REVIEW

Antiphospholipid antibodies and infections

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Ann Rheum Dis 2003;**62**:388–393

Many infections have been found to be associated with antiphospholipid antibodies (aPL), although a pathogenic role for these antibodies has not usually been obvious except in a few isolated cases. Two types of aPL have been referred to as "autoimmune" and "infectious" types. This distinction, however, has subsequently been found not to be absolute.

The detection of antiphospholipid antibodies (aPL)—namely, the lupus anticoagulant (LA) or anticardiolipin antibodies (aCL), is of considerable interest because of their importance in the pathogenesis of clotting in the antiphospholipid syndrome (APS), a condition present not only in the autoimmune diseases, particularly systemic lupus erythematosus (SLE), but also in patients who do not manifest any overt symptoms of autoimmune disturbance (primary APS) where the emphasis is primarily on vascular events.[1 2]

The aPL were originally detected in human serum by Wasserman[3] almost 100 years ago when his complement fixation test was first used for the diagnosis of syphilis and the Venereal Disease Research Laboratory test (VDRL) was described.[4] A phospholipid, called cardiolipin was the major tissue extract used in these tests. It was subsequently found that the VDRL was not specific for syphilis but aCL were also found in autoimmune diseases such as SLE itself. In 1983, at the Hammersmith Hospital, cardiolipin was used for the first time as the antigen in solid phase aPL-specific assays by Harris *et al*,[5] and the term APS was born.[6]

PATHOGENIC HYPOTHESIS

Syphilis was thus the first infection to be linked to the aPL. Since 1983, many other infections have been found to be associated with aPL positivity, although a pathogenic role for these antibodies was not usually obvious except in a few isolated cases. In 1990, it was found that binding of aPL to phospholipid was enhanced in autoimmune conditions by a "cofactor" known as β_2 glycoprotein I (β_2GPI)—a glycoprotein with anticoagulant properties, whereas the non-thrombogenic aPL did not require this cofactor to enhance binding.

The two types of aPL were referred to as "autoimmune" and "infectious" types.[7–10] This distinction, however, has subsequently been found not to be absolute. A recent study[11] found that only 1/35 lepromatous patients had anti-β_2GPI activity, and the authors postulated that aPL associated with infection do not possess anti-β_2GPI activity and are not associated with thrombotic complications. However, other investigators investigating the same condition found increased levels of anti-β_2GPI antibodies in a significant proportion of their patients with leprosy.[12] Indeed, this observation was confirmed by others who found that these β_2GPI dependent aCL in patients with leprosy were associated with thrombosis.[13] Similar aCL binding characteristics were then detected in B19 parvovirus infection.[14]

This has led to the hypothesis that perhaps infections may be a "trigger" for the induction of pathogenic aPL in certain predisposed subjects. The β_2GPI induced by infections may bind to "self" aPL thus forming an immunogenic complex against which aPL are then produced.[15] What constitutes this predisposition is unknown at this time, but clearly genetic factors might have a significant role. The antibodies produced by infectious "triggers" are therefore heterogeneous in their dependency on β_2GPI, and a minority may resemble the "autoimmune" type.

Viruses and microbial agents may induce autoimmune disease by several differing mechanisms. The mechanism which concerns the production of aPL and indeed the APS is known as "molecular mimicry".[16–18] A hexapeptide, TLRVYK was recently identified by Blank *et al*.[19] This hexapeptide is recognised specifically by a pathogenic anti-β_2GPI monoclonal antibody. Blank and coworkers evaluated the pathogenic potential of microbial pathogens carrying sequences related to this hexapeptide in mice by infusing intravenously into naïve mice IgG specific to the peptide.

> "Syphilis was the first infection to be linked to aPL"

High titres of antipeptide anti-β_2GPI antibodies were seen in mice immunised with *Haemophilus influenzae, Neisseria gonorrhoea*, and tetanus toxoid. Significant thrombocytopenia, prolonged activated partial thromboplastin times, and increased fetal loss were seen. Thus, it is apparent that experimental APS can be induced by immunisation with certain microbial pathogens which share epitope homology with the β_2GPI molecule.

