Editorial

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 CAPS[2] 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 MAPS[1] 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 Hospital[4], 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 clinicians[7].

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 groups[8-11]. 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 Meroni[14] 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 monocytes[21-24] as well as on platelets is now also well described[25]. 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 studies[26], classification difficulties constantly arise as evidenced by guidelines proposed at the 11th International Congress on Antiphospholipid Antibodies held in Sydney 2 years ago[27]. 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 pathological[28]. A recent editorial attempted to differentiate conditions associated with aPL positivity into thrombotic and nonthrombotic subsets[7], 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 perturbation[29].

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 components[30-35]. Regarding infections, there may also be an added immunological disturbance associated with (e.g., in HIV infection) a reduction in Treg cells[35]. 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 documented[36]. 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 1988[37], 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 PHT[38], 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 only[39] 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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