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Review

Complement and thrombosis in the antiphospholipid syndrome☆

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ABSTRACT

The involvement of complement activation in the pathophysiology of antiphospholipid syndrome (APS) was first reported in murine models of antiphospholipid antibody (aPL)-related pregnancy morbidities. We previously reported that complement activation is prevalent and may function as a source of procoagulant cell activation in the sera of APS patients. Recently, autoantibodies against C1q, a component of complement 1, were reported to be correlated with complement activation in systemic lupus erythematosus. These antibodies target neoepitopes of deformed C1q bound to various molecules (i.e., anionic phospholipids) and induce accelerated complement activation. We found that anti-C1q antibodies are more frequently detected in primary APS patients than in control patients and in refractory APS patients with repeated thrombotic events. The titer of anti-C1q antibodies was significantly higher in refractory APS patients than in APS patients without flare. The binding of C1q to anionic phospholipids may be associated with the surge in complement activation in patients with anti-C1q antibodies when triggered by 'second-hit' biological stressors such as infection. Such stressors will induce overexpression of anionic phospholipids, with subsequent increases in deformed C1q that is targeted by anti-C1q antibodies.

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Antiphospholipid syndrome (APS) is a clinical condition characterized by recurrent thrombosis and pregnancy morbidity in the presence of antiphospholipid antibodies(aPL). Despite the strong association between aPL and clinical manifestations of APS, the pathogenic role of aPL has not been fully elucidated; however, this role is possibly multifactorial in nature contributed by the various molecules of the immune system [1].

The complement system is composed of a series of proteins that are sequentially activated by external stimuli such as bacteria and represents one of the effector arms of antibody-mediated immunity. Among the three complement pathways, the classical pathway is activated mainly by the immune complexes. The immune complexes are bound to C1q, a subcomponent of the C1 protein, and activate C1r and C1s to cleave C2 and subsequently C4. Hypocomplementemia is prevalent in systemic lupus erythematosus (SLE), which is predominantly due to chronic inflammation, and forms the basis of the pathophysiology of this immune complex-mediated disease.

☆ The English in this document has been checked by at least two professional editors, both native speakers of English. For a certificate, please see: http://www.textcheck.com/certificate/Alx9v8.

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1. Complement activation in APS murine models

Antiphospholipid syndrome shares many clinical characteristics with SLE, including hypocomplementemia. The involvement of complement activation in the pathophysiology of APS was first reported in murine models of aPL-related pregnancy morbidities [2,3]. Briefly, complement-derived inflammatory mediators (anaphylatoxins) such as C4a, C3a, and C5a mainly contribute to the pathophysiology of complement-induced placentae inflammation. They increase vascular permeability, activate platelets or neutrophils [4], and promote the release of cytokines such as tumour necrosis factor (TNF) alpha from monocytes [5], which secondarily induces and accelerates systemic inflammation and coagulation. The involvement of the complement system in the manifestation of pregnancy morbidities in patients with APS was suggested from the analysis of the histopahology in the placentae of women with aPL [6] or by the registry of the patients [7].

However, there were fewer reports on engagement of the complement proteins in the pathogenesis of aPL-related thrombosis. An activated complement system itself has been shown to be associated with a prothrombotic state via the membrane attack complex or anaphylatoxins, particularly C5a. Anaphylatoxins via the specific receptors on the cell surfaces, activates monocytes or endothelial cells and induce productions of prothrombotic molecules such as tissue factors. Recently, the mutual interference of the complement system and platelets are reported that may also contribute to the complement-related thrombogenicity [8]. Using a murine model, Pierangeli *et al.* [9] reported that complement activation is essential for increasing thrombus size in aPL-related thrombosis model. Briefly, IgG extracted from the sera of APS patient was administered to mice and thrombus formation was examined. $C3^{-/-}$ and $C5^{-/-}$ mice had decreased thrombus formation compared to wild-type mice. The authors also reported that mice that received a monoclonal anti-C5 antibody showed a reduction in thrombus size. These data indicate the importance of the role of C3 or C5 in APL-related thrombosis. However, the thrombus of this murine model was surgically induced and the model did not produce spontaneous thrombosis such as in APS patients. In addition, few reports have shown that complement activation is related to the pathology of APS in humans.

