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EDITORIAL OPEN ACCESS

Triple positive and seronegative antiphospholipid syndrome: The same disorder?

Gary W. Moore

Antiphospholipid syndrome (APS) is an autoimmune disorder defined by vascular thrombosis or pregnancy morbidity in the presence of persistent antiphospholipid antibodies (aPL) [1]. The main clinical features are commonly encountered in clinical practice and are non-specific for APS, the diagnosis thus being reliant on accurate and timely detection of aPL [2]. The three criteria aPL for APS diagnosis are lupus anticoagulants (LA), which are detected in blood coagulation assays [3], and IgG/IgM anticardiolipin antibodies (aCL) and IgG/IgM anti-β_2 glycoprotein I antibodies (aβ_2GPI), which are detected in solid-phase assays [4]. The 2006 APS classification criteria indicate that persistent positivity with one or more assays for these antibodies is sufficient to fulfill serological diagnostic criteria [1]. Antibody persistence is evidenced by repeating aPL analysis on new blood samples no less than 12 weeks (or more than five years) from the time of initial detection. More recently, several studies have concluded that thrombotic risk increases with the number of positive aPL assays, and that positivity for all three of LA, aCL and aβ_2GPI, so-called triple positivity, confers the highest risk for thromboembolic events and their recurrence, and pregnancy loss [2, 5, 6].

An important potential complication in APS diagnosis is incomplete standardization of the coagulation and solid-phase assays employed to detect the criteria aPL [3, 4], which leads to low sensitivity and diagnostic inconsistency [2]. Furthermore, non-pathogenic aPL sub-types can manifest in the assays and there is a risk of misdiagnosing APS in patients with just one positive test if the epitope specificity is unrelated to the syndrome [2]. These antibodies tend to be epiphenomenal to other clinical states and transient, hence the requirement to evidence persistence. For instance, the clinical signs and symptoms of APS are not present in all patients who are positive in aβ_2GPI assays because only the antibodies with specificity for Domain 1 of β_2GPI (aDm1) are associated with the clinical manifestations of APS [7, 8]. Thus, detection of aβ_2GPI in a patient who is negative for LA and aCL may not be sufficient to accurately diagnose APS. Evidence is accumulating to indicate that triple-positivity is due to the presence of antibodies directed to a limited epitope on Domain I of β_2GPI [8, 9] and that they are indeed pathogenic [7, 8]. So compelling is the evidence that it has been proposed to only consider patients positive for all three criteria aPL as having definite APS, and that repeat analysis to confirm persistence of such antibodies is unnecessary [10]. At first sight this seems entirely logical because of the proven higher risk of thrombosis and recurrence, and pregnancy morbidity, and that triple positive patients tend to have higher aPL titres. However, this is not necessarily the entire picture. Whilst double positivity does appear to confer lower risk, and single positivity little or no risk, there are patients with proven thrombosis or pregnancy loss who present with such aPL profiles. Some will have experienced their non-specific clinical presentations for reasons other than APS despite the presence of what are usually low-titre aPL, although low-titre aCL and/or aβ_2GPI positivity may be relevant to obstetric but not thrombotic APS. It is possible, however, that some of these patients are unrecognized triple positives because of the well documented inter-assay and inter-laboratory variability [3, 4], such that a patient triple positive in one laboratory could be classified differently in another purely as a function of the reagents, analytical equipment, cut-off generation and interpretation strategies employed locally [3, 4, 11, 12]. The higher titres found in triple positive patients make it unlikely this is the only explanation, an alternative being

Gary W. Moore

Affiliation: Consultant Biomedical Scientist, Department of Haemostasis and Thrombosis, Viapath Analytics at Guy's and St. Thomas' Hospitals, London, United Kingdom.

Corresponding Author: Dr. Gary W. Moore, Department of Haemostasis and Thrombosis, Viapath Analytics, St. Thomas' Hospital Westminster Bridge Road, London, United Kingdom, SE1 7EH; Email: gary.moore@viapath.co.uk

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that aDm1 are not the only relevant antibodies. This is partly borne out by recent studies showing that not all symptomatic patients positive for LA, aCL and aβ_2GPI are also positive for aDm1 [9, 13]. The same studies also reveal aDm1 in some double positive patients. Antibody heterogeneity amongst aDm1 could be the cause of some of the negative results, but what is the evidence for other antibodies being relevant to APS?

Pathogenic aPL are, in fact, directed against protein epitopes combined to phospholipids not phospholipids themselves [14], although antibodies directed against phospholipids and other proteins also occur. Whilst β_2GPI is accepted as the dominant antigen, numerous other antigenic targets have been identified, many accompanied by plausible theories of pathogenic mechanisms, such as prothrombin, protein C, protein S, annexin A5, annexin 2, and vimentin [14–16]. The association between APS and antibodies to prothrombin, detected in solid phase assays with purified prothrombin (aPT) or the phosphatidylserine/prothrombin complex (aPS/PT) as antigen, has been investigated with initially conflicting conclusions [17]. More recent evidence attests to the clinical utility of aPS/PT in the diagnosis of APS, suggesting they are an independent risk factor for thrombosis and can identify APS in patients negative for the three criteria antibodies [17, 18]. Studies investigating wider antibody profiles have shown that triple positivity for LA, aβ_2GPI and aPS/PT has the best diagnostic accuracy for APS [17, 18]. Inclusion of aPS/PT in the pantheon of APS criteria assays seems imminent. Evidence continues to build for other antibody specificities being clinically significant, and also, IgA isotypes of aCL and aβ_2GPI, leading to suggestions that patients displaying clinical features of APS who are negative for current criteria antibodies should undergo second-line testing for non-criteria biomarkers [15, 19, 20]. This growing body of evidence provides an immediate potential explanation for the apparently contradictory term of seronegative APS, which in reality may well translate to current criteria antibody-negative APS, or perhaps more specifically, aDm1-negative APS?

