idiopathic) thrombocytopenic purpura (ITP) is an autoimmune disease defined by a low platelet count secondary to accelerated platelet destruction by antiplatelet antibodies that generally recognize platelet membrane glycoproteins (GPs). Antiphospholipid syndrome (APS) is characterized by arterial and venous thrombosis, recurrent fetal loss, and thrombocytopenia in the presence of antiphospholipid antibodies (APAs).

Thrombocytopenia is reported in about 20% to 40% of patients with APS and is usually mild.[1] Although there is direct evidence that APAs may bind platelet membranes and cause platelet destruction, the relation between APA positivity and thrombocytopenia is still unclear. Some investigators suggest that antibodies other than APA, mainly those against GPIIb-IIIa and other membrane GPs, cause thrombocytopenia in patients with APS.[2,3]

Although Harris et al[4] found anticardiolipin antibodies (ACAs) in 30% of ITP patients at the time of diagnosis, many researchers have questioned the clinical significance of this observation. Elevated levels of APAs are common in ITP and often do not change significantly with immunosuppressive therapy. In addition, ITP patients with normal and elevated levels of APAs had similar clinical profiles.[5] The development of APS was found to be uncommon in the long-term observation of chronic ITP patients.[6] Because of this observed lack of clinical association between these antibodies and ITP, the American Society of Hematology ITP Practice and Guideline Panel recommended that evaluating ITP patients for APAs is unnecessary.[7] Similarly, in a recent symposium on APS, thrombocytopenia was not included in the preliminary classification criteria for APS.[8]

Because of our observation that some ITP patients with persistently positive APAs developed thrombosis after several years of follow-up, we decided to investigate APA-positive ITP patients prospectively for the development of APS. In the present study, newly diagnosed ITP patients were prospectively evaluated for APA positivity and clinical features of APS.

Patients and methods

We studied 82 patients who were newly diagnosed with ITP in our Hematology Division between July 1993 and July 1999. Their median age was 31 years (range, 16-70 years) at the time of diagnosis (Table 1). Median follow-up was 32 months (range, 6-72 months). ITP was diagnosed by medical history, physical examination, peripheral blood smear, and bone marrow aspiration. Patients who were referred with bleeding complaints (easy bruising, purpura, mucosal bleeding) and had isolated thrombocytopenia with no history of other clinical conditions that can cause thrombocytopenia were included in our study. Peripheral blood smears and bone marrow smears were examined to rule out other causes of thrombocytopenia in all patients. At the time of the ITP diagnosis, patients were excluded from further study if they had a history or clinical findings of APS, systemic lupus erythematosus (SLE), other autoimmune disorders, acquired immunodeficiency syndrome, or malignancies. Although the upper limit for thrombocytopenia was accepted as 140×10^9/L, only 5 patients had platelet counts greater than 100×10^9/L (maximum level

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Table 1. Characteristics of the patients

	Total	APA+	APA−	*P*
Number of patients	82	31	51	
Median age, y	31 (16-70)	33 (16-66)	31 (20-70)	
Male/female	16/66	4/27	12/39	NS
Initial platelet count				
0-50 × 10^9	62 (75.6%)	22 (70.9%)	40 (78.4%)	NS
51-100 × 10^9	15 (18.2%)	8 (25.8%)	7 (13.7%)	NS
101-140 × 10^9	5 (6%)	1 (3.2%)	4 (7.8%)	NS
Response to therapy				
No therapy	11 (13.4%)	8 (25.8%)	3 (5.8%)	.017
CR with MP	26 (31.7%)	7 (22.5%)	19 (37.2%)	NS
PR with MP	22 (26.8%)	12 (38.7%)	10 (19.6%)	NS
Splenectomy	19 (23.1%)	4 (12.9%)	15 (29.4%)	NS
Others	4 (4.8%)	0	4 (7.8%)	NS

NS indicates not significant; CR, complete remission; MP, methylprednisolone; PR, partial remission.

was 117 × 10^9/L). Patients with mild thrombocytopenia (101-140 × 10^9 platelets/L) or moderate thrombocytopenia (51-100 × 10^9 platelets/L) did not receive any therapy unless they had bleeding symptoms or were to have surgical intervention. Patients who had moderate to severe thrombocytopenia (0-50 × 10^9 platelets/L) with bleeding complications received oral methylprednisolone at 1-mg/kg doses for 1 month. The methylprednisolone doses were tapered in those patients who responded to therapy. Splenectomy was performed in patients who were resistant to methylprednisolone. Patients unresponsive to splenectomy received additional treatment with other drugs (azathioprine, vincristine, danazol, or intravenous immunoglobulin) (Table 1).

