

# Are Anti-Phospholipid Syndrome and Systemic Lupus Erythematosus Two Different Diseases? A 10-Year Late Remake

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**KEY WORDS:** antiphospholipid antibodies, antiphospholipid syndrome, systemic lupus erythematosus (SLE), autoantibodies, T cells

IMAJ 2018; 20: 491–493

Recurrent thrombosis and miscarriages have been reported in patients with systemic lupus erythematosus (SLE) who test positive for lupus anticoagulant (LA) [1]. LA was later found to be caused by antiphospholipid antibodies (aPL) that are detectable by more sensitive solid phase assays (anticardiolipin [aCL] and anti-beta2-glycoprotein I [ $\beta$ 2GPI]) [2]. Positive aPL assays and recurrent thrombosis and/or miscarriages are diagnostic/classification criteria for the so-called antiphospholipid syndrome (APS) [3]. aPL positivity can be found in up to 40% of SLE patients, among whom the full-blown APS is frequent [4].

Some APS patients exhibited no features of underlying connective tissue disease and the concept emerged that APS could exist as a primary syndrome. Nevertheless, SLE and APS are still commonly perceived as two closely related diseases [4,5]. Shoenfeld and colleagues [3] discussed this issue 10 years ago and raised concerns about the proximity between primary APS (PAPS) and SLE. In the present editorial, we

address the same point because of the progress of our knowledge in the field.

## PRIMARY ANTIPHOSPHOLIPID SYNDROME AND SYSTEMIC LUPUS ERYTHEMATOSUS: STILL TWO DISTINCT CLINICAL ENTITIES

Multiple pathogenic pathways involving both innate and adaptive immunity responses operate in patients with SLE. The heterogeneity of the pathogenesis in SLE justifies the multifaceted clinical expression of the disease [6-9]. However, an autoantibody-mediated coagulopathy does represent the pathogenic mechanism responsible for the main clinical manifestations of APS, which are recurrent arterial/venous thrombosis and miscarriages [2,10].

Thrombosis at the placental level was originally thought to also be the cause of recurrent miscarriages associated to APS; however, recent studies have shown that direct damage mediated by aPL rather than clotting is involved [10,11]. Comparable direct aPL-mediated damage is now an accepted explanation in additional clinical manifestations that do not seem to be related to abnormal clotting such as thrombocytopenia, APS nephropathy, and cognitive abnormalities [2,12]. Such clinical manifestations are making the clinical picture of APS much more heterogenous than initially expected, and in some ways are still marking the proximity between SLE and PAPS. However, as stated by Shoenfeld and co-authors [3], there are clear differences that have been further clarified in the last years [Table 1].

## THE MARCH FROM PRIMARY ANTIPHOSPHOLIPID SYNDROME TO SYSTEMIC LUPUS ERYTHEMATOSUS: GENETIC STUDIES ARE AGAINST IT

The reports of patients initially diagnosed with PAPS that subsequently evolved into full blown SLE or lupus-like disease over time suggested that APS may be just a variant of SLE. However, larger studies conducted over a longer follow-up period demonstrated that the proportion of such patients is small (10–15% of patients) [5,13].

Recent genetic studies using large-scale, case control, candidate gene studies as well as genome-wide association studies have identified more than 30 robust genetic associations with SLE including genetic variants of human leukocyte antigen and Fc $\gamma$  receptor genes as well as IRF5, STAT4, PTPN22, TNFAIP3, BLK, BANK1, TNFSF4, and ITGAM genes [14]. We reported that PAPS displays a strong genetic association with STAT4, BLK, and IRF5 (rs2070197) but not with other IRF5 single nucleotide polymorphisms (rs10954213 and rs2004640) and BANK1 [15,16]. This finding further supports the differences between PAPS and SLE from a genetic point of view and explains why PAPS cannot be eventually considered as a preliminary step towards SLE.

