Antiphospholipid Antibodies in Response to Infection

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An association between infections and antiphospholipid antibodies (aPL) has been reported in several epidemiologic and experimental studies. Infection-induced aPL have been traditionally regarded as transient and were generally not associated with clinical features of antiphospholipid syndrome. The distinction between autoimmune and postinfectious aPL on the basis of requirement of binding cofactor is not absolute, and in recent years, several reports demonstrated that some patients can produce pathogenic antibodies in response to infection. Infections most frequently associated with antiphospholipid syndrome include parvovirus B19, cytomegalovirus, varicella-zoster virus, HIV, streptococcal and staphylococcal infections, gram-negative bacteria, and *Mycoplasma pneumoniae*.

Introduction

Antiphospholipid syndrome (APS) is a multisystem autoimmune disease characterized by vascular thrombosis, recurrent fetal loss, thrombocytopenia, and other clinical manifestations in the presence of persistent circulating antiphospholipid antibodies (aPL) (ie, anticardiolipin antibodies [aCL], anti-β_2 glycoprotein I antibodies [anti–β_2-GPI], and/or lupus anticoagulant [LA]) [1]. The factors causing production of aPL remain largely unknown, and growing evidence suggests that infectious agents such as viruses, bacteria, and parasites can induce aPL. In recent years, the association between infections and APS has been reported in several epidemiologic and experimental studies that support the idea of infectious induction of aPL [2•,3•]. However, most of the data on aPL and APS in response to infections came from isolated case reports or small case series, and well-designed prospective studies are still rare. The connection between infections and aPL is supported also by some indirect evidence, such as the seasonal distribution of aPL [4] and high frequency of aCL in healthy children who frequently suffer from a wide range of common viral infections [5].

The majority of postinfectious aPL differ immunochemically from those seen in patients with autoimmune diseases and do not require the presence of cofactor plasma proteins such as β_2-GPI for their binding [6]. Infection-induced aPL have been traditionally regarded as transient phenomena and generally are not associated with clinical features of APS. However, this classification has been challenged by several recent reports describing thrombotic events following infection and in particular by the association of the most aggressive form of APS, called catastrophic APS, with infectious triggers [2•,7]. The aim of this review is to summarize recent clinical and experimental evidence on the association between aPL and infectious diseases and to emphasize a possible association with immunizations.

Epidemiology and Clinical Features Associated with Infection-induced aPL

Viral infections

Viral infections were most commonly implicated as an infectious trigger for induction of aPL (Table 1). In spite of the significant progress in immunobiology of aPL in the last decade, few data exist on the incidence of aPL following commonly acquired viral infections such as respiratory tract infections, gastroenteritis, and viral exanthemas in childhood. Kratz et al. [8] investigated the frequency of aPL in 88 children with infections, the majority of whom had upper airway infections, and found positive immunoglobulin (Ig) M aPL in 30% and IgG aPL in 15% of patients. In a study of 37 children with common infections and prolonged activated partial thromboplastin time, at least one subtype of aPL was detected in 89% of cases [9]. Vaarala et al. [10] collected paired serum samples from 149 young adult patients with acute infections and demonstrated significantly raised aCL levels in 43% (20/47) of patients with adenovirus, 33% (3/9) with rubella, 20% (2/10) with chicken pox varicella, and 54% (7/13) with mumps. Significant changes in the aCL level between the first and the second sample occurred in 26% of the cases,

Table 1. Clinical manifestations of antiphospholipid syndrome reported in association with viral infections and presence of antiphospholipid antibodies

Infectious agent	aCL	anti–β_2-GPI	LA	Clinical manifestations
Parvovirus B19	+	+	+	Thrombosis, thrombocytopenia, HA
CMV	+	+	-	Thrombosis
VZV	+	+	+	Thrombosis, purpura fulminans
EBV	+	+	+	Thrombosis
HCV	+	+	+	Thrombosis, thrombocytopenia
HBV	+	-	-	-
HAV	+	-	-	Thrombosis
HIV	+	+	+	Thrombosis
HTLV-1	+	-	-	-
Adenovirus	+	+	-	Thrombocytopenia
Influenza	+	-	-	Thrombosis
Rubella	+	-	-	-
Mumps	+	-	-	-

aCL—anticardiolipin antibodies; anti–β_2-GPI—anti-β_2 glycoprotein I antibodies; CMV—cytomegalovirus; EBV—Epstein-Barr virus; HA—hemolytic anemia; HAV—hepatitis A virus; HBV—hepatitis B virus; HCV—hepatitis C virus; HTLV-1—Human T lymphotropic virus type 1; LA—lupus anticoagulant; VZV—varicella zoster virus.

and in nearly half of these cases the level declined, suggesting transient presence of infection-induced aCL [10].