A predefined protocol for APS was used for the assessment of all patients included in the study. All patients with APS were seen by one of our authors (M.İ.) who is a member of the rheumatology unit. The final diagnoses were made for all patients by 2 of the authors. The diagnosis of thromboembolic events was done by other specialists in emergency situations without knowledge of the patient's APA status, and later patients had consultations with the authors.

APS was diagnosed in patients who had arterial or venous thrombosis and/or recurrent fetal losses in the presence of ACAs, lupus anticoagulant (LA), or both. Doppler ultrasonography, ventilation and perfusion scanning of the lung, computed tomography, magnetic resonance imaging, and retinal angiography were used for documentation of thrombotic complications. Three or more unexplained spontaneous abortions were considered recurrent fetal losses. ITP patients who had 2 unexplained fetal losses and had positive tests for APAs were also regarded as having APS and were treated with aspirin or low-molecular-weight heparin in their consecutive pregnancies. ACA immunoglobulin G (IgG) and IgM levels were screened by enzyme-linked immunosorbent assay as described elsewhere.[9] Samples of 0 to 10 GPL or MPL units (measuring IgG and IgM anticardiolipin antibodies, respectively) were regarded as negative, 11 to 19 units were regarded as low positive, 20 to 60 units were regarded as positive, and more than 60 units were regarded as high positive for both ACA IgG and ACA IgM. LA was diagnosed according to the criteria of the International Society of Haemostasis and Thrombosis.[10] Fresh citrated venous blood samples were used for LA testing. All plasma samples were centrifuged at 2000*g* for 15 minutes and filtered through 0.22-μ filters, and both the activated partial thromboplastin time (aPTT) and the kaolin clotting time (KCT) were measured twice. The results were compared with those from filtered, normal pooled plasma, which was collected from at least 10 normal controls. The aPTT and KCT were considered to be prolonged if they were more than 3 SDs longer than the control (39 seconds for aPTT; 88 seconds for KCT). In mixing studies, the patients' plasma samples were mixed 1:1 with normal pooled plasma, and both aPTT and KCT were performed on all samples. Frozen-thawed platelets were used for the platelet neutralization test. Although it has been recommended that partial correction might suggest phospholipid dependence,[10] complete correction was obtained in all LA-positive samples. The LA and ACA levels were repeated at intervals of more than 2 months.

A total of 31 patients (37.8%) were found to be positive for APAs at the time of diagnosis (Table 1). Fourteen patients developed thrombosis or fetal loss in the presence of APAs (group A). APA-positive ITP patients without APS symptoms were classified as group B. The clinical and laboratory findings of the 2 groups were compared. Kaplan-Meier procedure, log-rank test, and Fisher exact test were used for statistical analysis. Relative risks (RRs) and confidence intervals (CIs) were calculated with the Instat (Graphpad Software, San Diego, CA) and SPSS (Prentice Hall, Upper Saddle River, New Jersey) computer programs.

Results

Thirty-one patients (37.8%) were found to be positive for APAs at the time of the ITP diagnosis (Table 1). We found no statistically significant differences between the APA-positive and APA-negative groups for gender ratio, initial platelet counts, or response to methylprednisolone therapy. Although the initial platelet counts were similar, follow-up with no treatment was found to be higher in APA-positive patients (χ^2: $P = .017$; RR = 0.4; 95% CI, 0.15-1.0). Only one patient developed thrombosis or recurrent fetal losses in the APA-negative group. Only one patient developed acute myocardial infarction at the 14th month of follow-up in the APA-negative group.