## SIMILAR SEROLOGY BUT WITH DIFFERENCES

PAPS was originally described as a condition characterized by the vascular and/or obstetric manifestations and the persistent positivity for medium/high titer of aPL with

**Table 1.** The main clinical similarities and differences with regard to manifestations between systemic lupus erythematosus and primary anti-phospholipid syndrome

Clinical manifestations	Similarities and differences
Thrombocytopenia	Usually mild
Haemolytic anemia/Coombs' test positivity	
Heart valve disease	Additional risk for secondary thromboembolism in APS
Myocardial Infarction	In the absence of traditional risk factors
Cardiomyopathy	Likely linked to microangiopathy rather than to myocarditis
Livedo reticularis	
Ulcers	Likely linked to microangiopathy rather than to true vasculitis
Renal artery stenosis	Linked to thrombosis
Renal venous thrombosis	
APS nephropathy (APSN)	A vasculopathy rather than immune vasculitis is playing a role at variance of lupus kidney involvement
Migraine/headache	Controversial association
Epilepsy	In many but not all cases secondary to ischemic events; conflicting data on the relationship between aPL and seizure in SLE because of the association of seizure with lupus itself
Multiple sclerosis-like disease	
Cognitive impairment	Frequent, but controversial association
Dementia	Resulting from chronic or recurrent ischemic events
Ocular manifestations	Amaurosis fugax; retinal vessels thrombosis (arteries and veins)
Transverse myelopathy	Strong correlation with aPL in SLE patients
Pulmonary alveolar hemorrhage	Very rare
Pleural effusion	Pulmonary embolism may be responsible for effusion

aPL = antiphospholipid-binding proteins, APS = anti-phospholipid syndrome, SLE = systemic lupus erythematosus

no other serological markers [1]. However, several studies reported that a serological lupus signature can be found even in PAPS patients, including the positivity for high titer ANA with specificity for nucleosome and dsDNA antigens [2,7]. The main difference with SLE was the presence of low titers of anti-dsDNA at variance with what we have found, particularly in active lupus patients [2]. However, anti-Sm antibodies are not commonly detectable in PAPS, and other anti-extractable nuclear antigens specificities were also not frequently noted.

Circulating immune complexes (CIC) are the hallmark of SLE and represent one of the main pathogenic mechanisms for tissue damage [17]. Although some studies reported the presence of CIC in PAPS, their prevalence was low and their pathogenic role did not seem to be crucial [12].

As for CIC, complement activation is widely accepted to be a feature of lupus [11]. In addition, the lack of early components of the cascade are associated with

autoantigen overload (e.g., apoptotic materials) to the afferent limb of the immune response resulting in susceptibility to systemic autoimmunity [17]. The message that complement activation plays a key role in APS came from animal models of the syndrome in which a complement blockade was shown to protect animals from both aPL-mediated thrombosis and fetal loss [20]. Such strong evidence in animals has not yet been supported by comparable evidence in patients, in whom the evidence of complement activation can be found at least in acute thrombotic events and even at the placental levels but much sounder data are needed [20].

It is generally accepted that antibodies against  $\beta$ 2GPI are the true diagnostic/prognostic aPL and more recently the epitope specificity of these autoantibodies was shown to display additional diagnostic/prognostic value [21]. In particular, the reactivity against domain 1(D1) is significantly associated with the clinical manifesta-

tions and the double/triple positivity for aPL assays in contrast to antibodies against D4 or 5 [21-23]. Accordingly, the ratio between anti-D1/D4,5 was suggested to represent a tool for ranking the risk for APS clinical manifestations, being a high ratio associated with higher risk and a low ratio with lower one [22,23].  $\beta$ 2GPI epitope specificity does not seem to be different in PAPS and in SLE with APS or aPL positivity.

#### T CELL BIOLOGY MAKES ANOTHER DIFFERENCE

Aberrant T cell activation pathways in SLE plays a critical role in addition to the tissue damage mediated by immune complex deposition [24]. Molecular characterization of T cell-dependent pathways was suggested to be critical for personalized medicine and to overcome the troubles in clinical trials, in which the heterogeneity of the patients is a problem. In fact, common biomarkers are not strong enough to enroll homogenous series of patients and/or to evaluate of the efficacy of the therapy. This finding was thought to represent a critical point that may affect the chances of positive results in the clinical trials [25].