Accumulating evidence indicates that parvovirus B19 infection may be an initial trigger of for various autoimmune processes, including aPL production. The close association between parvovirus B19 infection and development of aPL was clearly demonstrated in a study of 88 children with rheumatic diseases [11]. Twenty-four (27%) of the 88 children had detectable levels of IgG aPL, and 21 (88%) of the aPL-positive patients showed presence of persistent or past parvovirus B19 infection [11]. An association between parvovirus B19 infection and the production of aPL has been observed also in other autoimmune diseases, in particular in patients with systemic lupus erythematosus (SLE) [12,13]. Loizou et al. [12] showed that parvovirus B19-associated aCL requires the presence of β_2-GPI as a binding cofactor, similar to aCL found in patients with SLE but unlike antibodies found in patients with other viral infections. Because of remarkable similarities in the clinical presentation of patients with parvovirus B19 infection and SLE or APS (ie, thrombocytopenia, hemolytic anemia, spontaneous abortion, livedo reticularis, arthritis), parvovirus B19 has been implicated as a trigger for the development of aPL in systemic autoimmune diseases. To our knowledge, there have been at least two reports of thrombotic events associated with aPL and parvovirus B19 infection. A healthy young man with acute parvovirus B19 infection developed splenic infarction associated with the presence of IgM and IgG aCL [14], and a 21-year-old woman developed multiple pulmonary emboli in association with transient presence of LA and IgM aCL [15].

Herpes viruses are common among humans and have been reported in association with aPL-related clinical features in several case reports. Thrombosis associated with aPL were described in at least three immunocompetent patients with cytomegalovirus (CMV) infection [16–18]. In all three case reports, aCL were observed at the onset of the disease, and both IgM and IgG titers declined about 6 months later. Labarca et al. [16] described a healthy 35-year-old male with a mild congenital deficit of protein S who developed mesenteric and femoropopliteal thrombosis associated with the transitory presence of β_2-GPI–dependent aCL during acute CMV infection. Several mechanisms were proposed to explain the role of CMV in thrombosis. This virus infects endothelial cells and can directly damage vascular endothelium, activate coagulation factors, and induce production of aPL [18].

Thrombotic events associated with transient aPL have also been reported in a few cases of varicella-zoster virus (VZV) and Epstein-Barr virus infection [19–20]. Recently, Losurdo et al. [21] described two pediatric cases with varicella-associated cerebrovascular disease that had positive IgM anti–β_2-GPI antibodies and that became negative after 1 month. A specific clinical entity described in several pediatric case reports is a life-threatening purpura fulminans after chickenpox infection linked to the presence of LA and acquired protein S deficiency [22,23]. Manco-Johnson et al. [22] studied seven children with post-varicella purpura fulminans or thrombosis and found in all children the presence of LA and an autoantibody to protein S, which results in acquired free protein S deficiency.

The prevalence and clinical significance of aPL have been studied intensively in patients with chronic viral

Table 2. Clinical manifestations of antiphospholipid syndrome reported in association with bacterial and parasitic infections and presence of antiphospholipid antibodies

Infectious agent	aCL	anti–β_2-GPI	LA	Clinical manifestations
Streptococcus	+	+	+	Thrombosis
Staphylococcus	+	+	+	Thrombosis
Mycoplasma pneumoniae	+	+	+	Thrombosis
Escherichia coli	+	+	-	Thrombosis
Salmonella	+	+	+	Thrombosis
Coxiella burnetti	+	-	+	-
Chlamydia	+	+	-	-
Fusobacterium necrophorum	+	-	+	Thrombosis
Syphilis	+	+	-	-
Leptospirosis	+	+	-	-
Tuberculosis	+	+	-	Thrombosis
Leprosy	+	+	+	Thrombosis
Malaria	+	+	-	Thrombosis
Kala-azar	+	+	-	-

aCL—anticardiolipin antibodies; anti–β_2-GPI—anti-β_2 glycoprotein I antibodies; LA—lupus anticoagulant.

