Extra-criteria clinical manifestations of antiphospholipid antibody should not be ignored

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To the Editor: Antiphospholipid syndrome (APS) is a disorder characterized with thrombotic and obstetric events in patients with persistent positive antiphospholipid antibodies (aPL), including lupus anticoagulant (LA), anticardiolipin antibody (aCL), and anti-β2 glycoprotein-I antibody (anti-β2GPI). The clinical symptoms of APS include many non-thrombotic manifestations, also called extra-criteria manifestations, including thrombocytopenia, aPL nephropathy, livedo reticularis, valve heart disease, and neurological manifestations.[1] Previous study found primary obstetric APS patients with extra-criteria manifestations might have risk of developing thrombosis,[2] and certain aPL types correlated with non-criteria manifestations.[3] We conducted a retrospective study to analyze aPL-associated clinical phenotypes, especially extra-criteria manifestations. This study was approved by the Medical Ethics Committee of Peking Union Medical College Hospital. Signed informed consent was obtained from all patients.

A total of 731 serum samples were tested for aPL during 2018 November and December, positive aPL samples were enrolled. Detection of LA was concurrent with the recommended criteria from the International Society on Thrombosis and Haemostasis. The aCL and anti-β2GPI antibodies were detected by enzyme-linked immunosorbent assay using commercially available kits. Definition of a moderate-to-high titer of aCL or anti-β2GPI antibody was 40 or more GPL or MPL units, and a low titer was 20 to 39 GPL or MPL units. Persistent was defined as tested on two or more occasions at least 12 weeks apart. The extra-criteria manifestations were defined as follows. Thrombocytopenia was defined as platelets level $<$100,000 mm^3 on two occasions. Livedo reticularis was assessed by a dermatologist. aPL-associated nephropathy was diagnosed with renal biopsy. Valve heart disease was confirmed with echocardiogram. Neurological manifestations included migraines, seizures, chorea, longitudinal myelitis, and cognitive dysfunction in the absence of stroke, which were diagnosed by a neurologist.

A total of 200 aPL positive patients were enrolled, 20 patients turned negative after 12 weeks, 180 were persistent. Among them, 131 were female and 49 male, the average age was 40.3 years old; 149 cases were anti-β2GP1 positive, 107 were aCL positive, 65 were LA positive, and 46 patients were triple aPL positive. 61 (33.9%) fulfilled the 2006 revised Sydney classification criteria for APS, 27 were primary and 34 were secondary. While thrombosis occurred in 44 (24.4%) patients and pregnant morbidity in 17 (9.4%), 119 (66.1%) patients were just persistent aPL positive only, 77 (42.8%) were totally asymptomatic, and 42 (23.3%) presented extra-criteria manifestations independently. Since there were also 30 APS patients with extra-criteria manifestations, the total frequencies of aPL associated extra-criteria manifestations were 40% (72/180).

The most common extra-criteria manifestations were thrombocytopenia (31.7%), neurological manifestations (10.0%), and valve heart disease (8.3%), they were more common in secondary APS compared with primary APS and non-APS-aPL+ patients [Table 1]. We compared aPL+ patients with and without extra-criteria manifestations and found that patients secondary to systemic lupus erythematosus (SLE) (47.2% *vs.* 24.1%, P = 0.002), with LA (50.0% *vs.* 26.9%, P = 0.002), moderate-to-high titer anti-β2GPI antibody (59.7% *vs.* 44.4%, P = 0.049), and triple aPLs (40.3% *vs.* 15.7%, $P < 0.001$) were more likely to present with extra-criteria manifestations.

The 2006 Sydney revised classification criteria for APS emphasize the presence of aPL as an essential component. Patients with autoimmune disease, thrombocytopenia, elevated activated partial thromboplastin time, false-

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Table 1: Prevalence of extra-criteria manifestations in persistent aPL-positive patients.