Zhang *et al* recently identified a *Staphylococcus aureus* protein Sbi which also binds β_2GPI and serves as a target molecule for IgG binding.[20]

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Accepted
30 November 2002

Abbreviations: aCL, anticardiolipin antibodies; AIDS, acquired immunodeficiency syndrome; aPL, antiphospholipid antibodies; APS, antiphospholipid syndrome; CMV, cytomegalovirus; EBV, Epstein-Barr virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HTLV, human T lymphotrophic virus; LA, lupus anticoagulant; PHT, pulmonary hypertension; SLE, systemic lupus erythematosus; TTP, thrombotic thrombocytopenic purpura; VDRL, Venereal Disease Research Laboratory test

Table 1 Infections in which aPL have been detected

1. Viral	
Hepatitis C	Varicella
EBV	Vaccinia
HIV	Mumps
CMV	Rubella
Parvovirus B19	HTLV-1
Adenovirus	
2. Bacterial	
Leprosy	Staphylococci, streptococci
Tuberculosis	*Coxiella burnetii* (Q fever)
M pneumoniae, M penetrans	Bacterial endocarditis
Salmonella	
3. Spirochaetal	
Syphilis	Lyme disease (*Borrelia*
Leptospirosis	*burgdorferi*)
4. Parasitic	
Malaria	Toxoplasmosis
Kala azar	

Gharavi *et al* also showed that synthetic peptides which share structural similarity with the putative phospholipid binding region of the β_2GPI molecule and which share a high homology with cytomegalovirus (CMV) could induce aPL in NIH/Swiss mice.[21] No features of the APS were, however, seen. The pathogenic effect of these aPL was later determined and reported.[22] The epitope in this study was located in the fifth domain of the β_2GPI molecule as opposed to the work of Blank *et al*,[19] where the target epitope was found to be against the third domain. The target molecule studied was also mimicked by several microbial pathogens and is, therefore, probably responsible for the generation of pathogenic anti-β_2GPI antibodies.

INFECTIONS AND ANTIPHOSPHOLIPID ANTIBODIES

A great variety of infections are accompanied by increases in aPL (table 1). Although there is a propensity for the IgM isotype, increases in IgG may also be detected. Some of these infections will be considered in more detail.

Viral infections

Hepatitis C virus (HCV)

Sera from patients with chronic HCV infection were studied by Ordi-Ros *et al*,[23] Prieto *et al*,[24] and Sthoeger *et al*.[25] Raised levels of aCL were found by Ordi-Ros *et al*[23] in 3.3% and these were all β_2GPI independent. Higher frequencies (22%) were found by Prieto *et al*, and these authors related the presence of thrombocytopenia, portal hypertension and previous thrombotic events to raised titres of aCL.[24] Sthoeger *et al* found raised levels of aCL in 44% of patients, but once again no relationship with any APS related clinical manifestations was evident.[25] Dalekos *et al* found that 37.3% of his patients with HCV in northern Greece had aCL positivity.[26] In a group of patients with SLE and APS studied they detected no evidence of HCV infection. Caccoub *et al*, in 2000, studying 321 patients, found aCL positivity in 27% of their patients with chronic HCV infection.[27] Muñoz-Rodríguez *et al* studied HCV infection in 88 patients with APS and found only two with anti-HCV antibodies. They concluded that HCV infection was not involved in the pathogenesis of the syndrome.[28]

However, several patients with HCV and thrombosis have been reported. One patient with thalassaemia and HCV infection who developed thrombosis has been documented.[29] Baid *et al* studying aCL and renal allograft thrombosis in 18 patients with HCV positivity before transplant, found that renal thrombotic microangiopathy with aCL positivity had developed in five, compared with only one of 13 without microangiopathy.[30] Malnick *et al* also reported the case of a 54 year old man with chronic HCV infection and high levels of aCL who developed a lacunar brain infarction.[31]

In summary, therefore, it appears that, although latent HCV infection is usually not detectable in patients with APS, low levels of aCL may be found in patients with HCV infection and, in a minority, may be accompanied by thrombotic complications.

