Autoimmune Disease and Thrombosis

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Introduction

It has been recognized for decades that patients with autoimmune disorders are at risk for thrombotic events. Perhaps the most well known entity is the antiphospholipid antibody syndrome (APS). In this condition, antiphospholipid antibodies (APL) are markers for an increased risk of recurrent thrombosis and/or pregnancy loss. APS is intimately associated with systemic lupus erythematosus (SLE), and can occur as a primary entity or secondary to SLE. Even in the absence of APL, there is an increased risk of thrombosis that is associated with SLE. In addition to these two autoimmune disorders, it is recognized that the presence of other autoimmune diseases, such as inflammatory bowel disease, rheumatoid arthritis, or Bechet’s disease can increase the risk for thrombotic disease. Finally, while not typically thought of as an autoimmune disease, heparin induced thrombocytopenia (HIT) produces limb- and life-threatening thromboses primarily through an immune mediated component.

Antiphospholipid Syndrome (APS)

In 1941 it was found that sera from patients with syphilis reacted to cardiolipin, a phospholipid found in extracts of beef hearts\(^1\), \(^2\), and later in 1952 that patients with SLE acquired an “anticoagulant” that predisposed patients towards hemorrhage\(^3\). However, ensuing reports implicated these antibodies, not with syphilis or a hemorrhagic diathesis, but with thrombosis\(^4\), \(^5\). In 1975, recurrent miscarriages with this circulating anticoagulant (“antithromboplastin”) was described\(^6\).
Shortly thereafter, numerous reports began to appear, describing the clinical coexistence of a circulating anticoagulant, thrombotic events, and recurrent miscarriages. Eventually, this condition was termed “Antiphospholipid Syndrome” (APS) and grew to include manifestations in other organ systems. Other possible manifestations that are not part of the formal diagnostic criteria of APS include: thrombocytopenia, valvular heart disease, neurologic manifestations, and livedo reticularis. The formal criteria for the diagnosis of APS are based upon clinicopathologic criteria (Table 1). Clinical criteria require the documented occurrence of vascular thrombosis and/or pregnancy loss. Laboratory examinations require the presence of antiphospholipid antibodies (APL): lupus anticoagulant, anti-cardiolipin antibodies, and/or anti-b2-glycoprotein I that are persistent over 12 weeks from initial testing. When APS exists without the co-expression of another autoimmune disease, such as SLE, it is labeled as “Primary” APS; if it occurs with SLE, then it is called “Secondary APS.”

While the presence of APL in thrombotic disorders has been known for decades, the precise mechanisms remain unclear. APL that are purified from affected individuals and injected into mice, or APL that are provoked in mice from vascular injury lead to thrombosis. Furthermore, individual APL’s are found to have a broad range of reported actions, affecting the pro-thrombotic as well as anticoagulant pathways. Some of these reported mechanisms include: chronic platelet activation, as measured by micro-particle formation and CD62P; endothelial cells activation, as measured by the expression of tissue factor or generation of endothelial micro-particles; activation of monocytes, leading to the cell surface expression of tissue factor.

However, there appears to be a separate mechanism for pregnancy loss that is independent of thrombosis. Pathologic examinations of placentas do show thrombosis, but an inflammatory component has been noted. Drawing mainly from research performed in the murine model of APS and recurrent fetal wasting, complement activation appears to be the pathway behind recurrent pregnancy loss in APS. Use of mice that are deficient in C3 or C5, blockade of C3 or C5, or use of heparin, reduces the rate of fetal wasting in mice. Yet, when alternative anticoagulants are used, such as fondaparinux or hirudin, there is no protection against fetal loss, arguing that anticoagulation in and of itself is insufficient to prevent pregnancy loss.
Table 1. Criteria for the diagnosis of APS per international guidelines.
Systemic Lupus Erythematosus

A disease closely linked with APS is Lupus, sharing similar auto-immune profiles and end-organ manifestations. As stated above, SLE is another autoimmune disorder where thrombosis is a prevalent manifestation. When compared to patients without SLE, the incidence of a thrombotic event is nearly 100x greater in SLE patients\textsuperscript{22}.

Patients with SLE may have APL, particularly the Lupus Anticoagulant, Anticardiolipin Antibodies, as well as antibodies against b\textsubscript{2}-GPI. While the prevalence of these antibodies in the general population is only about 10\%, in the SLE cohorts the prevalence of these autoimmune markers may approach 50\%. However, this is tempered by the observation that patients with SLE who do not have APL are still at an increased risk for thrombosis.

