42 Infection and Drug-Induced Antiphospholipid Antibodies

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Introduction

Antiphospholipid antibodies (aPL) have been subject of great interest for the past 90 years, first because they were found to be serological markers for syphilis, and later because of their association with clinical complications. A major sub-set of aPL are associated with infections. especially syphilis [1], and another sub-set of aPL are associated with an autoimmune disorder characterized by recurrent thrombosis, fetal death, and thrombocytopenia, called antiphospholipid syndrome (APS) [2, 3]. Neither the relationship between these 2 sub-groups, nor the cause and mechanism of production of aPL in these conditions are clearly understood.

Historical Background

Serological Test for Syphilis (STS)

aPL were detected for the first time in sera from patients with syphilis. Wassermann et al [1] in 1906 used saline extract of liver and spleen of fetus with congenital syphilis as an antigen in a complement fixation test and demonstrated positive reaction with syphilitic sera. The antibody was called Wassermann reagin and the test was introduced as a serological test for syphilis (STS). Although these investigators first believed that in this test, sera reacted with specific antigens derived from *Treponema pallidum,* within a year it was shown that extract of normal human or animal tissues reacted similarly with syphilitic sera [4]. The antigenic component of this test was isolated and identified from bovine heart extracts as cardiolipin by Pangborn [5] in 1941. Later, a flocculation test using suspension of liposomes containing cardiolipin, lecithin, and cholesterol was adopted as a serodiagnostic test for syphilis referred to as the VDRL (Venereal Disease Research Laboratory) test [6].

False Positive STS Using The Complement Fixation Test for Syphilis and VDRL

The presence of aPL detected as Wassermann reagin in conditions other than syphilis was reported as early as 1907 [4]. Detection of Wassermann reagin in the

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serum of a person who did not have syphilis was called "biological false-positive serological test for syphilis" (BFP-STS) and in a retrospective study of false positive reactors, Moore and Mohr identified 2 distinct groups of patients with acute and chronic reactions [7]. Acute reactions are transient and are seen during non-syphilis infections such as viral pneumonia, viral hepatitis, measles, varicella, and scarlet fever [8]. Vaccination against smallpox may also cause BFP-STS [9]. The chronic BFP-STS reactors whose BFP test persisted for a period of 6 months or more had a high prevalence of autoimmune disorders such as systemic lupus erythematosus (SLE), Sjögren syndrome, autoimmune hemolytic anemia, Hashimoto's thyroiditis, and rheumatoid arthritis [7, 9–11]. In 1957, Laurell and Nilsson found that the so-called lupus coagulation inhibitor or "lupus anticoagulant" (LA) was frequently associated with BFP-STS [12] and Lee and Saunders [13] showed that these were aPL, and this observation was confirmed by later studies using monoclonal antibodies [14]. In clinical studies, Bowie et al reported that the LA was associated paradoxically with thrombotic episodes [15].

2.3. Solid Phase Immunoassays for Anticardiolipin Antibodies

In 1983, Harris, Gharavi, and Hughes designed a radioimmunoassay using cardiolipin as antigen [16] to detect antibodies to cardiolipin in SLE patients with a positive LA test. LA tests detect the ability of aPL to prolong phospholipid dependent clotting reactions (such as the activated partial thromboplastin time) in vitro. This assay that was later converted to an enzyme-linked immunoassay (ELISA) [17], was subsequently standardized in several international workshops [18] and gave a new dimension to the field of aPL. The anticardiolipin (aCL) ELISA was first thought to be just a more sensitive test for detecting aPL than STS. However, it was recognized soon that the 2 tests detected somewhat different antibody populations and not all sera with positive STS were always positive in solid phase assay for cardiolipin [19]. In fact, the aCL ELISA did not help diagnosing more patients with syphilis, but it resulted in the recognition of a new syndrome characterized by thrombosis, recurrent abortion, and thrombocytopenia associated with aPL, the Antiphospholipid Syndrome (APS) [20]. The aCL ELISA is now commonly used to detect autoimmune aCL present in APS.

This assay also detected aPL in patients with other infections [21], such as Lyme disease [22], mycoplasma [23], tuberculosis [24], leprosy [25], legionnaires disease [26], Q fever [27], Mediterranean spotted fever [28], etc. Furthermore, aPL in viral infections have also been reported. These include cytomegalovirus [29], Varicella Zoster virus [30], human immune-deficiency virus (HIV) [31], and hepatitis C [32]. Furthermore, transient LA activity has been reported in patients with Epstein–Barr virus infections [33].

Infection-induced aPL

Differentiation of Autoimmune and Infectious-induced aPL: β_2-glycoprotein I

The association of the aPL detected by solid phase assays with serious clinical complications such as venous and arterial thrombosis, recurrent spontaneous abortion,