Antiphospholipid antibodies in systemic sclerosis: a double oxidative hit?

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Received: 11 May 2009 / Accepted: 20 May 2009 / Published online: 10 June 2009
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In their paper regarding kidney function in systemic sclerosis (SSc) Wielosz et al. describe increased serum cystatin C and decreased glomerular filtration rate in SSc patients positive for antiphospholipid antibodies (aPL) measured as anti cardiolipin (aCL) and anti beta-2-glycoprotein I (β_2 GPI) compared to SSc patients negative for such aPL [1]. The authors found that serum IgG aCL positively predicted serum cystatin C and negatively creatinine clearance alongside IgG β_2 GPI. Moreover pulmonary arterial hypertension (PAH), proteinuria and scleroderma renal crisis were more frequent in aPL positive patients though none of the patients had clinical features of the antiphospholipid syndrome (APS) [1]. Other studies on SSc have described the occurrence of PAH more commonly in SSc patients positive for aPL [3–5] and for anti-phosphatidyl serine/prothrombin antibodies of IgM [6] and IgG isotype [7].

Altogether these are interesting data due to the interconnectedness of some vascular manifestation of SSc and the pathogenicity of aPL. Lipid peroxidation is the process through which arachidonic acid present in cell membranes and low-density lipoproteins transforms into cyclic compounds via a free radical process independent of cyclo-oxygenase. Of these cyclic compounds, 8-epi-prostaglandin-F₂alpha (8-epi-PGF₂ α) appears to be one of the most powerful vaso-active molecules existing [8] and is able to stimulate endothelin-1 (ET-1) production in

pulmonary vascular cells [9]. Over-generation of 8-epi-PGF₂ α has been found in SSc [10–13] particularly in relation to PAH [12] the pathogenesis of which in SSc is strongly dependent on ET-1 [14].

The same vaso-active compounds are implicated in the pathogenesis of the antiphospholipid syndrome: aPL induces endothelial cell production of ET-1 the serum level of which was particularly elevated in patients with arterial disease [15] whereas elevated serum 8-epi-PGF₂ α correlated to the titre of IgG aCL and to diastolic blood pressure [16]. Therefore SSc and APS share some pathogenetic pathways or putting it differently the pathogenicity of aPL adds to that of SSc worsening some clinical manifestations of the latter. However, the average serum level of aCL of the current and previous articles [3–5] are below the cut-off required for the diagnosis of APS Miyakis and very few of the SSc patients in these studies had thrombosis or miscarriages [3–7] though clinical overlaps may occur [17].

This leads to two important issues related to the significance of low titre aCL and to the treatment of SSc. With regards to the first issue are low titres aCL pathogenetic or not? Leaving aside the concepts of affinity and avidity of individual aPL, these SSc/aPL studies imply that on an appropriate oxidative background low titre aPL may worsen some vascular clinical manifestations through enhanced lipid peroxidation and ET-1 production. In a similar fashion, primary APS patients who also had elevated plasma homocysteine (that associates with increased lipid peroxidation) developed thrombosis at an earlier age than those primary APS patients who had normal plasma homocysteine: the average plasma IgG aCL of the former APS patients was lower than that of the latter [19]. The threshold of 40 GPL set by the expert committee relates to the occurrence of thrombosis and miscarriage to allow a diagnosis of APS [2] but should not necessarily

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preclude assignment of any pathogenicity to aCL at a level below 40 GPL. With regards to the second issue would anti-oxidant treatment benefit SSc? A case control study of probucol in SSc, a lipid lowering agent with anti-oxidant properties, induced a significant reduction in frequency and severity of Raynaud's attacks in SSc patients who received the drug for the 12-week trial period, associated with increased resistance to oxidation of low density lipoprotein [19]. A similar study in primary APS showed significant quenching of lipid peroxidation, decreased plasma levels of ET-1, decreased thrombin generation and improvement of fibrinolysis after three weeks of probucol [20].

Given these positive effects of probucol one wonders whether it would be appropriate to consider probucol as a long-term preventative drug to retard the development of selected vascular districts involvements of SSc such as lung and kidney or as an adjuvant in the management of similar SSc manifestations alongside ET-1 receptor blockade. These answers may only come from specific trials with adequate clinical endpoints.

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