

# Is there a microangiopathic antiphospholipid syndrome?

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## Revealing the evolution of the term APS and its commonalities with other microangiopathic disorders

The occurrence of small-vessel occlusions (thrombotic microangiopathy) in association with anti-phospholipid antibodies (aPL) affecting, for example, the retinal vessels,<sup>1</sup> the nail fold,<sup>2,3</sup> the skin,<sup>4</sup> or major intrabdominal organs such as the kidney, the liver or the bowel,<sup>5</sup> although uncommon, is well documented. These occlusions have been described in the simple or classic antiphospholipid syndrome (APS), whether or not associated with systemic lupus erythematosus (SLE), or in the primary APS,<sup>6</sup> but they do not in any way dominate the clinical picture in these conditions. However, with the description and definition of the catastrophic APS (also known as Asherson's syndrome) in 1992<sup>7,8</sup> (a new subset of the APS, often fatal, with many distinguishing characteristics separating it from the simple APS),<sup>9–11</sup> there has been renewed interest in the thrombotic microangiopathies and their association with aPL. Although large-vessel occlusions do occur in catastrophic APS, they do not dominate the clinical picture, and their frequency is completely different from that encountered in the classic APS itself. Additionally, the catastrophic APS is frequently accompanied by a systemic inflammatory response syndrome (SIRS).

The term thrombotic microangiopathic haemolytic anaemia (TMHA) was originally introduced by Symmers<sup>12</sup> in 1952 to describe a clinical state with localised or diffuse microvascular thrombosis in association with haemolytic anaemia and fragmented red cells referred to as schistocytes. Indeed, the great haematologist John Dacie and his colleagues<sup>13</sup> published a seminal paper on TMHA and related the condition to vascular damage some 10 years later. TMHA encompasses a spectrum of disorders including thrombotic thrombocytopenic purpura (TTP), haemolytic-uraemic syndrome (HUS), malignant hypertension, postpartum renal failure, pre-eclampsia and catastrophic APS. Recent articles still refer to the difficulty in distinguishing among these conditions<sup>14,15</sup> as the overlap is so great.

With the advent of refined testing for aPL, many cases of TTP were published with this association,<sup>16–21</sup> although Kincaid-Smith<sup>22</sup> in 1988 had already pointed out the existence of renal thrombotic microangiopathy with lupus anticoagulant positivity. The next major advance in this field was the identification of the cleaving enzyme—a von Willebrand factor Disintegrin and Metalloproteinase Thrombospondin protein (ADAMTS-13). Three patients with TTP and aPL have been reported so far.<sup>23,24</sup> Espinosa *et al*<sup>25</sup> in 2005 reviewed the association of aPL with TMHA comprehensively and found an association of TMHA with catastrophic APS rather than with classic APS. The association of HUS with aPL has also been anecdotically documented.<sup>26–28</sup> Simultaneous with the TTP and aPL story came the association of patients with the haemolysis, elevated liver enzymes and low platelets (HELLP) syndrome and aPL.<sup>29–35</sup> Hepatic infarctions,<sup>36</sup> retinal vascular occlusions<sup>37</sup> and deep venous thrombosis (DVT)<sup>38,39</sup> have now been reported in patients with HELLP syndrome.

Three recent papers have speculated as to whether a continuum exists between several of these conditions (TTP, HUS, HELLP syndrome and catastrophic APS).<sup>40–42</sup> This has been prompted by the reports of TTP and HELLP syndrome in patients in whom aPL has been demonstrated and alluded to above and also by recent case reports of patients with HELLP syndrome and catastrophic APS.<sup>43,44</sup> To these conditions must also be added disseminated intravascular coagulation (DIC), another situation where microvascular thromboses may be seen because of the hypercoagulability, and this may often be accompanied by a haemorrhagic state. There is usually strongly enhanced inflammatory activity, activated coagulation and impaired fibrinolysis in DIC, with a major role proposed for granulocytes.<sup>45,46</sup> Its frequency in catastrophic APS has also been highlighted recently,<sup>47</sup> and there have also been studies pointing out the frequency

of positive aPL demonstrated in DIC itself.<sup>48</sup> Indeed, the index case for catastrophic APS demonstrated serological evidence of DIC.<sup>49</sup> It should be stressed, however, that TTP, HUS, HELLP and DIC display abnormalities in the coagulation that are not usually associated with classic APS and are responsive to treatment regimens not effective in APS.

It is therefore time to address this topic objectively and to evaluate whether indeed there is a case to be made for another separate “subset” of the APS—namely, a microangiopathic APS.<sup>39</sup> The primary APS<sup>6,50</sup> and the catastrophic APS have certainly stood the test of time as unique conditions in the APS spectrum. We now know that patients with primary APS may develop SLE with time, and also that >80% of patients with catastrophic APS have a history of simple APS.