We compared the thrombosis-free survival of patients who were APA positive (n = 31) with those who were APA negative at presentation (n = 51) by Kaplan-Meier test (Table 2). After 5 years of follow-up, cumulative thrombosis-free survival rates of APA-positive and APA-negative ITP patients were 39.9% and 97.7%, respectively (Figure 1A). These data were found to be highly statistically significant by log-rank test ($P = .0004$). We also analyzed the effect of the positivity of LA, ACA total, ACA IgG (both greater than 10 GPL and greater than 20 GPL), and ACA IgM (both greater than 10 MPL and 20 MPL) on thrombosis-free survival of ITP patients (Table 2). We found a highly statistically significant difference for LA positivity ($P = .0001$ by log-rank test) (Figure 1B). Although ACA IgG levels greater than 10 GPL units were found to be a risk marker for developing thrombosis in patients with ITP, we found no significant difference for ACA total (Figure 1C) or ACA IgM positivity (Table 2). The comparisons of both the LA-positive and ACA-positive (greater than 10 GPL/MPL) patients with the others were also found to be statistically nonsignificant (Table 2).

The patients who presented with ITP and subsequently developed APS were designated group A (Table 3). Thirteen of them (92.8%) were positive for LA. KCT was prolonged in all LA-positive patients (100%), and aPTT was prolonged in 10 patients (77%). Twelve patients were screened for ACAs; 7 had ACA IgG positivity, IgM positivity, or both (Table 3). The median interval between the diagnosis of ITP and the first clinical symptom of APS was 38 months (range, 5-72 months).

Four patients (nos. 2, 4, 8, and 12) did not receive any therapy at the time of ITP diagnosis because of mild or moderate thrombocytopenia with no bleeding symptoms, and all subsequently developed thrombosis. One patient (no. 9) achieved normal platelet counts after methylprednisolone therapy, and APA positivity persisted. She has experienced 2 second-trimester fetal losses during follow-up. Six patients (nos. 1, 5, 10, 11, 13, and 14) achieved partial remission of thrombocytopenia after methylprednisolone therapy. Five of 6 have developed thrombosis. Three patients who had no response to methylprednisolone underwent splenectomy (nos. 3, 6, and 7). One of them (no. 7) developed deep

Table 2. Thrombosis-free survival analysis of the patients by Kaplan-Meier procedure

	n	Cumulative TFS (%) at 5 y	Mean TFS time, mo	Standard error	95% CI	*P* (log rank)
APA negative	51	97.7	70.6	1.3	68.1-73.2	.0004
APA positive	31	39.9	50	4.8	40.5-59.4	
LA negative	62	96.3	69.8	1.5	66.8-72.7	.0001
LA positive	20	33.1	46.2	5.6	35.1-57.4	
ACA negative	67	65.6	61.3	3.1	55.1-67.4	.47
ACA positive (> 20 GPL/MPL)	15	63.4	55.5	8.0	39.7-71.4	
ACA negative	60	73.9	62.4	3.2	56-68.8	.2
ACA positive (> 10 GPL/MPL)	22	52.6	55.6	6.1	43.5-67.7	
ACA IgG negative	73	67.8	61.9	2.9	56.1-67.7	.12
ACA IgG positive (> 20 GPL)	9	50	48.5	10.1	28.5-68.4	
ACA IgG negative	65	76.3	63.2	3	57.3-69.1	.03
ACA IgG positive (> 10 GPL)	17	40	50.8	7.4	36.1-65.4	
ACA IgM negative	71	67.7	61.8	2.9	56-67.7	.18
ACA IgM positive (> 20 MPL)	11	53.3	50.9	9.6	32-69.8	
ACA IgM negative	67	66.7	61.4	3.1	55.3-67.5	.42
ACA IgM positive (> 10 MPL)	15	63.4	55.5	8	39.7-71.4	
Both LA and ACA positive*	12	48	52.6	7.98	36.9-68.2	.15
Others†	70	74.3	62.3	3.11	56.2-68.4	

TFS indicates thrombosis-free survival.
*The patients who had both LA positivity and ACA IgG and/or IgM levels greater than 10 GPL/MPL units were included in this group.
†The group included patients who had APA negativity and either LA positivity alone or ACA positivity alone.

vein thrombosis and pulmonary embolism during the postoperative period, and one patient (no. 6) developed mesenteric embolism immediately before splenectomy. These 2 patients had platelet counts greater than 100×10^9/L at the time of thrombosis (Table 4).

