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Letter to the Editor

Clinical course of primary immune thrombocytopenia with positive antiphospholipid antibodies

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Antiphospholipid antibodies (aPL) are frequently detected in immune thrombocytopenia (ITP) and whether they play a role in ITP prognosis is controversial. Previous studies have shown that aPL positivity may not be associated with either platelet counts or response to treatment [1–4]; however, heterogeneity in the classification of ITP outcomes and high variability of aPL assays performed across studies may affect results consistency.

Due to the lack of evidence on the association of aPL positivity and ITP outcomes, aPL-positive primary ITP is considered neither a distinct clinical feature of ITP nor a manifestation of APS [5]. However, more evidence is needed from the perspective of primary ITP. In this study, we evaluated the role of persistent aPL seropositivity in the clinical course of primary ITP, taking into account current recommendations for aPL detection [6] and ITP related outcomes and treatment response [7].

This prospective cohort study enrolled consecutive patients with newly diagnosed primary ITP treated at the Hematology Center of the University of Campinas between 2008 and 2016. Primary ITP was diagnosed according to established criteria [7]. The diagnoses of systemic lupus erythematosus, hepatitis B and C, HIV infection and malignancy were excluded in all patients. Treatment was prescribed in case of platelets below 30×10^9/L or bleedings. Antiphospholipid testing was performed during ITP diagnostic work-up. Persistent aPL positivity was defined as persistent positive lupus anticoagulant (LAC); persistent positive IgG or IgM anticardiolipin (aCL) at moderate to high titers (> 40 GPL or MPL) or persistent positive (> the 99th percentile) IgG/IgM anti-beta2 glycoprotein 1 (aβ2GP1), on two occasions, at least 12 weeks apart [8]. Solid-phase assays were performed following the guideline from the International Society of Thrombosis and Haemostasis (ISTH) [9], and LAC assays were performed following the guidelines from both ISTH [10] and Clinical and Laboratory Standard Institute (https://clsi.org/standards/products/hematology/documents/h60/).

ITP related treatment response and outcomes were defined according to the International Working Group on standardization of terminology, definitions and outcome criteria in ITP [7]. Lack of response to corticosteroids was further separated into corticosteroid-refractoriness and corticosteroid-dependency. Bleedings were classified as major, moderate or mild bleeding events according to the criteria established by ISTH [11]. Thrombotic events that occurred before the diagnosis of ITP were self-reported by the patients. Those occurring during the follow-up period were confirmed by imaging examinations. SPSS (version 15.0, IBM Corp, USA) was used for statistical analysis. Regression models, adjusted for age and sex, were used to evaluate the association of aPL antibodies with response to the treatment, bleeding complications, platelet counts and incident thrombosis.

Two hundred sixty-two patients newly diagnosed with primary ITP were enrolled for the study. Exclusions were due to lack of aPL test (47 patients) or a follow-up period shorter than 3 months (19 patients). The final cohort consisted of 196 patients with primary ITP. Table 1 presents the patients' features at diagnosis. The mean platelet count at diagnosis was 54×10^9/L (range 1×10^9/L to 98×10^9/L). Corticosteroid and dapsone were the most commonly prescribed first- and second-line drug, respectively. During follow-up, 142 patients fulfilled criteria for persistent ITP and 103 fulfilled criteria for chronic ITP. The risk of developing persistent ITP or chronic ITP was similar in aPL-positive and aPL-negative patients. The relative risk of persistent ITP was 1.41 (95% CI 0.66 to 3.01) and of chronic ITP was 1.28 (95% CI 0.62 to 2.65) in aPL-positive as compared to aPL-negative patients. Corticosteroids were prescribed for 166 patients during the follow-up, 53 patients were corticosteroid-refractory, and 65 patients were corticosteroid-dependent. The risk for either refractoriness or dependence to corticosteroids was similar between aPL-positive and aPL-negative patients. The relative risk for corticosteroid-refractoriness was 0.57 (95% CI 0.23 to 1.46) and for corticosteroid-dependence was 1.06 (95% CI 0.46 to 2.40) in aPL-positive patients as compared to aPL-negative patients. The mean duration of corticosteroid treatment was 3 months in both aPL-positive (SD 4.4) and aPL-negative (SD 3.8) patients.

Platelet counts were also similar between groups at diagnosis and during follow-up. At diagnosis, mean platelet count was 55.5×10^9/L (SD 97.0) in aPL-negative and 52.7×10^9/L (SD 73.5) in aPL-positive patients, resulting in a mean difference in platelet counts of -2.90×10^9/L (95%CI -32.9 to 27.2). At 3 months of follow-up, mean platelet count was 122.7×10^9/L (SD 111.0) in aPL-negative and 103.1×10^9/L (SD 116.5) in aPL-positive patients, resulting in a mean difference in platelet counts of -18.2×10^9/L (95%CI -54.8 to 18.4). At 12 months of follow-up, the mean platelet count was 126.6×10^9/L (SD 110.2) in aPL-negative and 117.3×10^9/L (SD 119.4) in aPL-positive patients, resulting in a mean difference in platelet counts of -10.3×10^9/L (95%CI -49.6 to 29.0).

