

Microangiopathic Antiphospholipid-Associated Syndromes Revisited — New Concepts Relating to Antiphospholipid Antibodies and Syndromes

In a recent issue of *Annals of the Rheumatic Diseases*¹ we proposed a case for a “microangiopathic antiphospholipid syndrome” (MAPS) encompassing several conditions mainly affecting the microvasculature of selected organs: the liver in the HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet count); kidney, brain, and skin in thrombotic thrombocytopenic purpura (TTP) and related syndromes; the bowel where it is predominant in patients with catastrophic antiphospholipid syndrome (CAPS, Asherson’s syndrome) in whom no large-vessel occlusions are manifest (approximately 70%) and in patients with disseminated intravascular coagulation (DIC) whatever the cause (usually sepsis) who might also demonstrate antiphospholipid antibody (aPL) positivity. It was our intention initially to include those patients who might also demonstrate evidence of a microangiopathic hemolytic process (and in whom schistocytes might be demonstrable) as well as those patients who, in addition to demonstrating aPL positivity, did not demonstrate large-vessel occlusions so typical of classic APS. Moreover, we have since analyzed a small group of patients with relapsing CAPS² who resemble TTP and are thus “TTP-like” and have concluded that a group of patients may exist in whom the presence of aPL positivity might not imply that they are in fact pathogenic but that their appearance might be consequent on endothelial cell damage/injury. Pulmonary hypertension (PHT) is one of these conditions and will be discussed further. Infection-induced aPL may also be included, but a detailed discussion of this topic is beyond the scope of this editorial. A minority only of infections with aPL positivity may be accompanied by manifestation of the APS. This might be because of individual susceptibility to form aPL (? genetic) and, perhaps, only certain of the antibody populations primarily induced may be pathogenic, affecting coagulation factors, and cells leading to large-vessel occlusions, thrombocytopenia, etc.

It may therefore now be necessary to modify our original concept of MAPS¹ to mean *microangiopathic antiphospholipid-associated syndromes*. It is important to add the qualification of “associated.” These microangiopathic antiphospholipid-associated syndromes would comprise those situations where the aPL do not appear to be initially pathogenic and do not seem to alter the clinical manifestations of the basic syndromes. Our concept of MAPS is that it is separate

from the microvascular occlusions that often form part of the APS itself. This explanation and modification might lead to a better understanding of our hypothesis, given the old adage that “nothing in medicine ever turns out to be simple.”

The differential diagnosis between patients with CAPS and those with sepsis and aPL positivity may indeed cause major problems in intensive care units and has recently been emphasized in an editorial by Espinosa, *et al*³. Although no data are available on the frequency of aPL in patients with sepsis, studies are now being planned to address this particular problem.

The APS today, some 20 years later, remains an enigma. The original definition of the syndrome, primarily suggested by the group at the Hammersmith Hospital⁴, has been greatly expanded and covered in detail in several publications^{5,6}.

In 2007, an expanded concept of the APS bears little relationship to the original of venous and arterial thromboses and/or recurrent fetal losses, although these hold true. Indeed, nonthrombotic manifestations of the APS seem to assume more clinical significance and are of more interest to clinicians⁷.

There is no question as to the pathogenicity of some aPL, as has been so dramatically demonstrated in animal models by Shoenfeld and Pierangeli and their respective groups⁸⁻¹¹. The pivotal role of complement and its activation in the pathogenesis of fetal loss and thrombosis has recently also been instrumental in unravelling the mysteries of pathogenic mechanisms in APS, as shown in animal models^{12,13}. The many complex pathways involved in intracellular signalling resulting in the conversion of cells, particularly endothelial, to a prothrombotic state, as reported by Meroni¹⁴ and Pierangeli, *et al*¹⁵⁻²⁰, has also led us to a greater understanding of the actions of the aPL. The influence of these antibodies on monocytes²¹⁻²⁴ as well as on platelets is now also well described²⁵. It is also known that aPL are heterogeneous in function and in specificity and that more than one type may be present in any individual with APS. It is clear then that APS is a multiorgan-multisystem disease with multiple possible clinical manifestations.