hepatitis. The reported frequencies of aCL in patients with hepatitis C virus (HCV) infection have ranged from 3% to 44% [24,25]. Anticardiolipin antibodies in patients with HCV infection showed no β_2-GPI dependency, and were only rarely associated with the development of thrombotic events or thrombocytopenia [24–26]. Muñoz-Rodríguez et al. [27] investigated the prevalence of HCV infection in 88 consecutive patients with APS and found positive anti-HCV antibodies in only two (2.2%) patients. Data on aPL in patients with hepatitis B virus infection are rare, and only two studies reported that the prevalence was lower than in patients with HCV infection [28]. Ertem et al. [29] described two pediatric cases with Budd-Chiari syndrome associated with high levels of IgM aCL during the course of acute hepatitis A virus infection.

HIV-infected patients may produce aPL, in particular of IgM isotype, but full-blown clinical features of APS are distinctly uncommon [30]. LA was described in 43% of asymptomatic HIV-infected persons and 44% of patients with AIDS [31]. The association of aCL with HIV infection was first reported in male homosexuals and subsequently confirmed in several studies [30,32]. APS clinical features were observed both in pediatric and adult HIV-infected patients [33,34]. Antiphospholipid antibody–related thrombotic events in HIV patients may occur in association with concomitant CMV infection, which in these cases usually represents a reactivation of infection [35]. Of note, aCL described in HIV patients were of both the pathogenic (β_2-GPI–dependent) and postinfectious (non–β_2-GPI–dependent) type that is more typical of postinfectious aCL and is presumably nonthrombogenic [30,36].

Taken together, infection with parvovirus B19, CMV, VZV, Epstein-Barr virus, HCV, and HIV have been associated with the development of aPL-related thrombotic events. Postinfectious aPL were present more than 12 weeks in some patients with thrombosis, fulfilling the consensus criteria for definite APS. Sera from patients with parvovirus B19, CMV, and HIV exhibited β_2-GPI–dependent aCL as found in autoimmune diseases. However, the presence of aCL in viral infections is principally non–β_2-GPI dependent, and assessment of cofactor dependency is suggested to distinguish patients most likely to experience aPL-related clinical features.

Bacterial infections

Originally, aCL were first detected in human serum in 1906, when Wasserman developed a complement fixation test for the diagnosis of syphilis and when the Venereal Disease Research Laboratory test was described. The test used the phospholipid cardiolipin as the major tissue extract antigen. Syphilis was thus the first infection associated with aPL, and subsequently many other bacterial infections have been linked with the presence of aPL. These include streptococcal and staphylococcal infections, *Mycoplasma pneumoniae*, *Coxiella burnetii*, *Escherichia coli*, other gram-negative bacteria, tuberculosis, and leprosy (Table 2) [2•].

Streptococci are among the most common causes of bacterial infection in childhood and have been shown to trigger production of aPL. Ardiles et al. [37] investigated the frequency of aCL in patients with acute poststreptococcal glomerulonephritis and streptococcal impetigo.

Positive IgG aCL were detected in 12 (44%) of the 27 patients with poststreptococcal glomerulonephritis and 4 (33%) of the 12 patients with streptococcal impetigo without any thrombotic events [37]. Controversy still exists over the prevalence and clinical significance of aCL in acute rheumatic fever. Figueroa et al. [38] demonstrated that a majority (80%) of 35 patients with acute rheumatic fever with or without Sydenham's chorea or carditis were positive for aCL, and the antibody level titer was related to disease activity. However, these results were not confirmed in later studies, which found no significant difference in aCL levels between patients with rheumatic fever or streptococcal pharyngitis and healthy controls [39].

M. pneumoniae is a major cause of respiratory infections in school-aged children and young adults and also has been associated with the presence of aPL, particularly in patients with severe infection and in patients with high titer of cold hemagglutinins [40]. Recently, *M. pneumoniae* infection was reported in several pediatric cases with thrombotic events secondary to aPL, including cardiac thrombus, internal carotid artery occlusion, and two cases with splenic infarcts [41,42].