There are a number of proposed mechanisms to explain this increased risk of thrombosis in SLE. One intriguing mechanism is the disruption of the protective effects of Annexin V. Annexin V forms a “shield” over the blood vessel wall, protecting against thrombosis. When plasma from patients with lupus was incubated with vascular endothelial cells, it was observed that annexin V function was inhibited\textsuperscript{23}. In most cases, this effect appears to be due to antiphospholipid antibodies; however, there are other non-immune factors that impact upon the incidence of thrombosis in SLE. It has been observed that cigarette smoking, older age, and prolonged or severe history of SLE predisposed to thrombosis\textsuperscript{24}. Surprisingly, patients that used the medication hydroxychloroquine appeared to be protected against thrombosis\textsuperscript{25}.

Other Autoimmune Diseases

Behçet’s Disease

This disease is characterized by recurrent oral and genital ulcers, uveitis, and neurological involvement\textsuperscript{26}. Thrombotic events are noted in as many as 33\% of affected patients, usually occurring in the deep or superficial veins of the lower extremities\textsuperscript{26}. Affected patients may also have thrombotic events in their hepatic veins, known as Budd-Chiari syndrome\textsuperscript{27}, which can be life-threatening. Some do not consider this to be a true auto-immune disorder, as the hallmark of Behçet’s Disease is vascular endothelial injury; however, there are many immune components that are implicated in this condition. While the mechanism(s) for clot formation in Behçet’s Syndrome remain elusive, several hypotheses have been put forward. Investigation of patient’s with Behçet’s Syndrome has implicated the involvement of IgM antibodies to phosphatidylyserine and prothrombin\textsuperscript{28}; elevated levels of serum endothelial protein C receptor\textsuperscript{29}; and decreased levels of activated protein C\textsuperscript{30}.

Wegener’s Granulomatosis
Wegener’s granulomatosis is an auto-immune disease affecting small- and medium-sized blood vessels that is clinically characterized by hematuria, hemoptysis, and sinus involvement. Patients appear to be at an increased risk of thrombotic events, particularly during acute flares of their disease\textsuperscript{31}. Further analysis of affected patients reveals that traditional risk factors for thrombosis, such as APL or mutations in Factor V or in the 3’ region of Factor II, are not likely to contribute to the observed thrombotic events\textsuperscript{32}.

\textit{Inflammatory Bowel Disease}

Crohn’s Disease and Ulcerative Colitis are complicated by a 3-fold increased risk of thrombosis that is independent of an increased hospitalization rate\textsuperscript{33}. As with Wegener’s Granulomatosis, there does not appear to be an increase in the incidence of the typical hypercoagulable states. Rather, research has implicated an imbalance in the fibrinolytic system in patients with IBD\textsuperscript{34}, as well as damage to the endothelial layer causing an increase in platelet and neutrophil activation, leading to an increase in platelet and leukocytes aggregation in vessels, possibly increasing the risk for thrombosis\textsuperscript{35}.

\textit{Other}

Venous thromboembolism has been reported in patients with other autoimmune disorders, but less frequently than the disorders listed above. Autoimmune disorders that exhibit a very mild risk for venous thromboembolism include rheumatoid arthritis\textsuperscript{36}, Sjogren’s syndrome\textsuperscript{37}, and psoriasis\textsuperscript{38}. 
**Heparin Induced Thrombocytopenia**

Heparin Induced Thrombocytopenia (HIT) is a known complication of treatment with unfractionated heparin (UFH) and, rarely, with low molecular weight heparin (LMWH). Based upon the research performed over the last 30 years, an immune component has been uncovered. HIT is a unique autoimmune disorder, in which use of an anticoagulant leads to thrombocytopenia, that is paradoxically associated with limb- or life-threatening thrombosis.

The pathogenesis of HIT begins with UFH binding to Platelet Factor 4 (PF4), leading to the formation of a neoepitope that induces an auto-immune response. While IgM and IgA are formed in HIT, these isotypes are not felt to be pathogenic. Instead, the IgG that is formed is responsible for to the pathophysiology of HIT. The IgG that recognizes the UFH:PF4 complex forms an “ultralarge” complex of IgG:UFH:PF4. The Fc portion of all the IgG upon the ultralarge complex binds to its platelet receptor, FcγRIIA, cross-linking them and leading to platelet stimulation. This autoimmune response leads to platelet aggregation, release of intracellular contents, including additional PF4 release, which leads to a positive feedback cycle. Platelet micro-particles, which are known to be procoagulant, also lead to thrombin generation. This cascade of events: platelet activation, aggregation, and micro-particle formation leads to an uncontrolled thrombin generation. In addition, immune mediated endothelial cell activation further potentiates this cascade, leading to the devastating thrombotic complications observed in HIT.

**References**


