Do Not Forget Lupus Anticoagulant in the Era of Antiphospholipid Antibodies

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Dear Sir,

Though nearly a century has gone by since antiphospholipid antibodies (APA) were first discovered, we are still dealing with the problems of what antigen is exactly recognized and whether and why this recognition is casually involved in overt clinical complications. There were three steps of detection:

First Step. APA were described by Was-serman et al. in 1906 [after ref. 1] in the VDRL test, in which the antigen was a mixture of cardiolipin (alcohol extract of bovine heart), lecithin and cholesterol. Patients with chronic false positive results were often found to have underlying autoimmune diseases.

Second Step. When the first description of the lupus anticoagulant (LA) phenomenon was made, an association with the presence of chronic biological false positive serologi-cal tests for syphilis was noticed [2].

Third Step. In the middle of the 1980s, more sensitive immunoassays were developed: solid phase radioimmunoassay for an-ticardiolipin (ACA), which is up to 400 times more sensitive than the VDRL test, and ELISA systems for IgG, IgA, IgM with specificity for six different phospholipid antigens (APA).

LA, VDRL, ACA and APA are thought to represent incomplete overlapping populations of antibodies [3]. Functional tests (LA) and immunoassays (ACA, APA) share about 50% of consensual results: 45% of APA/ ACA-positive patients with systemic lupus erythematosus (SLE) who were examined had LA, and 59% of LA-positive SLE patients had ACA/APA; in addition, both

modes of detecting APA are associated with a false positive VDRL: 48% of false positive VDRL patients had LA and 32% had ACA/ APA [references in 4]. Antigens recognized by functional test or immunoassays could be similar but not identical. This applies not only to the single phospholipid involved (i.e. cardiolipin or phosphatidylserine or phos-phatic acid) but also to the charge (negative or positive) as well as to the conformational shape (lamellar or hexagonal) or to the presence of serum cofactor, for example β i-glyco-protein[1, 5-7].

Immunoassays have gained credit in that they seem to be more sophisticated ways of detection, putatively able to provide a better understanding of the antigens involved in the reaction. Furthermore, immunoassays are sometimes the only way for APA detection in retrospective studies which use frozen stored serum samples of patients, while LA test needs plasma collected with anticoagulant. Lastly, LA may be not routinely measured in patients who are receiving anticoagulant treatment.

However, current evidence suggests that LA is a better predictor of thrombotic complications than the APA/ACA detected by immunoassays, while high-titer (> 40 U/ml) IgG APA/ACA obtained by ELISA are more sensitive for identifying pregnancies at risk for fetal death [5, 8]. In patients with thrombosis, LA is often associated with high-titer IgG APA or ACA [3, 9, 10], while high-titer IgG APA or ACA in the absence of a contemporarily positive LA test may not be associated with overt clinical complications. Since immunoassays have been extensively employed to look for APA in different clinical contexts, they have provided positive results in a consistent percentage of subjects, including normal populations, in whom clinical associations are lacking [11]. The same is not true for LA, which is present more often in association with overt clinical events [5, 8]. For example, APA/ACA with few, if any, LA-positive tests have been detected in systemic sclerosis [12, 13], idiopathic thrombocytopenic pur-pura [14] and SLE patients at low risk for thrombosis [9].

Therefore, apart from the context of pregnancy loss, immunoassays seem to be more prone to recognize antibodies lacking overt clinical implication. As a marker for risk of thrombosis in SLE patients, LA (with or without APA/ACA) is better than APA/ ACA without LA.

We confirm these assumptions after studying 80 patients satisfying ARA criteria for SLE followed in our Nephrologic Unit since 1980. LA test was positive in 33 patients and persistently negative in 47 [15, 16]. A gross comparison between LA-positive and LA-negative patients showed a significant prevalence of thrombosis (64.5 vs. 11 %), central nervous system involvement (70.5 vs 2.7%), false positive VDRL test (63 vs. 29%), thrombocytopenia (66 vs. 20%) in the former. IgG APA detected by immunoas-say were present only in 45% of LA-positive patients, and no significant laboratory or clinical differences were detected between LA-positive patients with or without APA.

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Vice versa, APA have been detected in the absence of LA-positive results in only 2 patients without thrombosis. We conclude that, as screening for evaluating high risk of thrombosis in SLE patients, LA has not to be forgotten as first step choice.

Before immunoassays for APA became routine, LA was sufficient to identify patients with biological markers of risk for thrombosis [17-20]. Contemporarily assessing for LA, ACA or APA may offer interesting information for a better understanding of clinical associations in prospective studies, but ACA/APA immunoassays should not be the only first screening step in SLE patients.

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234

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