

## 'Non-criteria' antiphospholipid antibodies and thrombosis

FEBRUARY 2018

**TO THE EDITOR:** We read with great interest the excellent article on thrombosis secondary to antiphospholipid antibody syndrome.<sup>1</sup> We wish to comment on the section "Antiphospholipid antibodies are not all the same," specifically on question 6: "Which of the following antiphospholipid antibodies have not been associated with an increased thrombotic risk?"

The answer offered was antiphosphatidylserine, and the authors stated, "While lupus anticoagulant, anti-beta-2-glycoprotein I, and anticardiolipin antibodies are associated with thrombosis, antiprothrombin antibodies (including antiprothrombin and antiphosphatidylserine antibodies) are not."<sup>1</sup>

Antiphospholipid antibody testing in antiphospholipid antibody syndrome is complicated, but we feel the information provided was inaccurate. It should be noted that 3 antibodies are under discussion: in addition to antiphosphatidylserine (aPS) antibodies, antiprothrombin antibodies are heterogeneous, comprising antibodies to prothrombin alone (aPT-A) and antibodies to the antiphosphatidylserine-prothrombin complex (aPS/PT). While the diagnostic utility of these antibodies is in evolution, there are numerous studies on their association with thrombosis or antiphospholipid antibody syndrome, or both.<sup>2,3</sup> Most recently, a systematic review (N = 7,000) concluded that prothrombin antibodies (aPT, aPS/PT) were strong risk factors for thrombosis (odds ratio 2.3, 95% confidence interval 1.72–3.5).<sup>4</sup>

The revised Sapporo (Sydney) guidelines referenced by the authors addressed these "non-criteria" antiphospholipid antibodies.<sup>5</sup> At that time (2006), it was thought premature to include these antibodies as independent criteria for definite antiphospholipid antibody syndrome, even though their asso-

ciation with the syndrome was recognized by the committee. The guidelines considered an interesting scenario: What if a case fulfills the clinical criteria of antiphospholipid antibody syndrome, but serology is positive only for these "non-criteria" antibodies? It was suggested that these cases be classified as "probable" antiphospholipid antibody syndrome. Also, aPS/PT was proposed as a confirmatory assay for lupus anticoagulant testing.

In 2010, the International Congress on Antiphospholipid Antibodies concluded that aPS/PT is truly relevant to thrombosis and antiphospholipid antibody syndrome, with the possibility of aPS/PT becoming a criterion for the syndrome in the future.<sup>6</sup> Studies have already started on this.<sup>7</sup> Since then, 2 scoring systems to quantify the risk of thrombosis and obstetric events have incorporated aPS/PT—the Antiphospholipid Score (2012) and the Global Anti-Phospholipid Syndrome Score (2013).<sup>8,9</sup>

In conclusion, these antibodies are associated with thrombosis, can be considered features of antiphospholipid antibody syndrome in the right clinical context, and have a role in contemporary discussion of this disease.

SATISH MAHARAJ, MBBS  
University of Florida College of Medicine,  
Jacksonville  
satish.maharaj@jax.ufl.edu

SIMONE CHANG, MBBS  
Holtz Children's Hospital  
Jackson Memorial Medical Center  
Miami, FL

MARWAN SHAIKH, MD  
University of Florida College of Medicine,  
Jacksonville

### REFERENCES

1. Serhal M, Evans N, Gornik HL. A 75-year-old with abdominal pain, hypoxia, and weak pulses in the left leg. *Cleve Clin J Med* 2018; 85(2):145–154. doi:10.3949/ccjm.85a.16069
2. Khogeer H, Alfattani A, Al Kaff M, Al Shehri T, Khojah O, Owaidah T. Antiphosphatidylserine antibodies as diagnostic indicators of antiphospholipid syndrome. *Lupus* 2015; 24(2):186–190. doi:10.1177/0961203314552462
3. Sciascia S, Bertolaccini ML. Antibodies to phosphatidylserine/prothrombin complex and the antiphospholipid syndrome. *Lupus* 2014; 23(12):1309–1312. doi:10.1177/0961203314538332