The outstanding contributions made by the aforementioned investigators have added important pieces to the aPL jigsaw puzzle. However, for us as clinicians, because of the

ubiquity of these antibodies, occurring in up to 8% of healthy subjects in some studies²⁶, classification difficulties constantly arise as evidenced by guidelines proposed at the 11th International Congress on Antiphospholipid Antibodies held in Sydney 2 years ago²⁷. Recently, Joan Merrill admirably addressed the basic problem of why aPL exist normally and are even beneficial to host defences, and why, in patients with APS, they become pathological²⁸. A recent editorial attempted to differentiate conditions associated with aPL positivity into thrombotic and nonthrombotic subsets⁷, emphasizing that, in certain inaccessible organs where histopathological or radiological techniques are unable to provide answers, microthrombosis cannot be proven or disproven. This applies particularly to central nervous system tissues, e.g., brain or spinal cord (as in chorea, cognitive dysfunction, presumed microvascular ischemia with a clinical picture resembling multiple sclerosis in some, or transverse myelitis), or bone (as in osteonecrosis).

We know that histopathologically proven small-vessel occlusions (e.g., involving mainly renal, retinal, and skin vessels) occur in simple or classic APS. CAPS includes the condition of small-vessel occlusions that occur mainly in intraabdominal vessels (kidneys, liver, spleen, gut) causing extensive tissue necrosis resulting in the systemic inflammatory response syndrome with its major accompaniment of acute respiratory distress syndrome and multiorgan failure. It is assumed that in the HELLP syndrome, as well as TTP and DIC, there is major endothelial dysfunction. More importantly, there are virtually no large-vessel occlusions in patients with HELLP syndrome and a total absence of large-vessel occlusions in TTP, even in the minority of those patients who demonstrate aPL. In the HELLP syndrome, hepatic infarctions are not uncommonly documented, and are undoubtedly due to small-vessel perturbation²⁹.

We also suggest including in a broader subset of MAPS PHT associated with connective tissue disorders accompanied by elevations of aPL and with other possible autoimmune components³⁰⁻³⁵. Regarding infections, there may also be an added immunological disturbance associated with (e.g., in HIV infection) a reduction in Treg cells³⁵. There is also a greatly increased frequency of PHT in patients with HIV infection. Interestingly, this same disturbance can be seen in selected patients with PHT, where its occurrence in patients with a mutation of the *AIRE* gene is well documented³⁶. This gene is found on chromosome 21 and is denoted as the autoimmune regulator gene. In PHT there is therefore a combination of both endothelial and immunological mechanisms.

In the large series of PHT documented in 1988³⁷, we were struck that patients with the highest titers of aPL had no other manifestations of the APS. Additionally, in the recent French study of a 10-year followup of patients with systemic sclerosis and PHT³⁸, the authors found no relationship of PHT to levels of aPL. Correlations were possible

with von Willebrand factor antigen estimations, again suggesting major endothelial disturbances. The remarkable recent case report of a patient with Ehlers-Danlos syndrome with complicating dissection of the renal arteries and transient high levels of aPL during the acute phase only³⁹ again draws one to the conclusion that aPL can be produced by exposure of phospholipid occurring during cellular damage to the endothelial system, apoptosis, and consequent secondary production of aPL. Might some of the aPL produced in this way be pathogenic and then lead to disturbances of coagulation with resulting large-vessel occlusions? An intriguing hypothesis indeed.

CONCLUSION

Our current proposal is that the broad term MAPS be taken to mean microangiopathic aPL-associated syndromes. By adding the term "associated," we would emphasize that the majority of conditions included in this category probably do not form part and parcel of the APS. CAPS with large-vessel occlusions may represent an "overlap" situation with the APS, the population of aPL induced initially by endothelial cell damage then secondarily affecting phospholipid-dependent coagulation systems as in the APS itself.

It may be important for clinicians to note that in these conditions therapy needs to be directed towards the underlying condition and not to the presence of the aPL, unless there are complicating large-vessel occlusions, as in some patients with CAPS.