Epstein-Barr virus (EBV)

A single case of a 25 year old woman who presented with a deep vein thrombosis and pulmonary embolus in association with an EBV antibody positive viral infection has been reported by Yamazaki *et al*.[32] She had a positive LA and aCL and the antibody titre reverted to normal after six months.

Varicella virus

An adult patient who had a pulmonary embolus during the course of a varicella infection accompanied by transiently raised levels of aCL and β_2GPI was documented in 2000,[33] and Uhtman *et al* recorded a 16 year old youth who developed an iliofemoral thrombosis one week after a chicken pox infection.[34] IgM aCL were raised and persisted for six weeks after the illness. Manco-Johnson *et al* studying seven children with varicella reported an association with thrombosis in four who demonstrated aPL.[35] Peyton *et al* documented two men who developed profunda femoris and tibial arteries thromboses with free protein S deficiency.[36] One had positive IgG and IgM aCL and the second had positive LA. Barcat *et al* reported a case of varicella complicated by deep vein thrombosis with transient increases of aCL and LA.[37]

Human T lymphotrophic virus (HTLV)-1

Faghiri *et al* studied 50 patients with HTLV-1 associated myelopathy-tropical spastic paraparesis and found that aCL but not anti-β_2GPI antibodies were associated with HTLV-1 infection.[38]

Parvovirus B19

Loizou *et al* measured a variety of aPL in the sera of 12 patients with parvovirus B19 infection.[14] The aCL were found to be β_2GPI dependent, as in SLE, unlike the antibodies from patients with other viral infections examined

Cytomegalovirus (CMV)

Labarca *et al* documented a patient who developed mesenteric and femoropopliteal thrombosis during the course of a CMV infection.[39] Uthman *et al* also described a patient with an APS and CMV infection.[40]

Opportunistic infections with cytomegalovirus (CMV) in patients with human immunodeficiency virus (HIV) infection have been reported in several cases associated with thrombosis[41] and will be discussed in the HIV section. CMV has been demonstrated locally within affected tissues (digital infarcts) as well as in blood by Smith *et al*.[42] This is not unique to HIV infected subjects, as CMV infection has also been associated with thrombosis after liver transplantation.[43]

HIV

LA were first described in 44% of patients with acquired immunodeficiency syndrome (AIDS) and in 43% of asymptomatic HIV positive subjects (in which they may be transient) by Bloom *et al* in 1986.[44] In 1987, Canoso *et al* reported aCL positivity with HTLV-3 infection.[45] In 1991, the association of aCL with HIV infection in male homosexuals was reported,[46] and several studies since then have confirmed these original findings. Coll *et al* tested 84 patients infected with HIV in 1992 and found that 59.5% of the patients were IgG aCL positive.[47] None had any thromboembolic phenomena. No significant differences were found in the sex of patients, risk factors, and stage of the disease. They stated that the aCL did not appear to

be a prognostic marker in HIV infected subjects but were indicative of impaired humoral immunity found in these patients. Falco *et al*, in 1993, examined 39 HIV positive and 20 aCL SLE sera and found that in the HIV sera reduced binding was evident if the cofactor (β_2GPI) was added.[48] On the contrary, in SLE sera, addition of the cofactor improved the binding. These authors concluded that the aCL in HIV infection appeared to have a different specificity from those found in SLE. Weiss *et al*, in 1995, found aCL in 47% of HIV positive subjects,[49] and other authors have also confirmed this association.[50–53]