4. Sciascia S, Sanna G, Murru V, Roccatello D, Khamashta MA, Bertolaccini ML. Anti-prothrombin (aPT) and anti-phosphatidylserine/prothrombin (aPS/PT) antibodies and the risk of thrombosis in the antiphospholipid syndrome. A systematic review. *Thromb Haemost* 2014; 111(2):354–364. doi:10.1160/TH13-06-0509
5. Miyakis S, Lockshin MD, Atsumi T, 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. doi:10.1111/j.1538-7836.2006.01753.x
6. Bertolaccini ML, Amengual O, Atsumi T, et al. 'Non-criteria' aPL tests: report of a task force and pre-conference workshop at the 13th International Congress on Antiphospholipid Antibodies, Galveston, TX, USA, April 2010. *Lupus* 2011; 20:191–205. doi:10.1177/0961203310397082
7. Fabris M, Giacomello R, Poz A, et al. The introduction of anti-phosphatidylserine/prothrombin autoantibodies in the laboratory diagnostic process of anti-phospholipid antibody syndrome: 6 months of observation. *Auto-Immunity Highlights* 2014; 5(2):63–67. doi:10.1007/s13317-014-0061-3
8. Otomo K, Atsumi T, Amengual O, et al. Efficacy of the antiphospholipid score for the diagnosis of antiphospholipid syndrome and its predictive value for thrombotic events. *Arthritis Rheum* 2012; 64(2):504–512. doi: 10.1002/art.33340
9. Sciascia S, Sanna G, Murru V, Roccatello D, Khamashta MA, Bertolaccini ML. GAPSS: the Global Anti-Phospholipid Syndrome Score. *Rheumatology (Oxford)* 2013; 52(8):1397–1403. doi:10.1093/rheumatology/kes388

doi:10.3949/ccjm.85c.06001

**IN REPLY:** We appreciate the response of Drs. Maharaj, Chang, and Shaikh. Antiphospholipid antibody testing and the diagnosis of antiphospholipid antibody syndrome are quite complex. We recognize that there is controversy with regard to the role of antiphosphatidylserine (aPS) antibodies, antiprothrombin antibodies, (aPT-A), and antibodies to the antiphosphatidylserine-prothrombin complex (aPS/PT).

In the systematic review cited, the authors concluded that measurement of aPS/PT may be helpful in determining the thrombotic risk in a subset of patients with prior thrombosis and systemic lupus erythematosus (SLE).<sup>1</sup> However, the majority of the studies

included in the systematic review enrolled patients with antiphospholipid antibody syndrome and SLE. Our patient did not have SLE. Additionally, most of the studies were small. Therefore, the independent association between aPS/PT and thrombosis in patients without known SLE or previously known antiphospholipid antibody syndrome is challenging to infer on the basis of available data.<sup>1</sup>

At our institution, we do not routinely test for these “non-criteria” antibodies as part of our evaluation of suspected antiphospholipid antibody syndrome. However, we agree that this is an area that warrants further investigation. There is a need for prospective trials or, more likely, longitudinal observational studies to further delineate the association of aPT-A, aPS, or aPS/PT with clinical features of antiphospholipid antibody syndrome.<sup>2</sup>

MAYA SERHAL, MD  
Department of Cardiovascular Medicine  
Cleveland Clinic

HEATHER GORNIK, MD, RVT, RPVI  
Department of Cardiovascular Medicine  
Cleveland Clinic

NATALIE EVANS, MD, RPVI  
Department of Cardiovascular Medicine  
Cleveland Clinic

#### REFERENCES

1. Sciascia S, Sanna G, Murru V, Roccatello D, Khamashta MA, Bertolaccini ML. Anti-prothrombin (aPT) and anti-phosphatidylserine/prothrombin (aPS/PT) antibodies and the risk of thrombosis in the antiphospholipid syndrome. A systematic review. *Thromb Haemost* 2014; 111(2):354–364. doi:10.1160/TH13-06-0509
2. Miyakis S, Lockshin MD, Atsumi T 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. doi:10.1111/j.1538-7836.2006.01753.x

doi:10.3949/ccjm.85c.06002