

Immune Thrombocytopenia in Antiphospholipid Syndrome

Subjects: **Biochemistry & Molecular Biology**

Contributor: Mariasanta Napolitano

Antiphospholipid syndrome (APS) is frequently associated with thrombocytopenia, in most cases mild and in the absence of major bleedings. In some patients with a confirmed APS diagnosis, secondary immune thrombocytopenia (ITP) may lead to severe thrombocytopenia with consequent major bleeding. At the same time, the presence of antiphospholipid antibodies (aPL) in patients with a diagnosis of primary ITP has been reported in several studies, although with some specific characteristics especially related to the variety of antigenic targets.

antiphospholipid antibodies

antiphospholipid syndrome

thrombocytopenia

lupus anticoagulant

immune thrombocytopenia

1. Introduction

Antiphospholipid antibody syndrome (APS) is an autoimmune acquired thrombophilia characterized by recurrent thrombosis and pregnancy morbidity in the presence of antiphospholipid antibodies (aPL), namely anticardiolipin antibodies (aCL), anti- β 2 glycoprotein I (Anti- β 2GPI) antibodies, and lupus anticoagulant (LA) [1][2][3]. The aPL are a heterogeneous group of antibodies that react with phospholipids (PLs), PL-protein complexes, and PL-binding proteins. The main antigenic targets of these antibodies are β 2GPI and prothrombin, which together account for more than 90% of the antibody-binding activity in APS; antigenic targets also include tissue plasminogen activator (tPA), phosphatidylserine (PS), plasmin, annexin 2, activated protein C (APC), thrombin, antithrombin III (AT-III), and annexin V [4][5][6][7][8][9][10]. Antiphospholipid antibodies represent the strongest acquired risk factors for arterial and venous thrombosis and also the most common acquired thrombophilia. Clinical symptoms of APS include thrombosis in any blood vessel of any organ, with no substantial differences between veins and arteries.

Primary immune thrombocytopenia (ITP) is an autoimmune disorder characterized by isolated thrombocytopenia due to both immune-mediated platelet destruction by antiplatelet antibodies that generally recognize platelet membrane glycoproteins (GPs) and impaired platelet production without other causes or disorders that may be associated with low platelets count. Primary ITP leads to an increased risk of bleeding, although some patients may be asymptomatic [11].

2. APS and Thrombocytopenia

Thrombocytopenia occurs in APS with a frequency ranging from 20% to 50%, and the estimated bleeding risk associated with it is much lower than the thrombotic risk associated with aPL. That said, it is important to explore the mechanism behind thrombocytopenia in order to establish the most appropriate treatment strategy in these patients, especially when anticoagulant or antiplatelet agents are needed [12].

The pathogenesis of thrombocytopenia in antiphospholipid antibody-positive patients is not fully understood. However, based on currently available data [13][14][15][16][17][18][19], we here summarize four different mechanisms, reported in [Table 1](#).

Table 1. Pathogenetic mechanisms involved in thrombocytopenia within the context of APS.

Pathogenesis Hypothesis	Pathway
Secondary Immune Thrombocytopenia	<ul style="list-style-type: none"> Expression of platelet membrane glycoproteins, especially GPIIb/IIIa, increases after aPL stimulation, and the binding of anti-β2GPI-β2GPI complex to receptors on the platelet membrane induces the activation and aggregation of platelets.
Decreased platelet production	<ul style="list-style-type: none"> Antibodies directed against GP on the cell wall of platelets (GPIIb/IIIa, GPIb/IX, GPIa/IIa, and GPIV) have been identified in 40%–70% of thrombocytopenic patients with APS.
Increased platelet pooling	<ul style="list-style-type: none"> APS can associate with Hemophagocytic Syndrome, although it is extremely rare, and bone marrow necrosis. Both conditions may cause a decrease in platelet production.
Increased platelet consumption	<ul style="list-style-type: none"> This condition can be suspected in patients with splenomegaly secondary to portal vein or splenic vein thrombosis due to APS. aPL can mediate upregulation of Von Willebrand Factor (vWF) production by endothelial cells and by direct platelet activation, resulting in an increased vWF-platelet binding.

Clinical Significance of APL-Positivity in ITP

An international consensus introduced the definition of “aPL-associated thrombocytopenia” when the laboratory findings of aPL are associated with thrombocytopenia in the absence of APS-defining criteria [3].