Items	All ($n=180$)	PAPS ($n=27$)	SAPS ($n=34$)	Non-APS aPL+ ($n=119$)	*P* values
Female, *n* (%)	131 (72.8)	18 (66.7)	26 (76.5)	87 (73.1)	0.687
Age (years), mean (SD)	40.3 (17.6)	37.8 (11.0)	37.7 (15.4)	41.6 (19.4)	0.384
Anti-β2GPI antibody, *n* (%)	149 (82.8)	25 (92.6)	29 (85.3)	95 (79.8)	0.259
aCL, *n* (%)	107 (59.4)	18 (66.7)	24 (70.6)	65 (54.6)	0.175
LA, *n* (%)	65 (36.1)	13 (48.1)	17 (50)	35 (29.4)	0.032
Triple aPL+, *n* (%)	46 (25.6)	11 (40.7)	14 (41.2)	21 (17.6)	0.003
pt w/extra-criteria, *n* (%)	72 (40.0)	9 (33.3)	21 (61.8)	42 (35.3)	0.016
Thrombocytopenia, *n* (%)	57 (31.7)	6 (22.2)	18 (52.9)	33 (27.7)	0.011
Livedo reticularis, *n* (%)	3 (1.7)	0 (0)	2 (6.5)	1 (0.8)	0.151
APL nephrology, *n* (%)	6 (3.3)	2 (7.4)	4 (12.9)	0 (0)	0.001
Valve heart disease, *n* (%)	15 (8.3)	2 (7.4)	7 (20.6)	6 (5.0)	0.015
Neurological, *n* (%)	18 (10)	3 (11.1)	8 (23.5)	7 (5.9)	0.010

Fisher's exact test. aCL: Anticardiolipin antibody; aPL: Antiphospholipid antibody; Anti-β2GPI antibody: Anti-β2 glycoprotein I antibody; LA: Lupus anticoagulant; PAPS: Primary antiphospholipid syndrome; SD: Standard deviation; SPAP: Secondary antiphospholipid syndrome.

positive syphilis test, thrombotic event, pregnancy complications, neurological manifestations were considered as suspected APS and might get aPL tested. In this study, only 27.4% sample was positive, >70% aPL tests ordered were not diagnostic, and 10% positive aPL was just transient. For persistent aPL-positive patients, only 38% were diagnosed with APS, which revealed >60% positive aPL were not due to APS. Even in 131 aPL positive patients with persistent moderate-to-high aPL profile, only 46.6% of patients fulfilled APS diagnosis. This reminds us that doctors need to order aPL tests based on sufficient clinical manifestations and view positive aPL dialectically.

Although thrombotic and obstetric manifestations are the only clinical events included in the APS classification criteria, there are numerous extra-criteria manifestations commonly observed in APS.[4] The prevalence of thrombocytopenia in APS ranges from 16% to 53% and thrombocytopenia in PAPS increasingly appears to be predictive of other APS complications and a higher adjusted Global APS Score.[5] The prevalence of valve abnormalities in primary APS was 30%, in aPL-positive SLE patients, the prevalence ranged from 14% to 86%. Central nervous system non-thrombotic manifestations in APS include cognitive dysfunction, migraine, seizures, multiple sclerosis-like syndrome, transverse myelitis, movement disorders, and psychiatric symptoms; among them, migraine might be the most common symptom in 20% of APS patients, chorea and transverse myelitis are rare but recommended to be included into APS criteria.[4] In this study, we found extra-criteria manifestations were not rare in APS patients (49.2%) and aPL+ only patients (35.3%), the total frequency (40%) was even higher than thrombotic (24.4%) and pregnant morbidity (9.4%) in aPL-positive patients, and they could present independently.

Our study was limited due to its retrospective, single-center design. However, the innovation is worthy of attention. Most studies focus on patients diagnosed with APS, we are interested in patients who get aPL tested, focus on the clinical manifestations associated with aPL, especially the extra-criteria manifestations. Single-center design ensured intact medical records and the consistency of diagnosis. We would like to have multiple centers, and we hope to do further studies on each extra-criteria manifestation.

In conclusion, 40% aPL-positive patients presented with extra-criteria manifestations regardless of thrombotic or obstetric events, more common in SLE patients. The most common extra-criteria manifestation was thrombocytopenia.

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Conflicts of interest

None.

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