In contrast, APS is a well-characterized autoantibody-mediated disease but few studies have addressed T cell response against the main APS autoantigens, such as  $\beta$ 2GPI [26]. More recently, T cell clones specific for  $\beta$ 2GPI were identified in the infiltrate of atherosclerotic plaques from both PAPS and APS associated with SLE [27,28]. Interestingly, T cell clones from PAPS and APS-SLE plaques displayed a Th1 phenotype but many more Th17 clones could be identified in atherosclerotic plaques from APS-SLE than from PAPS. Such a difference was suggested to be related to the systemic pro-inflammatory profile in SLE that it is absent in PAPS [29].

Another paper recently underlined the difference between T follicular helper ( $T_{FH}$ ) cells in SLE and in PAPS.  $T_{FH}$  cells are an integral part of the immunity against non-self antigens but they take part in autoantibody production as well.  $T_{FH}$  cells respond to extracellular ATP (eATP) via P2X purinoreceptor 7 (P2X7) signaling, which

triggers death pathways. In the absence of such a checkpoint, T<sub>HF</sub> cells can provide exaggerated autoantibody help. Faliti et al. [20] reported defective P2X7-mediated T<sub>HF</sub> regulation both in lupus animal model (the pristane-induced SLE) and in SLE patients. Using a control group, the authors investigated T<sub>HF</sub> cells from PAPS patients. They found that PAPS T<sub>HF</sub> cells are comparable to normal healthy cells further differentiating the T cell biology in SLE and PAPS.

## CONCLUSIONS

The differences between PAPS and SLE are much more tangible than the similarities. This is true not only from a biological point of view but from the clinical one as well. In this regard, there is no evidence that any immunosuppressive treatment may offer advantages for the PAPS vascular manifestations over the anticoagulant/anti-platelet approach.