According to ITP guidelines, when aPL are detected in an ITP patient without a history of thrombosis or obstetric complications, this finding will not change the diagnosis of primary ITP nor the recommended treatment (with an important caveat on thrombopoietin receptor agonists, discussed in a dedicated section). The latest ASH "ITP Practice and Guideline Panel" on the contrary, stated that evaluating ITP patients for aPL is unnecessary [20] due to the lack of good evidence of clinical association [21]. Several studies, on the other hand, go in a different direction:

- A study by Diz-Kucukkaya et al. found that 45.1% of a cohort of ITP patients who were persistently positive for aPL developed later APS [22];
- A study by Machin et al. showed that the statistically most relevant risk factor for thrombosis in patients with thrombocytopenia is the co-diagnosis of APS, over an average 5-years follow-up [23];
- A study by Hisada et al. found that the combination of aPL and thrombocytopenia doubled the risk of future thrombosis over an average 10-years follow-up [20]
- A study by Funauchi et al. demonstrated that women with ITP and aPL-positivity had increased thrombosis and obstetric complications risks when compared to the aPL-negative group [24];
- An interesting cross-sectional study reported that the platelet counts of patients with a diagnosis of high-risk APS (triple positive: LAC, anti-beta2-GPI, and aCL) decreased earlier before the appearance of a full clinical picture of CAPS [25]. Therefore, the screening for aPL may identify a subgroup of ITP patients at higher risk of thrombosis.
- The already mentioned International Consensus Panel stated that thrombocytopenia occurring in patients with persistent aPL-positivity is associated with increased thrombotic risk and therefore should be considered different from simple ITP [2];
- Data from the Italian Registry of Antiphospholipid Antibodies reported that 40% of the APS patients with moderate thrombocytopenia and 9% of the APS patients with severe thrombocytopenia developed thrombosis [17];
- A review by Frison et al. on the records of 233 outpatients with primary or secondary thrombocytopenia (platelet count $< 100 \times 10^9/L$) concluded that triple-positive patients had a significantly lower median platelet count compared to other patients with aPL-positivity [26].

Even though it does not enter the APS defining criteria, thrombocytopenia should be regarded as a warning sign, at least in the assessment of high-risk APS and thoroughly evaluated. At the same time, the presence of aPL during ITP should be assessed to stratify the risk of thrombosis.

3. The Treatment of Antiphospholipid Antibodies Syndrome

Standard care for thrombotic APS is long-term (LT) anticoagulation with a vitamin K antagonist (VKA) [27]. There is currently insufficient evidence to recommend the use of direct oral anticoagulants (DOACs) over VKA in thrombotic APS. The largest studies conducted on this topic showed that DOACs were associated with an increase in hemorrhagic adverse events and an increased thrombosis incidence when compared to VKA [28].

While the recommendation on VKA in APS with a history of venous thromboembolism (VTE) is strong, it is not yet clear if patients with APS and arterial thromboses can really benefit from long-term anticoagulation with VKA rather than prophylaxis with antiplatelet agents, such as LDA. Many experts, in fact, recommend VKA treatment for patients with APS and a history of arterial thromboses because they have a general tendency to recur, thus suggesting that a therapeutic approach based on long-term anticoagulation may be safer than LDA alone. Some authors indicate maintaining a INR target of 3–4 for APS patients with recurrent arterial thrombosis (versus 2–3 of APS patients with a history of recurrent VTE) [29]; however, patients with a history of stroke and a low-titer of aCL may be treated with LDA alone [27].

Pregnant women with thrombotic APS should be treated with LDA in association with therapeutic-dose heparin, regardless of the pregnancy history. LDA or prophylactic-dose low molecular weight heparin (LMWH) can be used in pregnant women with APS but no prior history of thrombosis (including 6 weeks postpartum) [27].

A combined therapy of anticoagulant treatment, glucocorticoids, plasma exchange (PEX), and intravenous high dose immunoglobulin (HD-IVIG) can be used in catastrophic APS (CAPS). Cyclophosphamide can also be used in CAPS when associated with a secondary autoimmune disease, such as SLE. Rituximab can be used in refractory cases, after failure or inability to take the above-mentioned combined therapies or in the presence of microangiopathic hemolytic anemia [27], [Table 2](#).

Table 2. Potential treatments of APS with or without thrombosis.