What is the role of the aPL (if any) in these microangiopathic conditions? Are they truly pathogenic, or are they simply “bystanders” induced by endothelial cell activation/apoptosis and exposure of phospholipid on the endothelial cell membranes of small vessels? In these conditions—for example, in TTP itself (apart from 20–30% of patients with catastrophic APS)—there are no large vascular occlusions. Hence, their relationship with the APS itself, with predominantly large-vessel occlusions, is distant, although a minority of patients with TTP demonstrate features of APS and the vast majority of patients with HELLP do not demonstrate larger vascular occlusions.

The first major player in this scenario must be the endothelial cells themselves and, in particular, those vascular endothelial cells present only on small vessels. The pathogenesis of the vascular occlusions affecting larger vessels causing DVT and strokes must then surely be different. The multifactorial pathogenesis of the APS has recently been well reviewed by Mackworth-Young.<sup>51</sup> The second major player in this scenario is the complement cascade, and both their roles will be briefly summarised here.

## ANTIPHOSPHOLIPID ANTIBODIES AND ENDOTHELIAL CELLS

Endothelial cell activation has been well demonstrated in both TTP<sup>52–56</sup> in APS<sup>57–61</sup> and, recently, in HELLP syndrome.<sup>62</sup> Studies have shown that endothelial cells express significantly higher amounts of adhesion molecules (intercellular cell adhesion molecule-1 (ICAM-1), vascular cell adhesion-1 (VCAM-1) and E-selectin) when incubated with aPL and  $\beta_2$ -glycoprotein I ( $\beta_2$ -GPI) in vitro.<sup>63</sup> Similarly, the incubation of endothelial cells with antibodies reacting with  $\beta_2$ -GPI has been shown to induce endothelial cell activation

with upregulation of adhesion molecules, IL6 production and changes in prostaglandin metabolism.<sup>63</sup> In published studies, Pierangeli *et al*<sup>64–66</sup> have shown, using mouse models, that human polyclonal and monoclonal aPL activate endothelium and enhance thrombus formation in vivo. Using ICAM-1, E selectin and P-selectin knockout mice and specific monoclonal anti-VCAM-1 antibodies, the same group demonstrated that these endothelial cell-activating properties of aPL are mediated by ICAM-1, E-selectin, P-selectin and VCAM-1.<sup>67–68</sup> Some investigators have shown increased levels of soluble adhesion molecules and soluble cytokines, such as VCAM-1 and P-selectin, in patients with aPL and thrombosis.<sup>69–70</sup> Hence, there is convincing evidence that aPL induce endothelial cell activation in vitro and in vivo.

Upregulation of tissue factor (TF) is one among the mechanisms suggested to explain the prothrombotic and proinflammatory activities of aPL. Evidence of upregulation of TF in patients with APS has also been reported by several investigators.<sup>71–74</sup> Recently, Zhou *et al*<sup>75</sup> demonstrated that IgG from patients with APS significantly increased TF function and transcription in monocytes. Some publications have also shown increased levels of soluble TF (sTF) in patients with APS and thrombosis.<sup>70</sup> Hence, there is evidence that aPL induce TF expression and procoagulant activity in vitro and in patients with APS.

Recently, the signal transduction mechanisms involved in aPL-mediated effects on endothelial cells and monocytes have been examined. Espinola *et al*<sup>68</sup> first reported that aPL-induced upregulation of adhesion molecules (ie, E-selectin) in endothelial cells induce activation of nuclear factor- $\kappa$ B (NF- $\kappa$ B) on endothelial cells in vitro. These findings were subsequently confirmed by others.<sup>76</sup> Vega-Ostertag *et al*<sup>77</sup> then examined the involvement of NF- $\kappa$ B and p38 mitogen-activated protein kinase (MAPK) in aPL-mediated induced transcription, expression and function of TF on endothelial cells. The effects of the specific p38MAPK inhibitor SB203580 (4-(4-fluorophenyl)-2-(4-methylsulfinylphenyl)-6-(pyridin-2-yl)imidazole) and of MG132 (carbobenzoxyl-leucyl leucylleucinal), a specific inhibitor of NF- $\kappa$ B, on aPL-induced TF expression and function on endothelial cells were evaluated in vitro. The investigators showed that aPL induce significant TF transcription, function and expression on endothelial cells, pronounced increase in proinflammatory cytokines (IL6 and IL8) and phosphorylation of p38 MAPK. By using SB203580 and MG132, they demonstrated that both p38MAPK phosphorylation and NF- $\kappa$ B activation are

required for in vitro aPL-induced TF upregulation.<sup>77</sup> These in vitro effects of aPL, mediated by p38MAPK and NF- $\kappa$ B, were recently confirmed in monocytes by Bohgaki *et al*.<sup>78</sup> Similarly, López-Pedraza *et al*<sup>79</sup> recently showed involvement of p38MAPK and ERK1/ERK2 in the activation of endothelial cells by aPL. Subsequently, Pierangeli *et al* showed that SB203580 significantly reduced TF function in carotid artery homogenates and in peritoneal macrophages and ex vivo expression of VCAM-1 detected by using quantum dot nanocrystal and dual-photon confocal microscopy in mice after infusion with aPL (unpublished results). These effects correlated with enhanced thrombosis and endothelial cell activation in vivo. Importantly, these findings may have important implications that may help to design new targeted treatments to treat the pro-inflammatory and pro-thrombotic effects of aPL in patients with APS.