A total of 6 venous thrombotic events were documented in group-A patients. Five patients (nos. 1, 4, 7, 12, and 13) experienced deep vein thrombosis, and 2 patients (nos. 4 and 7) also had pulmonary embolism documented with ventilation and perfusion scanning. They were treated with intravenous heparin and oral warfarin with a target international normalized ratio of greater than 3.0. All patients recovered with no problems. One patient (no. 2) was admitted with blurred vision in the left eye, and retinal vein thrombosis was found on retinal angiography. He recovered with decreased visual acuity. Five patients experienced arterial thrombotic events: 4 had stroke (nos. 5, 8, 10, and 14) and one had mesenteric artery embolism (no. 6). Permanent right-sided hemiplegia developed in one patient with stroke (no. 10), and the remaining patients recovered with residual impairment. The thromboembolic complications developed when the platelet counts exceeded 100×10^9 platelets/L in all but one patient. In patient 10, stroke developed with a platelet count of 30×10^9 platelets/L.

Five patients (nos. 3, 6, 9, 11, and 14) had spontaneous abortions (Table 4). Patients 3 and 6 had 3 first-trimester abortions, patient 11 had 2 first-trimester abortions, patient 9 had 2 second-trimester abortions, and patient 14 had a third-trimester stillbirth.

Three patients (nos. 3, 11, and 12) fulfilled the criteria for SLE during follow-up.

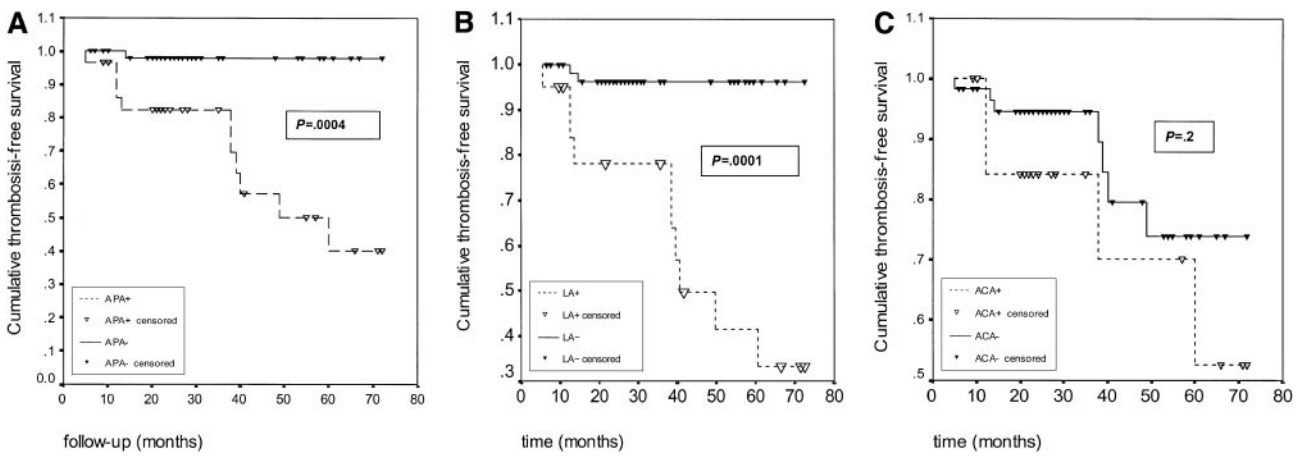

Figure 1. Thrombosis-free survival analysis of ITP patients by APA, LA, and ACA status. Thrombosis-free survival analysis of APA-positive and APA-negative (A), LA-positive and LA-negative (B), and ACA-positive (greater than 10 GPL/MPL) and ACA-negative (C) patients by the Kaplan-Meier method. Patients were censored for thrombosis. *P* values were calculated with the log-rank test. The data show that APA positivity, especially LA positivity, is an important risk factor for the development of thrombotic complications in patients who present with ITP.

