Microangiopathic Antiphospholipid Antibody-Associated Syndromes: A Tribute to Ronald Asherson

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The term "microangiopathic antiphospholipid antibody-associated syndromes" (MAPS) was recently proposed by Asherson et al. [1-5] to encompass several conditions that mainly affect the microvasculature of selected organs and in which aPL seem to play a role. These comprise the HELLP syndrome (which mainly affects the microvasculature of the liver), thrombotic thrombocytopenic purpura and hemolytic uremic syndrome (affecting the kidney, the brain and the skin), cases of disseminated intravascular coagulation, whatever the cause but usually sepsis, that might also demonstrate aPL positivity, as well as some cases of the catastrophic antiphospholipid syndrome in which no large vessel occlusions are manifested (approximately 70%).

The enigma of the APS as such remains today, some 25 years after its original description, but many concepts have since evolved [6,7]. There is no question as to the pathogenicity of some aPL, as has been so dramatically demonstrated in animal models [8-10]. The pivotal role of complement and its activation in the pathogenesis of fetal loss and thrombosis was recently recognized as the key in unravelling the mysteries of pathogenic mechanisms in antiphospholipid syndrome, also in animal models [11,12]. The many and complex pathways involved in intracellular signalling resulting in the conversion of cells, particularly endothelial, to a prothrombotic state have also contributed to our greater understanding of the actions of the aPL [13]. The role of these antibodies in monocytes [14] as well as platelets [15] is now well described. 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 [5,6].

However, because of the ubiquity of these antibodies, which occur in up to 8% of normal subjects in some studies [16], classification difficulties constantly arise. Recently, an attempt was made to differentiate the myriad of conditions associated with aPL positivity into thrombotic and non-thrombotic subsets [6], emphasizing that, in certain inaccessible organs where histopathological or radiological techniques are unable to provide answers, microthrombosis cannot be proved or disproved. This applies particularly to central nervous tissues, e.g., brain or spinal cord (as in conditions such as chorea, cognitive dysfunction or transverse myelitis) or bone (as in osteonecrosis). Hopefully, functional investigations (e.g., SPECT) in the future might further assist us with this problem and provide more insight.

Small vessel occlusions (involving mainly renal, retinal and skin vessels) do occur with the simple or classic APS. However, these are the key features in the catastrophic APS in which condition small vessel occlusions occur mainly in intraabdominal vessels (kidneys, liver, spleen, gut, etc.), causing extensive tissue necrosis that results in the systemic inflammatory response syndrome, with its major accompaniment of acute respiratory distress syndrome, and multiorgan failure [17]. It is assumed that in the HELLP syndrome, as well as thrombotic thrombocytopenic purpura, hemolytic uremic syndrome and disseminated intravascular coagulation, there is major endothelial dysfunction. More importantly, there is a paucity of large vessel occlusions accompanying the former and a total absence of large vessel occlusions in thrombotic thrombocytopenic purpura and hemolytic uremic syndrome, even in the minority of those patients who demonstrate aPL. In the HELLP syndrome, hepatic infarctions are commonly seen and have been documented, and these are undoubtedly due to small vessel perturbations [18].

To these conditions, pulmonary hypertension, in many occasions accompanied by elevations of the aPL and with a possible autoimmune pathogenesis, might also be included in the subset of MAPS [19]. Perhaps several other associations with the aPL could also be included under this umbrella, such as osteonecrosis, and infections and aPL positivity without the full syndrome (the majority).

The proposal was that the term MAPS be taken to mean microangiopathic aPL–associated syndromes. By including the term "associated," the authors wish to emphasize that the majority of conditions described earlier probably do not form part and parcel of the APS (with catastrophic APS and the rare cases of HELLP syndrome with large vessel occlusions being perhaps the only exceptions), but the aPL can be produced in these conditions by exposure of phospholipids occurring during cellular damage

aPL = antiphospholipid antibody
APS = antiphospholipid syndrome

MAPS = microangiopathic antiphospholipid antibody-associated syndromes

to the endothelial system. The importance of this concept for clinicians lies in the fact that in these conditions therapy should be directed towards the underlying condition and not to the presence of the aPL at all, unless there are in fact complicating large vessel occlusions, as in the case of catastrophic APS [3].

In the current issue of *IMAJ*, Sedlak et al. [20] present a case of severe hemolytic uremic syndrome, with aPL following bowel infection in the absence of major vascular occlusions. This may certainly be an example of MAPS. This was also one the last contributions of Ronald A. Asherson to our knowledge of this variant of the APS. Ron Asherson died last May. His friends, fellows and colleagues remain profoundly affected by this sudden loss, and wish to pay tribute to his memory and the immense human and professional legacy that he has left.

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