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## References

1. Meroni PL, Borghi MO, Raschi E, Tedesco F. Pathogenesis of antiphospholipid syndrome: understanding the antibodies. *Nat Rev Rheumatol* 2011; 7: 330-9.
2. Andreoli L, Pregnotato F, Burlingame RW, et al. Antinucleosome antibodies in primary antiphospholipid syndrome: a hint at systemic autoimmunity? *J Autoimmun* 2008; 30: 51-7.
3. Shoenfeld Y, Meroni PL, Toubi E. Antiphospholipid syndrome and systemic lupus erythematosus: are they separate entities or just clinical presentations on the same scale? *Curr Opin Rheumatol* 2009; 21: 495-500.
4. Rekvig OP. Systemic lupus erythematosus: definitions, contexts, conflicts, enigmas. *Front Immunol* 2018; 9: 387.
5. Meroni PL, Borghi MO, Grossi C, Chighizola CB, Durigutto P, Tedesco F. Obstetric and vascular antiphospholipid syndrome: same antibodies but different diseases? *Nat Rev Rheumatol* 2018; 14: 433-40.
6. Meroni PL, Chighizola CB, Rovelli F, Gerosa M. Antiphospholipid syndrome in 2014: more clinical manifestations, novel pathogenic players and emerging biomarkers. *Arthritis Res Ther* 2014; 16: 209.
7. Paule R, Morel N, Le Guern V, et al. Classification of primary antiphospholipid syndrome as systemic lupus erythematosus: Analysis of a cohort of 214 patients. *Autoimmun Rev* 2018; 17: 866-72.
8. Deng Y, Tsao BP. Updates in lupus genetics. *Curr Rheumatol Rep* 2017; 19: 68.
9. Yin H, Borghi MO, Delgado-Vega AM, Tincani A, Meroni PL, Alarcón Riquelme ME. Association of STAT4 and BLK, but not BANK1 or IRF5, with primary antiphospholipid syndrome. *Arthritis Rheum* 2009; 60: 2468-71.
10. Fredi M, Tincani A, Yin H, Delgado-Vega AM, Borghi MO, Meroni PL, Alarcón-Riquelme ME. IRF5 is associated with primary antiphospholipid syndrome, but is not a major risk factor. *Arthritis Rheum* 2010; 62: 1201-2.
11. Cook HT, Botto M. Mechanisms of disease: the complement system and the pathogenesis of systemic lupus erythematosus. *Nat Clin Pract Rheumatol* 2006; 2: 330-7.
12. Pérez D, Stojanovich L, Naranjo L, et al. Presence of immune complexes of IgG/IgM bound to B2-glycoprotein I is associated with non-criteria clinical manifestations in patients with antiphospholipid syndrome. *Front Immunol* 2018; 9:2644.
13. Tedesco F, Borghi MO, Gerosa M, et al. Pathogenic role of complement in antiphospholipid syndrome and therapeutic implications. *Front Immunol* 2018; 9: 1388.
14. Radin M, Cecchi I, Roccatello D, Meroni PL, Sciascia S. Prevalence and thrombotic risk assessment of anti-β2 glycoprotein I domain I antibodies: a systematic review. *Semin Thromb Hemost* 2018; 44: 466-74.
15. Andreoli L, Chighizola CB, Nalli C, et al. Clinical characterization of antiphospholipid syndrome by detection of IgG antibodies against β2 -glycoprotein I domain I and domain 4/5: ratio of anti-domain 1 to anti-domain 4/5 as a useful new biomarker for antiphospholipid syndrome. *Arthritis Rheumatol* 2015; 67: 2196-204.
16. Chighizola CB, Pregnotato F, Andreoli L, et al. Beyond thrombosis: anti-β2GPI domain 1 antibodies identify late pregnancy morbidity in antiphospholipid syndrome. *J Autoimmun* 2018; 90: 76-83.
17. Mizui M and Tsokos GC. Targeting regulatory T cells to treat patients with systemic lupus erythematosus. *Front Immunol* 2018; 9: 786.
18. Rauch J, Salem D, Subang R, Kuwana M, Levine JS. β2-glycoprotein I-reactive T cells in autoimmune disease. *Front Immunol* 2018; 9: 2836.
19. Benagiano M, Borghi MO, Romagnoli J, et al. Interleukin-17/Interleukin-21 and Interferon-γ producing T cells specific for β2 glycoprotein I in atherosclerosis inflammation of systemic lupus erythematosus patients with antiphospholipid syndrome. *Haematologica* 2019 Mar 14. pii: haematol.2018.209536.
20. Faliti CE, Gualtierotti R, Rottoli E, et al. P2X7 receptor restrains pathogenic Th cell generation in systemic lupus erythematosus. *J Exp Med* 2019; 216: 317-36.

## Capsule

### Hypertension-induced alarm signal

Human hypertension is a highly prevalent disease known to be associated with chronic low-grade inflammation. Zhao et al. used mouse models to look for hypertension-induced proinflammatory molecules that contribute to T cell activation and inflammation. They found consistent elevations in plasma levels of the alarmin molecule adenosine triphosphate in hypertensive mice. Increased adenosine triphosphate (ATP) concentrations promoted T cell responses by enhancing expression of the CD86 costimulatory molecule on antigen-

presenting cells, an effect mediated through the P2X7 purinergic receptor. Elevations of plasma ATP were also detected in a cohort of hypertensive human patients when compared with normotensive controls. Thus, ATP release and the ATP-P2X7 signaling axis represent potential targets to help rein in the proinflammatory sequelae associated with chronic hypertension.

*Sci Immunol* 2019; 4: eaau6426

Eitan Israeli

**“We make realities out of our dreams and dreams out of our realities. We are the dreamers of the dream”**

Roald Dahl (1916–1990), British novelist, short story writer, poet, screenwriter, and fighter pilot