Table 3. Features of APA-positive patients

	Group A*	Group B†	*P*
Number of patients	14	17	
Median age, y	37 (20-53)	30 (16-66)	NS
Male/Female	2/12	2/15	NS
Initial platelet count			
0-50 × 10^9	10 (71.4%)	12 (70.5%)	NS
51-100 × 10^9	3 (21.4%)	5 (29.4%)	NS
101-140 × 10^9	1 (7.2%)	0	NS
LA positivity	13 (92.8%)	7 (41.1%)	.0036
ACA IgG	n = 12	n = 17	
Negative (0-10 GPL)	5 (41.6%)	7 (41.1%)	NS
Low positive (11-19)	2 (16.6%)	6 (35.2%)	NS
Positive (20-59)	2 (16.6%)	2 (0.11%)	NS
High positive (> 60)	3 (25%)	2 (0.11%)	
ACA IgM	n = 12	n = 17	
Negative (0-10 MPL)	10 (83.3%)	5 (29.4%)	.007
Low positive (11-19)	0	4 (23.5%)	NS
Positive (20-59)	2 (16.6%)	7 (41%)	NS
High positive (> 60)	0	1 (5%)	
Response to therapy			
No therapy	4 (28.5%)	4 (23.5%)	NS
CR with MP	1 (7.1%)	6 (35.2%)	.09
PR with MP	6 (42.8%)	6 (35.2%)	NS
Splenectomy	3 (21.4%)	1 (5.8%)	NS

Abbreviations are explained in Table 1.
*APA-positive and APS-positive patients.
†APA-positive and APS-negative patients.

Group B consisted of 17 ITP patients with APA positivity who did not subsequently develop APS (Table 1). Their median age was 30 years (range, 16-66 years), and median follow-up was 35 months (range, 9-72 months). Seven patients had LA positivity (41.1%), and 15 (88.2%) were found to be positive for ACA IgG, IgM, or both (Table 3). Neither thrombotic events nor recurrent fetal losses were observed in group-B patients.

There were no differences between the APA-positive patients with or without APS for the initial platelet counts, response to the therapy, or ACA IgG or IgM positivity. Although there was a trend toward a decreased complete-remission rate with methylprednisolone therapy in group-A patients, the statistical analysis showed no difference between the groups. On the other hand, the prevalence of LA positivity was found to be significantly higher in group-A patients (χ^2: $P < .0036$; RR = 7.15; 95% CI, 1-47.6).

Discussion

The mechanism of thrombocytopenia in patients with APS is debated. It has been suggested that platelet-specific antibodies, rather than APAs, play a role in the pathogenesis of thrombocytopenia in APS. In one study, antibodies directed against the GPIIb-IIIa or GPIb-IX-V complexes were found in about 40% of the patients with APS who had thrombocytopenia.[11] Another study showed that anti-GP antibodies are rare in patients with SLE and APS with normal platelet counts.[2,3] Anti-GP antibodies in thrombocytopenic patients with APS do not cross-react with antibodies against phospholipids or β2 GP-I.[12] Immunosuppressive treatment of thrombocytopenia in patients with APS increases the platelet count and reduces the titers of anti-GP antibodies, but not the titers of APAs.[5] These data suggest that thrombocytopenia is a secondary immune phenomenon that may develop at the same time as APS. On the other hand, Fabris et al[13] showed that platelet antigens in thrombocytopenic patients with APS were different from those in ITP, and surface GPs were not involved. They also found that a 50- to 70-kd internal platelet protein had been specifically found in patients with APS and thrombocytopenia, but not in patients with ITP.[13]

Whether thrombocytopenia in patients with APS is related to APAs or not, another critical issue is the clinical importance of the presence of APAs in patients who present only with thrombocytopenia. In this study, we investigated the frequency of APAs in patients with ITP, and we found that more than one third of these patients (37.8%) had APAs at the time of diagnosis, a finding consistent with other reports.[4,5] Although many researchers have suggested that APA positivity is not correlated with the development of APS in patients with ITP,[5,7] there are case reports on the development of APS in patients who initially presented with ITP.[14] In this study, we found that 14 of 31 patients (45.1%) who were persistently positive for APAs developed APS in the follow-up period. When we evaluated APA-positive and APA-negative ITP patients for thrombotic events, we found that thrombosis-free survival at 5 years was 39.9% and 97.7%, respectively.