A review of 100 published case reports categorized as having APS associated with infection identified staphylococci in 4%, streptococci in 4%, *E. coli* in 4%, other gram-negative bacteria in 3%, mycoplasmas in 3%, and tuberculosis in 2% of all cases [2•]. Thrombotic events associated with bacterial-induced aPL were recently described also in Lemierre syndrome, an emerging clinical entity characterized by jugular vein thrombosis and septic pulmonary embolism. It is commonly associated with an anaerobic, gram-negative bacillus *Fusobacterium necrophorum*, a normal inhabitant of the oral cavity [43]. Goldenberg et al. [43] detected the presence of LA in three of the seven (43%) children with Lemierre syndrome at presentation, but LA was no longer present in two of three (67%) cases at follow-up, suggesting epiphenomena of the acute inflammatory prothrombotic state.

The prevalence of aPL subtypes was investigated in several studies in sera from patients with leprosy [44,45]. Of interest, aCL, anti–β_2-GPI, and LA were frequently detected without any clinical features of APS. Some reports suggested heterogeneity of leprosy aCL with respect to their β_2-GPI requirement for binding to cardiolipin [44]. Leprosy-related aCL and anti–β_2-GPI resembled those found in patients with autoimmune diseases, but the IgM isotype was much more prevalent in leprosy patients [45].

From these studies, it appears that aPL may be induced by several bacterial infections, but aPL-related thrombotic events seem less frequent in bacterial infections than in association with severe viral infections. Special concern is needed, particularly when dealing with patients with streptococcal and staphylococcal infections, gram-negative bacteria, and in particular *M. pneumoniae* infection.

Parasitic infections

Among parasitic infections, malaria and leishmaniasis have been linked with the production of aPL. Consigny et al. [46] found a high prevalence of serum cofactor independent aCL in 137 individuals chronically exposed to *Plasmodium falciparum* or vivax infections. Additionally, Santiago et al. [47] clearly showed a significant prevalence of anti–β_2-GPI (53%) but not aCL (6%) in 30 patients with visceral leishmaniasis (kala-azar disease), suggesting that the current assay for the detection of anti–β_2-GPI antibodies may not reliably estimate the potential risk of thrombosis associated with this infection. To our knowledge, there were only two published cases of APS associated with malaria [2•].

Antiphospholipid antibodies in response to immunizations

In the past few years, medical and public interest in the safety of vaccination has been heightened by reports of possible vaccine-induced autoimmune phenomena. Minimal accurate information exists regarding the induction of the synthesis of aPL following routine immunizations in humans, but useful data are beginning to emerge. Our group performed a prospective longitudinal study in 85 healthy volunteers after immunization with recombinant DNA hepatitis B vaccine [48]. We observed a transient increase of aCL titers in two participants and a transient increase of anti–β_2-GPI titers in one participant [48]. Moreover, one subject who initially had low positive IgG for anti–β_2-GPI showed a progressive increase of the antibody level during 6 months of follow-up. Despite the fact that our results generally do not support a clear-cut influence of hepatitis B vaccine on aPL induction, the risk of developing a continuous long-term aPL response in genetically predisposed individuals can not be excluded [48].

Tarjan et al. [49] investigated the changes in the aPL levels of 18 patients with SLE after the third of annually repeated influenza vaccinations. Following influenza vaccination, it was observed that the median titers of IgG aCL significantly decreased, and in contrast, the median values of IgG and IgM anti–β_2-GPI significantly increased during the 8-week follow-up period. It appears that the repeated influenza vaccination of patients with SLE may result in increased anti–β_2-GPI antibody production, and careful clinical and laboratory follow-up of the immunized patients was recommended [49]. A few cases of Henoch-Schönlein purpura with aPL have been described in children following influenza vaccination [50].

Infections and the catastrophic antiphospholipid syndrome

The induction of thrombosis following infections has been well described in patients with catastrophic APS. Catastrophic APS is a rare, potentially life-threatening variant of APS characterized by aggressive microvascular occlusive disease involving many organs, especially the

kidneys, lungs, central nervous system, heart, and skin. A review of 80 patients with catastrophic APS revealed that 24% of cases were preceded by respiratory (10%), cutaneous (4%), urinary tract (4%), gastrointestinal tract (2%), general sepsis (1%), or other (3%) infections [7].