The detection of antibodies to prothrombin and β_2GPI is significantly less in patients with HIV according to Guerin *et al*, who found LA positivity in 72% and aCL positivity in 67% of their patients.[54] A previous paper by the same authors demonstrated significantly raised antibodies to β_2GPI in patients with definite APS but only in 10% of those with HIV infection. Significantly fewer anti-prothrombin antibodies were detected in their patients with HIV, but recent work by Asherson *et al* demonstrated a high frequency of antibodies to prothrombin in a group of 100 HIV positive black patients in South Africa.[55] The antigen used in the enzyme linked immunosorbent assay (ELISA) performed in these patients was prothrombin alone and not prothrombin combined with cardiolipin. The findings for β_2GPI were subsequently confirmed by Petrovas *et al*, who investigated the phospholipid specificity, avidity, and reactivity with β_2GPI in 44 patients with HIV infection compared with six patients with SLE with secondary APS, 30 patients with SLE without APS, and 11 patients with primary APS.[51] The prevalence of aCL, antiphosphatidylserine, antiphosphatidylinositol, and antiphosphatidylcholine (36%, 56%, 34%, and 43%, respectively) was similar to that found in the patients with SLE/APS and those with primary APS. The prevalence of these antibodies was significantly higher than that found in patients with SLE and without APS. However, anti-β_2GPI antibodies were detected in only 5% of the HIV-1 infected patients in this series. A significant decrease of aPL binding after treatment with urea and NaCl was seen in the sera of HIV infected patients compared with patients with APS, indicating that aPL from patients with HIV have a low resistance to dissociating agents and low avidity of the antigen. Gonzales *et al* were also unable to detect anti-β_2GPI in serum samples from their patients with HIV despite the presence of high concentrations of aCL.[52]

Silvestris *et al* in 1996 studied antibodies to phosphatidylserine in patients with HIV among a panel of phospholipid antigens.[53] They found that in vitro apoptosis of T cells was increased in patients with high serum IgG antiphosphatidylserine antibodies. Together with other studies they concluded that, because phosphatidylserine is exteriorised by apoptotic lymphocytes, its persistence may cooperate with macrophages in the clearance of dead cells by an enhanced antibody dependent cellular cytotoxicity mechanism, and they postulated that this might explain the absence of thrombophilia in HIV positive patients with increases of the aPL.

There are many reports of thrombosis occurring in patients with HIV/AIDS and these include peripheral vein,[56 57] pulmonary embolism,[56] retinal vein,[58–61] cerebral vein,[62] portal vein,[63] and mesenteric[64 65] occlusions. The occurrence of both arterial and venous thromboembolic disease has been reported in one patient by Bosson *et al*.[66]

It has become clear that in HIV infection, both types of aCL (the pathogenic or β_2GPI dependent) as well as the non-pathogenic (non-β_2GPI dependent) antibodies may be detected and that there is diversity, not only of the isotypes, but also of the aPL including antiphosphatidylserine antibodies. In addition, there is a low frequency of antibodies directed towards β_2GPI in HIV infected patients. It is, therefore, not surprising that the APS and its manifestations are uncommon in HIV. Certainly, thrombotic and other manifestations are much more frequently encountered than with other viral infections, again pointing to a major immunological disturbance in HIV as opposed to other viral conditions. However, dual infection with HIV and CMV has been reported as being associated with the APS in a number of patients.[41 42 67 68]

The presence of aCL and stroke in an HIV positive patient was reported by Thirumalai and Kirshner in 1994[69] and by Keeling *et al*,[70] deep vein thrombosis of the extremities by Orbea-Rios *et al*,[71] and skin necrosis by Soweid *et al*.[72] Skin necrosis was also recently reported by Leder *et al* in a male patient with HIV who had testicular infarction requiring orchidectomy.[73] A 42 year old woman who had a 12 year history of HIV infection and who developed gangrene of both forefeet was reported by Cailleux *et al*.[74] Skin biopsy revealed intracapillary thrombi and severe necrosis of the hypodermis without any evidence of vasculitis. IgG aCL levels were raised.