It should be stressed, anyway, that endothelial perturbation and the induction of a pro-inflammatory and pro-coagulant phenotype is a pathogenic mechanism shared in common by several vasculopathies and vasculitic disorders. However, endothelial perturbation in APS seems to be closely linked to the ability of aPL to react with  $\beta_2$ -GPI expressed on endothelial cell membranes. This could mean that the lack of aPL in the majority of the non-APS microangiopathies makes these disorders different.

### ANTIPHOSPHOLIPID ANTIBODIES AND THE ACTIVATION OF THE COMPLEMENT CASCADE

The role of complement activation by the aPL has also received a great deal of attention. Complement involvement has also been reported in some cases of TTP and HUS. Recent studies have suggested that activation of the complement cascade is necessary for aPL-mediated thrombophilia and fetal loss.<sup>80–84</sup> Firstly, in a study from the group of Pierangeli and Salmon and collaborators,<sup>80</sup> it was found that inhibition of the complement cascade in vivo, using the C3 convertase inhibitor complement receptor 1-related gene protein  $\gamma$  (Crry)-Ig, blocks aPL-induced fetal loss and growth retardation and reverses aPL-mediated thrombosis. Furthermore, mice deficient in complement C3 and C5 (C3<sup>-/-</sup> and C5<sup>-/-</sup>, respectively) were resistant to thrombosis, endothelial cell activation and fetal loss induced by aPL.<sup>80–84</sup> Furthermore, an anti-C5 monoclonal antibody reversed thrombogenic properties of aPL in vivo, thereby confirming the involvement of C5 complement activation in aPL-induced thrombosis.<sup>80–84</sup> It has also been shown

that the interaction of complement component 5a (C5a) with its receptor (C5aR) is necessary for thrombosis of placental vasculature.<sup>82</sup> Hence, it was concluded that complement activation is a necessary intermediary event in the pathogenesis of thrombosis and fetal loss associated with aPL in experimental APS. These findings were recently confirmed in rats by Fischetti *et al*,<sup>85</sup> who showed that thrombus formation induced by antibodies to  $\beta_2$ -GPI require a priming factor such as bacterial lipopolysaccharide (LPS), and is complement dependent. The authors concluded, by using C6-deficient rats and anti-C5 miniantibody, that the terminal complement complex mediates the coagulation process.<sup>85</sup> Interestingly, hypocomplementaemia has been found in a significant proportion of patients with primary APS and was associated with thrombosis in one study and with livedo reticularis and thrombocytopenia in another publication.<sup>86–88</sup>

Thus, in summary, the following mechanism may be proposed for the pathogenic effects of aPL on thrombosis. Firstly, aPL bind to endothelial cells, induce their activation and a procoagulant state, as demonstrated by in vivo and in vitro studies. These include upregulation of adhesion molecules and TF expression. The aPL also induce platelet activation and interact with elements of the coagulation cascade. This activity however does not seem to be sufficient to cause thrombosis. Activation of the complement cascade by aPL may amplify these effects by stimulation of the generation of potent mediators of platelet and endothelial cell activation, including C3a and C5a and the C5b-9 MAC. Therefore, pathogenic aPL bind to target cells and they then activate the complement. The complement system in turn damages the endothelial cells, leading to a procoagulant state and undesirable thrombosis. We hypothesise that in patients with APS, owing to aPL deposition targeted to the endothelium, complement activation may be increased locally and may overwhelm normally adequate inhibitory mechanisms. Hence, activation of the complement may be a critical proximal effector mechanism in aPL-associated thrombosis. It is possible to speculate that inhibition of complement activation perhaps in the future should ameliorate vascular thrombosis in individuals with APS. Complement activation may be an important target that may allow us to create interventions that prevent, arrest or modify the thrombogenic and proinflammatory effects of aPL.

In conclusion, this in-depth overview raises the point whether or not there is

any relationship between microangiopathies and APS, and reviews the pathogenic processes that may be candidate mechanisms to support such a relationship (ie, endothelial cell and complement activation), thus providing some justification for their inclusion in a separate subset of the APS—namely, a microangiopathic APS.

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