Pathogenesis and Experimental Models for an Infectious Origin of APS

Several excellent reviews have been published in recent years supporting an infectious etiopathogenesis of APS [3•,51]. Two groups have supplied experimental data establishing a mechanism of molecular mimicry between the microbial agent and the β_2-GPI molecule as a cause of APS. Blank et al. [52] identified a hexapeptide (TLRVYK) that is specifically recognized by pathogenic anti–β_2-GPI monoclonal antibodies and has a high homology with peptidic domain of various bacteria and viruses. High titers of pathogenic antipeptide (TLRVYK) anti–β_2-GPI antibodies were detected in those mice immunized with *Haemophilus influenzae*, *Neisseria gonorrhoeae*, or tetanus toxoid. Mouse IgG specific to the TLRVYK peptide were affinity purified from the immunized mice and passively infused intravenously into naïve pregnant mice. These mice then developed significant thrombocytopenia and increased fetal loss [52].

Additionally, Gharavi et al. [53] demonstrated induction of pathogenic aPL in mice by following immunization with a CMV-derived synthetic peptide (TIFI) that shares structural similarity with the putative phospholipid binding region of the β_2-GPI molecule (GDKV). These antibodies were subsequently injected into mice and produced a significant increase in the number of leukocytes adhering to endothelial cells as well as enhanced thrombus formation, confirming their pathogenicity in vivo [53].

Von Landenberg et al. [11] suggested molecular mimicry between viral and host proteins as an explanation for aPL production in association with persistent parvovirus B19 infection in patients with rheumatic diseases. It has been hypothesized that a unique region of the minor capsid protein VP1 of the human parvovirus B19 particle, which has phospholipase A_2-like activity, may contribute to the inflammatory tissue reaction in combination with a particular genetic predisposition and by generation of abnormal cleavage products from cellular phospholipid compounds, which in turn induce aPL in combination with a particular genetic predisposition [11].

Another putative mechanism of the infectious origin of APS is represented by the engagement of the innate immune receptors together with microbial agents and anti–β_2-GPI antibodies [54]. Research has convincingly demonstrated that both human monoclonal and polyclonal affinity-purified anti–β_2-GPI antibodies can induce an endothelial signaling cascade comparable to that activated by lipopolysaccharide (LPS) through the involvement of Toll-like receptor (TLR)-4. TLRs are a key component of the innate immunity. They function as efficient receptors able to drive a prompt inflammatory response after interaction with specific microbial products including LPS. β_2-GPI molecule shares structural homology with a number of microbial products, and it was demonstrated that anti–β_2-GPI antibodies can react with their antigen β_2-GPI associated with TLR4 to trigger the endothelial signaling cascade [54]. Because infectious processes frequently precede the full-blown clinical expression of APS, a two-hit hypothesis has been suggested with synergistic involvement of TLRs by microbial components and anti–β_2-GPI antibodies. Recently, it has been found that IgG antibodies from APS patients produced significantly larger thrombi in LPS+/+ mice compared to LPS-/- mice, suggesting that TLR4 was involved in in vivo aPL interaction with endothelial cells [55].

Conclusions

Several viral and bacterial infections may induce synthesis of aPL, and in some people, these antibodies may be accompanied by clinical manifestations of APS. Infections most frequently associated with APS include parvovirus B19, CMV, VZV, HIV, streptococcal and staphylococcal infections, gram-negative bacteria, and *M. pneumoniae*. Prospective studies with serial aPL determination in patients with infectious diseases are rare; therefore, it is not well known how long these postinfectious aPL persist after the acute phase of an infectious process. Screening for possible infectious agents should be considered in patients presenting with APS, and if the infections are identified, APS may be transitory. The distinction between autoimmune and postinfectious aPL on the basis of the requirement of a binding cofactor is not absolute, and there are several reports demonstrating that some patients can produce pathogenic antibodies in response to infection. Mild inherited deficits of hemostatic factors such as heterozygous deficiencies of anticoagulant proteins may synergistically influence the development of thrombosis associated with infections.

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have been highlighted as:

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