Patient Group	Clinical History	I Line Therapy
non-triple-positive aPL carrier	No thrombotic events	No prophylaxis required
triple-positive aPL carrier	No thrombotic events	Primary prophylaxis with LDA may be considered
thrombotic APS	VTE	Secondary prophylaxis with LT-VKA (target INR 2.5, range 2–3)
thrombotic APS	Arterial thrombosis	Secondary prophylaxis with LT-VKA (target INR 3.5, range 3–4) or LDA
obstetric APS	VTE/arterial thrombosis	LDA + LMWH
CAPS	Without secondary CTD *	Anticoagulation + glucocorticoids + HD-IVIG + PEX

Patient Group	Clinical History	I Line Therapy
CAPS	Secondary CTD	Anticoagulation + glucocorticoids + HD-IVIG + PEX + cyclophosphamide
Thrombotic APS/CAPS	Refractory disease; Microangiopathic hemolytic anemia	Anticoagulation + glucocorticoids + HD-IVIG + PEX + rituximab

*: connective tissue disease, including SLE.

4. Management of aPL-Associated Thrombocytopenia

4.1. The Role of anti-CD20 MoAb in Treating aPL-Associated Thrombocytopenia

The chimeric anti-CD20 monoclonal antibody rituximab is commonly adopted as a second-line treatment for immune thrombocytopenia or other immune cytopenias; available studies have reported the efficacy of this treatment with response rates at 1 year ranging from 50% to 60% for immune thrombocytopenia [30] to 75% for warm autoimmune hemolytic anemias [31]. Rituximab has also been evaluated for its efficacy on renal and extra-renal symptoms of SLE. However, primary study endpoints were not reached in two trials [32][33]. An observational cohort study reported in patients with SLE treated with rituximab [34] a clinical response in up to 70% of cases. A pilot phase 2 study confirmed the safety of rituximab in aPL-positive patients and suggested, even in the absence of any change in aPL levels, the efficacy of rituximab in controlling some non criteria manifestations of APS [35]. There are no controlled clinical trials exploring if rituximab is effective in the antiphospholipid syndrome. However, it could balance the effect of bleeding and thrombosis in APS patients with severe thrombocytopenia. By reducing the production of autoantibodies, rituximab could simultaneously raise the platelets count and reduce the risk of thrombosis [36].

4.2. Thrombopoietin Receptor Agonists in the II Line Treatment of Connective Tissue Disease-Associated Thrombocytopenia

Thrombopoietin receptor agonists are a novel class of molecules that interact with the thrombopoietin receptor exposed by hematopoietic stem cells promoting proliferation and differentiation of megakaryocytes in the bone marrow, thus increasing peripheral blood functioning platelet count through a dose-dependent mechanism [37].

The TPO-RA Eltrombopag was approved by FDA in 2008 for the treatment of chronic ITP with a solid efficacy and safety profile that has been well defined in the course of the last ten years. There are currently no clinical trials evaluating the efficacy or safety of Eltrombopag in second or further lines treatment of secondary ITP or Connective Tissue Disease (CTD)-associated thrombocytopenia, with the unique exception of SLE. A few case reports showed that both Eltrombopag and Romiplostim can be successfully used in cases of SLE-associated thrombocytopenia, refractory to first-line immunosuppression therapy [38].

Some studies found an association between TPO-RA and incidence of VTE and arterial thrombosis in patients with chronic liver disease or acquired thrombophilia, such as aPL-positivity or APS. This may be due to the potential role of TPO-RA in enhancing the autoimmune response [39].

4.3. Hydroxychloroquine as a Possible Second Line Agent in APS-Associated Thrombocytopenia

HCQ is commonly adopted for the treatment of SLE. So far, only a few studies have explored the role of HCQ in the treatment of thrombocytopenia associated with SLE; in detail, combined treatment with prednisone and HCQ resulted effective in 7/11 (64%) patients among a cohort of 59 subjects affected by thrombocytopenia and SLE [40]. More recently, HCQ has been administered to treat thrombocytopenia after the failure of first-line oral prednisone treatment (N = 40), either in patients with SLE (N = 12) or with positive antinuclear antibodies (ANA), without overt SLE (N = 28) with a good response rate (60%), [41]. Interestingly, among the enrolled patients, LA, aPL, aCL, and anti β 2GP1 were also detected in the group without overt SLE. Based on these data, the administration of HCQ for the management of aPL-associated thrombocytopenia should be taken into account as a potential second-line option. Eular recommendations [42] have recently included in the “research agenda”, the evaluation of HCQ administration as a prophylactic treatment option in patients with high-risk aPL profile, including those with non criteria APS manifestations (i.e., thrombocytopenia). A study by Nuri et al. demonstrated that chronic therapy with HCQ can decrease aCL and anti- β 2GPI IgG and IgM titers with seemingly no impact on thrombosis risk [43].

HCQ may also be able to prevent paradoxical clots by decreasing endothelial dysfunction induced by aPL [44].

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