A 33 year old woman with AIDS who had had a cerebrovascular accident and who developed a splenic infarction was reported by Cappell *et al* in 1993.[75] A recent paper has also drawn attention to aPL associated complications and APS in HIV infection. Turhal *et al* reported four cases.[76] The first developed acute livedo reticularis; the second, probable avascular necrosis of the femoral head associated with demonstrable decreased blood flow; the third, thrombosis of the inferior vena cava and pulmonary emboli; and the fourth, a major pulmonary embolus. Avascular necrosis of bone has in fact been previously documented with HIV infection. Three cases of avascular necrosis of bone associated with aPL were documented in 1993 by Belmonte *et al*.[77] No other risk factors other than the presence of aPL were present in these patients. However, several other subsequent reviews of the association failed to detect aPL as a risk factor in this condition.[78–82] It is likely that hyperlipidaemia (associated with antiretroviral treatment), corticosteroid use, and alcohol abuse represent some of the risk factors in the pathogenesis of the condition, with aCL being present in a minority only.

Pulmonary hypertension (PHT), seen with the APS, may also be an aPL related complication. The incidence of HIV associated PHT is estimated to be 1/200, which is much higher than the 1/200 000 found in the general population.[83] The common reasons for PHT encountered in HIV infected patients are pulmonary infections, venous thromboembolism, and left ventricular dysfunction.[84] However, primary PHT has been reported in some patients without a history of thromboembolic disease, intravenous drug use, or pulmonary infections. Its pathogenesis remains poorly understood, and it has been suggested that HIV causes endothelial cell damage and mediator related vasoconstriction through stimulation by the envelope gp 120, including direct release and the effects of endothelin-1, the most potent vasoconstrictor, interleukin 6, and tumour necrosis factor α on the pulmonary arteries themselves. The frequency of aCL is raised in patients with primary PHT, but the frequency of increases in aCL in HIV related PHT has not been determined.

Thrombotic thrombocytopenic purpura (TTP) is a well described complication of HIV infection, often occurring during the early asymptomatic phase of HIV infection as well as with clinical AIDS. The clinical spectrum varies from a low grade asymptomatic thrombocytopenia with mild renal insufficiency to a severe illness with major neurological manifestations and renal failure.[85–88] Indeed, the presence of von Willebrand factor-cleaving protease inhibitor, which may be involved in the pathogenesis of TTP, has been demonstrated in the plasma of a patient with both AIDS and TTP.[89] Thrombotic microangiopathy, encompassing microangiopathic haemolytic anaemia, thrombocytopenia, and renal failure, is also one of the renal complications which can develop in HIV infected patients,[90] as it may with HCV infection.[30] This type of vascular lesion (more common in patients with HIV than in the normal population) may be one of the first manifestations of HIV infection and may be severe.[91] TTP has been infrequently associated with aPL, but thrombotic microangiopathy is relatively common in patients with APS.

Of paramount importance is what constitutes the pathogenicity of the various types of aPL and why thrombosis is seen only in selected patients with SLE and very infrequently with infections. The recent work of Sheng *et al*, who measured the effects of test antibody or plasma samples on in vitro thrombin formation,[92] will hopefully be extended in the future and may provide some clear information about this problem. Plasma and affinity purified antibodies from patients with APS inhibited thrombin generation significantly more so than from patients with aPL from other causes, and samples from patients with APS showed thrombin inhibition in the presence of anti-β_2GPI or antiprothrombin antibodies.

In summary, therefore, it seems that the pathogenesis of thrombotic complications in HIV infected patients and patients with AIDS is multifactorial, with the aPL playing a role in selected patients only. Although accounts of several studies have been published from various centres, reports of thrombotic complications accompanied by aPL positivity are few at present. Lipid disturbances consequent on antiretroviral treatment and their attendant vascular complications will no doubt overtake haematological and immunological disturbances seen in these patients as a cause of these complications. The discovery of new classes of antiretroviral compounds (for example, fusion inhibitors, integrase inhibitors) may in the future reduce the use of the protease inhibitors with their very serious vascular complications.