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REFERENCES

1. Asherson RA, Pierangeli S, Cervera R. Is there a microangiopathic antiphospholipid syndrome? *Ann Rheum Dis* 2007;66:429-32.
2. Asherson RA, Menahem S, Vinh J, Bucciarelli S, Espinosa G, Cervera R. Relapsing catastrophic antiphospholipid syndrome 2007. *Semin Arthritis Rheum* 2007; (submitted).
3. Espinosa G, Cervera R, Asherson RA. Catastrophic antiphospholipid syndrome and sepsis. A common link? *J Rheumatol* 2007;34:923-6.
4. Harris EN, Baguley E, Asherson RA, Hughes GRV. Clinical and serological features of the antiphospholipid syndrome (APS) [abstract]. *Br J Rheumatol* 1987;26 Suppl 2:19.
5. Asherson RA, Cervera R. The antiphospholipid syndrome: a

- syndrome in evolution. *Ann Rheum Dis* 1992;5:147-50.
6. Asherson RA, Cervera R, The antiphospholipid syndrome: multiple faces beyond the classical presentation. *Autoimmun Rev* 2003;3:140-51.
 7. Asherson RA, Cervera R, Shepshelovich D, Shoenfeld Y. Nonthrombotic manifestations of the antiphospholipid syndrome: Away from thrombosis? [editorial]. *J Rheumatol* 2006;33:1038-44
 8. Bakimer R, Fishman P, Blank M, Sredni B, Djaldetti M, Shoenfeld Y. Immunization with a human monoclonal antibody (H-3). *J Clin Invest* 1992;89:1558-63.
 9. Branch DW, Dudley DJ, Mitchell MD, et al. Immunoglobulin G fractions from patients with antiphospholipid antibodies cause fetal death in BALB/c mice: a model for autoimmune fetal loss. *Am J Obstet Gynecol* 1990;163:210-6.
 10. Pierangeli SS, Colden-Stanfield M, Liu X, Barker JH, Anderson GH, Harris EN. Antiphospholipid antibodies from antiphospholipid syndrome patients activate endothelial cells in vitro and in vivo. *Circulation* 1999;99:1997-2000.
 11. Jankowski M, Vreys I, Wittevrongel C, et al. Thrombogenicity of beta-2-glycoprotein I-dependent antiphospholipid antibodies in a photochemically induced thrombosis model in the hamster. *Blood* 2003;101:157-62.
 12. Pierangeli SS, Girardi G, Vega-Ostertag ME, Liu X, Espinola RG, Salmon J. Requirement of activation of complement C3 and C5 for antiphospholipid antibody-mediated thrombophilia. *Arthritis Rheum* 2005;52:2120-24.
 13. Salmon JE, Girardi G, Holers VM. Activation of complement mediates antiphospholipid antibody-induced pregnancy loss. *Lupus* 2003;12:535-8.
 14. Meroni PL, Raschi C, Testoni C, Borghi MO. Endothelial cell activation by antiphospholipid antibodies. *Clin Immunol* 2004;112:169-74.
 15. Pierangeli SS, Liu X, Espinola R, et al. Functional analyses of patient-derived IgG monoclonal anticardiolipin antibodies using in vivo thrombosis and in vivo microcirculation models. *Thromb Haemost* 2000;84:388-95.
 16. Pierangeli SS, Espinola RG, Liu X, Harris EN. Thrombogenic effects of antiphospholipid antibodies are mediated by intercellular cell adhesion molecule-1, vascular cell adhesion molecule-1, and P selectin. *Circ Res* 2001;88:245-50.
 17. Espinola RG, Liu X, Colden-Stanfield M, Hall J, Harris EN, Pierangeli SS. E-selectin mediated pathogenic effects of antiphospholipid antibodies. *J Thromb Haemost* 2002;1:843-8.
 18. Gharavi AE, Pierangeli SS, Colden-Stanfield M, Liu X, Espinola RG, Harris EN. GDKV-induced antiphospholipid antibodies enhance thrombosis and activate endothelial cells in vivo and in vitro. *J Immunol* 1999;163:2922-7.
 19. Simantov E, LaSala J, Lo SK, et al. Activation of cultured vascular endothelial cells by antiphospholipid antibodies. *J Clin Invest* 1995;96:2211-9.
 20. Del Papa N, Guidali L, Sala A, et al. Endothelial cells as target for antiphospholipid antibodies. Human polyclonal and monoclonal anti-beta-2-glycoprotein I antibodies react in vitro with endothelial cells through adherent beta-2-glycoprotein I and induce endothelial cell activation. *Arthritis Rheum* 1997;40:551-61.