The mean annual number of bleeding episodes was 1.7 (SD 1.9) in

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Table 1
Baseline characteristics of participants in the study.

	aPL negative (n = 147)		aPL positive (n = 49)		P
Age in years, mean (range)	42	(1–87)	42	(10–89)	0.8
Female, n (%)	91	(62)	33	(67)	0.6
Type of antiphospholipid antibody					
Lupus anticoagulant, n (%)	–	–	29	(59)	
Anticardiolipin (IgM or IgG), n (%)	–	–	25	(51)	
Anti-B2 glycoprotein, n (%)	–	–	20	(11)	
Triple positivity, n (%)	–	–	4	(8)	
Positive ANA[a] test	32	(22.2)	16	(33.3)	0.12
Platelet count at diagnosis, $\times 10^9$/L mean, (SD)	55.4	(97)	52.7	(74)	0.9
Need for initial treatment, n (%)	123	(84)	44	(90)	0.4

Continuous variables denoted as mean and standard deviation and their P values calculated using independent *t*-test. Categorical variables denoted as number and percentage (%) and the *P* values calculated using chi-square test.

[a] ANA anti-nuclear antibody. All patients were tested for ANA and a titer of 1: 80 and above was considered Positive. A homogeneous pattern was detected in 10 patients (21%) and a speckled pattern in 38 patients (79%).

both groups. Mild bleeding events occurred in 66.4% of aPL-negative and in 55.1% of aPL-positive patients (odds ratio [OD] 0.66, 95%CI 0.28–1.52), moderate bleeding events occurred in 12.3% of aPL-negative and in 16.3% of aPL-positive patients (OD 1.09, 95%CI 0.36–3.26) and major bleeding events occurred in 2.1% of aPL-negative and in 6.1% of aPL-positive patients (OD 2.44, 95%CI 0.42–14.13). During follow-up, a thrombotic event was diagnosed in one aPL-negative and two aPL positive female patients (log-rank *P* value 0.03; hazard ratio 2.27, 95% CI 0.19–27.61). The aPL-negative patient had an atrial fibrillation-related stroke, she was not receiving ITP treatment and her platelet count was 70×10^9/L on that occasion. One aPL-positive patient had a stroke, she was using corticosteroid and her platelet count was 25×10^9/L. The other aPL-positive patient had a spontaneous deep vein thrombosis; on that occasion, her platelet count was normal.

In conclusion, aPL positivity was not associated with clinical characteristics, response to treatment, disease outcomes or bleeding events in patients with primary ITP. The association between aPL and increased risk of thrombosis in ITP has been largely described, however this association was not precisely detected in this study due to the low incidence of thrombosis in the studied population. As the results point towards the direction of a lack of association between aPL positivity and primary ITP clinical manifestation, it is unlike that aPL-positive patients comprise a distinct population of primary ITP.

Declaration of Competing Interest

The authors state that they have no conflict of interests.

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References

[1] Frison L, Lombardi A, Caputo I, Semenzato G, Fabris F, Vianello F. Relevance of antiphospholipid antibody profile in the clinical outcome of ITP: a single-centre study. Hematology 2019;24(1):134–8.
[2] Dayama A, Dass J, Mahapatra M, Saxena R. Incidence of antiphospholipid antibodies in patients with immune thrombocytopenia and correlation with treatment with steroids in North Indian population. Clin Appl Thromb Hemost 2017;23(6):657–62.
[3] Comellas-Kirkerup L, Hernandez-Molina G, Cabral AR. Antiphospholipid-associated thrombocytopenia or autoimmune hemolytic anemia in patients with or without definite primary antiphospholipid syndrome according to the Sapporo revised classification criteria: a 6-year follow-up study. Blood 2010;116(16):3058–63.
[4] Pierrot-Deseilligny Despujol C, Michel M, Khellaf M, Gouault M, Intrator L, Bierling P, et al. Antiphospholipid antibodies in adults with immune thrombocytopenic purpura. Br J Haematol 2008;142(4):638–43.
[5] Abreu MM, Danowski A, Wahl DG, Amigo MC, Tektonidou M, Pacheco MS, et al. The relevance of "non-criteria" clinical manifestations of antiphospholipid syndrome: 14th international congress on antiphospholipid antibodies technical task force report on antiphospholipid syndrome clinical features. Autoimmun Rev 2015;14(5):401–14.
[6] Devreese KMJ, Ortel TL, Pengo V, de Laat B. Subcommittee on lupus anticoagulant/antiphospholipid A. laboratory criteria for antiphospholipid syndrome: communication from the SSC of the ISTH. J Thromb Haemost 2018;16(4):809–13.
[7] Rodeghiero F, Stasi R, Gernsheimer T, Michel M, Provan D, Arnold DM, et al. Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. Blood 2009;113(11):2386–93.
[8] Miyakis S, Lockshin MD, Atsumi T, Branch DW, Brey RL, Cervera R, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost 2006;4(2):295–306.
[9] Devreese KM, Pierangeli SS, de Laat B, Tripodi A, Atsumi T, Ortel TL, et al. Testing for antiphospholipid antibodies with solid phase assays: guidance from the SSC of the ISTH. J Thromb Haemost 2014;12(5):792–5.
[10] Pengo V, Tripodi A, Reber G, Rand JH, Ortel TL, Galli M, et al. Update of the guidelines for lupus anticoagulant detection. Subcommittee on lupus anticoagulant/antiphospholipid antibody of the scientific and Standardisation Committee of the International Society on thrombosis and haemostasis. J Thromb Haemost 2009;7(10):1737–40.
[11] Schulman S, Kearon C, Subcommittee on Control of Anticoagulation of the S, Standardization Committee of the International Society on T, Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost 2005;3(4):692–4.

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