Some symptomatic patients apparently single or double positive may be no more than victims of inter-assay/inter-laboratory variability, whilst some triple positive/aDm1-negative patients may be so due to heterogeneity within that antibody sub-population [21]. Triple positivity and potential explanations for not demonstrating it in a given patient centre on aDm1 being the only relevant antibodies. The array of other recognized antigenic targets, some accompanied by studies indicating strong associations with clinical criteria for APS, suggest that it may be too early to assign aDm1 as the exclusive culprit in APS [22].

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REFERENCES

1. 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 Feb;4(2):295–306.
2. Pengo V, Ruffatti A, Legnani C, et al. Clinical course of high-risk patients diagnosed with antiphospholipid syndrome. J Thromb Haemost 2010 Feb;8(2):237–42.
3. Moore GW. Recent guidelines and recommendations for laboratory detection of lupus anticoagulants. Semin Thromb Hemost 2014 Mar;40(2):163–71.
4. Favaloro EJ. Variability and diagnostic utility of antiphospholipid antibodies including lupus anticoagulants. Int J Lab Hematol 2013 Jun;35(3):269–74.
5. Ruffatti A, Tonello M, Cavazzana A, Bagatella P, Pengo V. Laboratory classification categories and pregnancy outcome in patients with primary antiphospholipid syndrome prescribed antithrombotic therapy. Thromb Res 2009;123(3):482–7.
6. Yelnik CM, Urbanski G, Drumez E, et al. Persistent triple antiphospholipid antibody positivity as a strong risk factor of first thrombosis, in a long-term follow-up study of patients without history of thrombosis or obstetrical morbidity. Lupus 2016 Jul 17.
7. de Laat B, Derksen RH, van Lummel M, Pennings MT, de Groot PG. Pathogenic anti-beta2-glycoprotein I antibodies recognize domain I of beta2-glycoprotein I only after a conformational change. Blood 2006 Mar 1;107(5):1916–24.
8. de Groot PG, Urbanus RT. The significance of autoantibodies against ß2-glycoprotein I. Blood 2012 Jul 12;120(2):266–74.

9. Iwaniec T, Kaczor MP, Celinska-Löwenhoff M, Polanski S, Musial J. Clinical significance of anti-domain 1 ß2-glycoprotein I antibodies in antiphospholipid syndrome. Thromb Res 2017 May;153:90–4.
10. Pengo V, Banzato A, Denas G, et al. Correct laboratory approach to APS diagnosis and monitoring. Autoimmun Rev 2013 Jun;12(8):832–4.
11. Moore GW, Maloney JC, de Jager N, et al. Application of different lupus anticoagulant diagnostic algorithms to the same assay data leads to interpretive discrepancies in some samples. Res Pract Thromb Haemost 2017;1:62–8.
12. Vanoverschelde L, Kelchtermans H, Musial J, de Laat B, Devreese K. Influence of the statistical approach on cut-off values of IgG/IgM anticardiolipin and anti-ß2-glycoprotein I antibodies in classification of antiphospholipid syndrome. Res Pract Thromb Haemost 2017;1 Suppl 1;588–90.
13. De Craemer AS, Musial J, Devreese KM. Role of anti-domain 1-ß2 glycoprotein I antibodies in the diagnosis and risk stratification of antiphospholipid syndrome. J Thromb Haemost 2016 Sep;14(9):1779–87.
14. Rand JH. Molecular pathogenesis of the antiphospholipid syndrome. Circ Res 2002 Jan 11;90(1):29–37.
15. Zohoury N, Bertolaccini ML, Rodriguez-Garcia JL, et al. Closing the serological gap in the antiphospholipid syndrome: The value of "non-criteria" antiphospholipid antibodies. J Rheumatol 2017 Nov;44(11):1597–602.
16. Sciascia S, Baldovino S, Schreiber K, et al. Thrombotic risk assessment in antiphospholipid syndrome: The role of new antibody specificities and thrombin generation assay. Clin Mol Allergy 2016 Jul 15;14:6.
17. Sciascia S, Bertolaccini ML. Antibodies to phosphatidylserine/prothrombin complex and the antiphospholipid syndrome. Lupus 2014 Oct;23(12):1309–12.
18. Forastiero R. Multiple antiphospholipid antibodies positivity and antiphospholipid syndrome criteria re-evaluation. Lupus 2014 Oct;23(12):1252–4.
19. Radin M, Cecchi I, Pérez-Sánchez C. Antiphospholipid antibodies negativization: Time for testing for non-criteria aPL? Lupus 2017 Nov;26(13):1457–8.
20. Conti F, Capozzi A, Truglia S, et al. The mosaic of "seronegative" antiphospholipid syndrome. J Immunol Res 2014;2014:389601.
21. de Moerloose P, Fickentscher C, Boehlen F, Tiercy JM, Kruithof EKO, Brandt KJ. Patient-derived anti-ß2GP1 antibodies recognize a peptide motif pattern and not a specific sequence of residues. Haematologica 2017 Aug;102(8):1324–32.
22. Lackner KJ, Müller-Calleja N. Pathogenesis of the antiphospholipid syndrome revisited: Time to challenge the dogma. J Thromb Haemost 2016 Jun;14(6):1117–20.

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