 21. Zhou H, Woldberg AS, Roubey RA. Characterization of monocyte tissue factor activity induced by IgG antiphospholipid antibodies and inhibition by dilazep. *Blood* 2004;104:2353-8.
 22. Vega-Ostertag M, Casper K, Swerlick R, Ferrara D, Harris EN, Pierangeli SS. Involvement of p38 MAPK in the up-regulation of tissue factor on endothelial cells by antiphospholipid antibodies. *Arthritis Rheum* 2005;52:1545-54.
 23. Bohgaki M, Atsumi T, Yamashita Y, et al. The p38 mitogen-activated protein kinase (MAPK) pathway mediates induction of the tissue factor gene in monocytes stimulated with human monoclonal anti-beta-2-glycoprotein I antibodies. *Int Immunol* 2004;16:1632-41.
 24. Lopez-Pedreria C, Buendia P, Cuadrado MJ, et al. Antiphospholipid antibodies from patients with the antiphospholipid syndrome induce monocyte tissue factor expression through the activation of NF kappa-B/rel proteins via the P38 mitogen activated protein kinase pathway and of the MEK/ERK pathway. *Arthritis Rheum* 2006;54:201-11.
 25. Vega-Ostertag ME, Harris EN, Pierangeli SS. Intracellular events in platelet activation induced by antiphospholipid antibodies in the presence of low doses of thrombin. *Arthritis Rheum* 2004;50:2911-9.
 26. Petri M. Epidemiology of the antiphospholipid syndrome. In: Asherson RA, Cervera R, Piette J-C, Shoenfeld Y, editors. *The antiphospholipid syndrome*. Amsterdam: Elsevier; 1996:13-27.
 27. Miyakis S, Lockshin MH, Atsumi T, et al. International consensus statement on an update of the international classification for definite antiphospholipid syndrome (APS). *J Thromb Haemost* 2006;4:295-306.
 28. Merrill JT. Do antiphospholipid antibodies develop for a purpose? *Curr Rheumatol Rep* 2006;8:159-61.
 29. Le Thi Thuong D, Tieulie N, Costedoat N, et al. The HELLP syndrome in the antiphospholipid syndrome: retrospective study of 16 cases in 15 women. *Ann Rheum Dis* 2005;64:273-8.
 30. Cervera R, Asherson RA. Primary pulmonary arterial hypertension and the systemic autoimmune diseases. *Israel Med Assoc J* 2006;8:277-9.
 31. Rich S, Kieras K, Hart K, Groves BM, Stobo JD, Brundage BH. Primary pulmonary hypertension. *J Am Coll Cardiol* 1986;8:1307-11.
 32. Holt PJ, Clague RB, Hay FC, Nineham IJ, Wade EG. Is idiopathic pulmonary hypertension a connective tissue disorder [abstract]. *Arthritis Rheum* 1980;23 Suppl:690.
 33. Karmochkine M, Cacoub P, Dorent R, et al. High prevalence of antiphospholipid antibodies in precapillary pulmonary hypertension. *J Rheumatol* 1996;23:286-90.
 34. Vanai-Landau H, Amital H, Bar-Dayana Y, et al. Autoimmune aspects of primary pulmonary hypertension. *J Pathobiol* 1995;63:71-5.
 35. Pellicelli AM, D'Ambrosio C, Vizza CD, et al. HIV-related pulmonary hypertension. From pathogenesis to clinical aspects. *Acta Cardiol* 2004;59:323-30.
 36. Korniszewski L, Kurzyna M, Stolarski B, Torbicki A, Smerdel A, Ploski R. Fatal primary pulmonary hypertension in a 30-yr-old female with APECED syndrome. *Eur Respir J* 2003;29:702-22.
 37. Asherson RA, Higgenbottam TW, Dinh Xuan AT, Khamashta MA, Hughes GRV. Pulmonary hypertension in a lupus clinic: experience with twenty four patients. *J Rheumatol* 1990;17:1292-6.
 38. Assous N, Allanore Y, Batteux F, et al. Prevalence of antiphospholipid antibodies in systemic sclerosis and association with primitive pulmonary arterial hypertension and endothelial injury. *Clin Exp Rheumatol* 2005;23:199-204.
 39. Asherson RA, Bosman C, Tikly M, Spiro F, Pope FM. Ehlers-Danlos syndrome in a young man. *J Rheumatol* 2006;33:2091-6.