Bacterial infections

Many bacterial infections demonstrate aPL. However, these increases in aPL are usually not associated with thrombotic events. Of interest, however, is that, although β_2GPI dependence is usually negative in this group, in patients with leprosy, the aCL may be β_2GPI dependent as is found with autoimmune diseases, particularly in patients with the multibacillary type of leprosy.[93] Lucio's phenomenon is a rare manifestation of leprosy in which the histopathological findings are related to microvascular thromboses in the absence of inflammatory infiltration of the vessel walls. Levy *et al* demonstrated that this type of leprosy was associated with β_2GPI dependency of the aCL.[94]

One patient, a young adult who developed an APS in childhood after a pulmonary infection with *M pneumoniae* has been documented.[95] Streptococcal infections may also be associated with increases in aCL, but there has been some controversy about rheumatic heart disease, with some investigators reporting raised titres and others not confirming these findings. Q fever, caused by *Coxiella burnetii*, is associated with a high frequency of aCL positivity and when patients only present with fever, an estimation of these antibodies may assist in the diagnosis.

THE CATASTROPHIC ANTIPHOSPHOLIPID SYNDROME

This unusual and potentially fatal subset of the APS was first defined in 1992.[96] Since then, more than 150 patients have been reported.[97] "Triggering" factors have become apparent and these have included trauma, withdrawal of anticoagulation, carcinoma, and also infections.[98] Infections preceding the appearance of catastrophic APS were reported in eight patients by Rojas-Rodríguez *et al*.[99] The latest analysis[97] has shown that 35% of cases of catastrophic APS were preceded by infections. These comprised respiratory (15%), cutaneous (including infected leg ulcers) (8%), urinary tract (6%), gastrointestinal (1%), general sepsis (1%), and others (9%). One patient in the last group, who developed catastrophic APS after typhoid fever, has been reported on in detail.[100] Another patient who developed two large vessel occlusions after typhoid fever has also been reported on recently[101] and, although this patient was represented as having catastrophic APS, small vessel occlusions, essential for the diagnosis of this condition, were absent. Leg necrosis—due to infection—which resolved after the leg amputation, has also been described in patients with catastrophic APS.[102] Molecular mimicry has been proposed for the development of catastrophic APS after infections.[103]

CONCLUSIONS

Of great interest is the fact that in several infections (leprosy, parvovirus B19), the aCL may be β_2GPI dependent, resembling those found in autoimmune diseases, and are clearly heterogeneous. Anti-β_2GPI antibodies are found at lower frequency in some patients with leprosy and, for example, in patients with HTLV-1 and HIV infections. Therefore, it seems that although many infections may demonstrate aPL and anti-β_2GPI antibodies, these increases are not often accompanied by any manifestations of the APS such as thrombosis. Specific viral infections, such as HIV (with known immunological disturbances), and CMV infection may, in a small number of cases, be accompanied by thrombotic complications associated with aPL positivity. Other viral infections, such as HCV, may also be associated with thrombotic complications related to aPL. On occasion (as in varicella), transient rises in aPL may be accompanied by thrombotic complications.

It is assumed that many of the "triggering" factors for catastrophic APS are viral and not bacterial. Specific bacterial infections seem to be rarely accompanied by thrombotic complications (although aPL are not infrequent), except in the two patients who had had typhoid fever and in these the lipopolysaccharide envelope of the infecting organisms might have been responsible and not any peptide sequences. Differing mechanisms may therefore be operating depending on the structure of the organism. There is no doubt, however, that there is a preponderance of viral as opposed to bacterial infections which are associated with thrombosis and rises in pathogenic aPL. These findings once again open up the question as to which viruses might in fact "trigger" the prototype autoimmune disease, SLE itself, in genetically predisposed subjects, not too dissimilar from the role of chlamydia, salmonella, shigella, and yersinia infections occurring in HLA-B27 positive subjects. No doubt, in the coming years, these questions will be resolved.

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