What are the predictors for the development of APS in APA-positive patients who present with ITP? To answer this question, we compared the APA-positive ITP patients with APS (group A) and those without APS (group B). During the follow-up

Table 4. Clinical and laboratory findings of ITP-onset APS (group A) patients

No.	Age, y	G	IPC, × 10^9	LA	ACA IgG	ACA IgM	APS clinical findings	TFE
1	53	F	12	(−)	63	36	DVT	12
2	38	M	110	(+)	14.9	4.7	RVT	12
3	37	F	47	(+)	26	6.9	FL and SLE	71
4	24	M	90	(+)	100	25	DVT + PE	38
5	36	F	50	(+)	2.6	1.6	Stroke	5
6	42	F	30	(+)	13.9	3.9	FL, MesO	60
7	46	F	15	(+)	7.1	5.5	DVT + PE	49
8	44	F	90	(+)	NA	NA	Stroke	13
9	27	F	22	(+)	86.7	7.2	FL	21
10	32	F	20	(+)	1.0	2.0	Stroke	38
11	42	F	30	(+)	5.9	4.6	FL, SLE	72
12	20	F	62	(+)	NA	NA	DVT, SLE	39
13	30	F	30	(+)	2.0	3.2	DVT	40
14	38	F	40	(+)	44	5.2	Stroke and FL	12

G indicates gender; IPC, initial platelet count; TFE, timing of first APS event (the time between ITP diagnosis and occurrence of the first thrombotic or obstetric event); DVT, deep vein thrombosis; RVT, retinal vein thrombosis; FL, fetal loss; SLE, systemic lupus erythematosus; PE, pulmonary embolism; MesO, mesenteric artery occlusion; NA, not available.

period, 6 of our patients experienced venous thrombosis (5 had deep vein thrombosis and pulmonary embolism; one had retinal vein thrombosis), 5 had arterial thrombosis (4 had stroke; one had mesentery artery thrombosis), and 3 patients had recurrent fetal losses (group A). Additionally, 3 patients in this group fulfilled the classification criteria for SLE in the follow-up period (Table 3). Group B comprised patients without recurrent fetal losses or thrombotic events. We found no differences between these groups regarding age, initial platelet counts, ACA IgG and IgM levels, or response to the methylprednisolone therapy. On the other hand, we found a significantly higher prevalence of LA positivity in group-A patients (χ^2: $P < .0036$; RR = 7.15; 95% CI, 1-47.6). Our data demonstrate that persistent positivity for LA is an important risk factor for the development of APS in patients who present with ITP. Further studies are required to definitively establish the RRs for LA versus ACA positivity.

The relation between LA positivity and high risk of thrombosis has been demonstrated by several groups.[15,16] It has been reported that the prevalence of thrombocytopenia is higher in LA-positive patients,[17] which may suggest an association between thrombocytopenia and thrombosis in LA-positive patients.

Eleven ITP patients in our study experienced thrombosis (6 patients had venous thromboembolism and 5 had arterial thrombosis). We noticed that thrombotic complications mostly developed after the platelet counts had exceeded 100×10^9/L after methylprednisolone therapy or splenectomy in ITP patients with persistent APA positivity. These data are consistent with the suggestion that severe thrombocytopenia might be a protective factor for the development of thrombosis in APS.[1] Prospective studies are needed to determine whether low-dose aspirin or other drugs have a prophylactic effect on thrombosis in these patients.

In conclusion, we propose that measurement of APAs, especially LA, in patients with an initial diagnosis of ITP may identify a subgroup of patients with a high risk of developing APS features (ie, thrombosis or fetal loss). The episodic nature of the clinical complications of APS, compared with the gradual development of other autoimmune diseases such as SLE, warrants a need for a serologic workup rather than clinical follow-up. A prophylactic drug regimen may avoid the potential complications of APS in patients with ITP and positive LA, considering the high correlation between LA positivity and thrombosis. Future research may determine other markers, including genetic factors, that may help to identify high-risk patients.

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