2. Complement activation in APS patients

We previously evaluated the prevalence and significance of hypocomplementemia in primary APS patients and found that complement activation is prevalent in thrombotic APS [10]. Patients with primary APS had lower serum levels of C3, C4, and CH50 compared to healthy volunteers and patients with non-lupus connective tissue disease. There were significant inverse correlations between C3 or C4 levels and increased levels of C3a or C4a in the sera of primary APS patients, suggesting that the hypocomplementemia in primary APS is due to the consumption of complement proteins and activation of the complement pathway. However, C5a, a molecule that is relevant to the pathogenesis of thrombosis formation as well as miscarriages in APS murine models, was not detected in any of our primary APS patients. In addition, C5 levels in APS patients were within normal range. However, the findings of negative or lower C5a compared to C3a and C4a are consistent with reports in other diseases including SLE [11] [12]. As C5a is a strong mediator of inflammation, several molecules play roles as inhibitors during the progression of activation beyond C3a. Complement regulatory factors such as factor H, membrane cofactor protein (MCP), decay accelerating factor (DAF), and complement receptor 1 (CR1) are representative molecules that play roles in these inhibitory systems [13] and avoid C5a production.

Defects in complement regulatory factors likely evoke abnormal activation of the complement system and thus enhance inflammation. Some complement regulatory factors share structural units, so-called short consensus repeat (SCR) elements or Sushi-domains, with beta-2 glycoprotein I (β_2GPI), a major target of the aPL. A recent report showed that this 50 kDa glycosylated human plasma protein functions as a complement regulator [14]. β_2GPI, located on the surface of apoptotic cells, changes its conformation to an elongated form that acquires C3/C3b binding activities. β_2GPI changes the conformation of C3 to facilitate the degradation of C3 and mediates further cleavage of C3/C3b compared to factor H alone and strengthens the function of factor H, an inhibitor of complement activation. Moreover, a recent report showed that autoantibodies against factor H are prevalent in patients with APS and are related to recurrent venous thrombosis [15]. These results may lead to the hypothesis that APS patients with anti-β_2GPI antibodies will have more severe complement activation and recurrence of thrombosis; however, based on a cross-sectional study in primary APS patients, complement activation is not specifically associated with the presence or titer of anti-β_2GPI antibodies [10]. In addition, the specific upregulation of the degradative products of early components in the complement pathway in the absence of C5a production suggests that complement activation in patients with APS is not simply accountable for the dysfunction of factor H or other complement regulatory proteins that mainly inhibit the production of C5a or the activation of late components of the complement pathway.

3. Initiator of complement activation in APS

The origin of complement activation in APS has not been fully elucidated. Generally, the classical pathway is triggered by activation of the C1 complex, activation that occurs when C1q binds to immune complexes and modifies its conformation [16] and subsequently cleaves C2. The structure of C1q consists of two major regions: a collagen-like domain at the C-terminus and a globular domain at the N-terminus. Thus, complement activation in APS patients has been hypothesized to be caused by activation of the immune complex-triggered classical pathway [17]. However, we previously reported that immune complexes remain at low levels in sera of APS patients [10]. Moreover, we and others [18–20] have reported that aPLs associated with APS are IgG2-dominant. IgG2-containing immune complexes have low potential for inducing complement activation. On the other hand, C1q binds to phospholipids [21] or anionic–phospholipid binding proteins [22] [23] and activates the complement pathway in the absence of immune complexes. The initiator of the classical complement pathway activation in APS patients remains uncertain.

4. Anti-C1q antibodies in APS thrombosis

We previously reported that antibodies against C1q trigger and multiply activation of the complement pathway in primary APS patients [24]. Previous reports have shown that anti-C1q antibodies are correlated with the manifestations of SLE [25] [26]. Evidence has indicated that anti-C1q antibodies are associated with lupus activity and thus may serve as a biomarker of lupus flare [27].

We found that, in 40 consecutive primary APS patients, anti-C1q antibodies were more prevalent compared to 42 patients with non-SLE connective tissue disease (15/42 vs. 1/40), and that the serum C4a level was correlated with the anti-C1q antibody titer. This was the first report to show that anti-C1q antibodies are frequently detected in the sera of APS patients. Leukocytopenia as well as nephritis have been reported to be significantly associated with the existence of anti-C1q antibodies in lupus patients [26]. None of our primary APS patients had leukocytopenia nor aPL-related nephropathy. In addition, neither the anti-Sm antibody nor the anti-double stranded DNA antibody was present in the sera of any of our primary APS patients. The titer of anti-C1q antibodies was associated with any specific clinical manifestation of APS or that of aPL. However, the severity of APS apparently correlated with anti-C1q antibodies. APS patients with recurrent manifestations ($n = 10$) had a higher