Blood Reviews 58 (2023) 101015

Contents lists available at ScienceDirect

Blood Reviews

journal homepage: www.elsevier.com/locate/issn/0268960X

Review

Hematological manifestations of antiphospholipid syndrome: Going beyond thrombosis

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ARTICLE INFO

Keywords:
Antiphospholipid
Thrombocytopenia
Bleeding
Hemolysis
Anemia
Bone marrow diseases

ABSTRACT

Thrombotic complications are a hallmark of antiphospholipid syndrome (APS). These vascular – arterial, venous, and/or small vessel – complications are well described and known to hematologists and healthcare providers caring for patients with this disease. In this review, we shed light on other hematological manifestations of the disease, including bleeding, thrombocytopenia, autoimmune hemolytic anemia, and thrombotic microangiopathy syndromes. While these manifestations are not bona fide clinical criteria for the diagnosis of APS, they frequently interact and contribute to the complexity of clinical management of APS.

1. Introduction

Antiphospholipid syndrome (APS) is a clinical autoimmune condition characterized by a thrombotic and/or pregnancy-related complications [1]. Despite the wide variation in laboratory findings and clinical manifestations, APS has a well-defined set of diagnostic criteria that were intended to identify homogenous groups of patients for clinical or translational research purposes (1; 2). These criteria include (i) laboratory criteria consisting of positive antiphospholipid antibodies (aPLs) and (ii) clinical criteria consisting of venous or arterial thrombosis and/or pregnancy loss or morbidity [2].

Certain clinical manifestations that were previously considered as part of the APS classification criteria were not included in the revised Sapporo classification criteria [2]. Examples of these manifestations include livedo reticularis, cutaneous ulcers, immune thrombocytopenia, autoimmune hemolytic anemia, cardiac valvular disease, and nephropathy. With advances in the laboratory and at the bedside [3], other standardized antibody specificities, such as IgG/IgM anti-phosphatidylserine/prothrombin antibodies, were found to play a central role in the pathophysiology of certain APS clinical manifestations [4]. However, given the lack of certainty regarding clinical significance, testing for antibodies other than anticardiolipin (aCL) and anti-beta2-glycorpotein I (anti-b2-GP1) antibodies is not routinely performed. These antibodies that have been linked to APS include antiprothrombin antibodies, anti-annexin V, anti-phosphatidylserine, and anti-phosphatidylinositol antibodies [5].

While vascular and thrombotic complications appropriately constitute the crux of the clinical criteria to diagnose APS, other hematological manifestations are often underdiagnosed. Therefore, we present this review of non-thrombotic (non-criteria) hematological manifestations of APS (Fig. 1) as a guide for clinicians – particularly hematologists, rheumatologists, and family practitioners – caring for the patient with APS.

2. Thrombocytopenia

2.1. Immune thrombocytopenia (ITP)

2.1.1. Epidemiology

Immune thrombocytopenia (ITP) is an acquired immune-mediated disorder characterized by isolated thrombocytopenia (platelet count <100,000/μL) in the absence of an underlying secondary cause [6]. Clinically, secondary ITP is commonly considered a potential complication associated with APS.

There is variable prevalence of aPL among patients with ITP [7,8]. Before the first APS international classification criteria were set, aPL, specifically aCL, were found in 30% of patients with ITP [8]. Among an Italian group of patients in 1994, an incidence of 46.3% was reported,

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https://doi.org/10.1016/j.blre.2022.101015

Available online 16 September 2022

with 36.2% of patients being positive for lupus anticoagulant (LAC) [9]. In a French cohort, around 26% of patients with ITP had at least one positive aPL, with a majority being positive for anti-β2 glycoprotein 1 (b2GP1) antibodies [10]. In a study from India, approximately 12% of patients with ITP had positive aPL [11]. In a study from the pediatric sphere, 27.5% of patients with ITP were positive for LAC [12]. While these epidemiologic descriptions have been reported, clinical practice guidelines do not recommend evaluating patients with ITP for aPL due to the absence of solid evidence for clinical association in comparison with appropriate controls [13,14]. In addition, aPL positivity does not typically change the management of ITP except if other criteria of APS are satisfied or raised.

Patients with APS present with thrombocytopenia at frequencies ranging between 20% and 40% [10]. The bleeding risk associated with thrombocytopenia within the context of APS is typically lower than the thrombotic risk. This is supported by reports of higher adjusted Global APS Score (aGAPSS) [15] in patients with thrombocytopenia [16]. However, it is important to examine this complication closely especially that patients with APS are frequently on anticoagulant or antiplatelet agents.

Severe thrombocytopenia ($<30 \times 10^9$/L) has been reported in catastrophic APS (CAPS) [17]. While these patients may not present any significant clinical or serological features that can distinguish them from APS patients without thrombocytopenia [18], some evidence suggests increased risk for thrombosis [13,19].

2.1.2. Pathophysiology

Platelets, neutrophils, endothelial cells, and monocytes are involved in the pathogenesis of thrombosis in APS [20]. Circulating platelet- and endothelial-derived microparticle levels are elevated in patients with APS [21]. In murine models, platelets were found to be the first target for circulating anti-b2-GPI-b2-GPI complexes which promote endothelial activation [22]. Specific receptors and mediators can play a role in the activation of platelets and aPL, potentially leading to thrombocytopenia (Table 1).

it is important to note that, while Table 1 summarizes the proposed mechanisms of thrombocytopenia in APS, these have not been clearly established or validated. Another mechanism leading to thrombocytopenia in APS patients is splenomegaly. Splenomegaly may lead to the sequestration of platelet-derived complexes and subsequent thrombocytopenia [23]. In APS patients, splenomegaly can be found without an underlying cause such as infections, hematological disorders, portal hypertension, or malignancy [23]. Very rarely, the presence of aPL has been linked to Evans' syndrome [24,25], an autoimmune disorder characterized by autoimmune hemolytic anemia (AIHA), thrombocytopenia, and/or neutropenia [26].

2.1.3. Management

The first step is to confirm that thrombocytopenia is not secondary to an alternative etiology such as medications or infection. In most cases, thrombocytopenia is usually mild, and thus the bleeding risk is minimal with APS treatment [27]. Anticoagulation is considered safe with a stable platelet count of >50,000/μL [28]. In the absence of alternative etiologies, thrombocytopenia to a level lower than 30,000/μL should raise the concern for microangiopathy [28].

The treatment of severe thrombocytopenia in patients with APS follows principles similar to ITP treatment otherwise [29]. Fig. 2 discusses the role of ITP therapies in APS.

2.2. Heparin-induced thrombocytopenia (HIT)

Patients with APS can rarely develop HIT. aPL can bind to heparin [30]. aPL have been identified at the site of vascular injury in systemic lupus erythematosus (SLE) [31]. Because of platelet activation, platelet

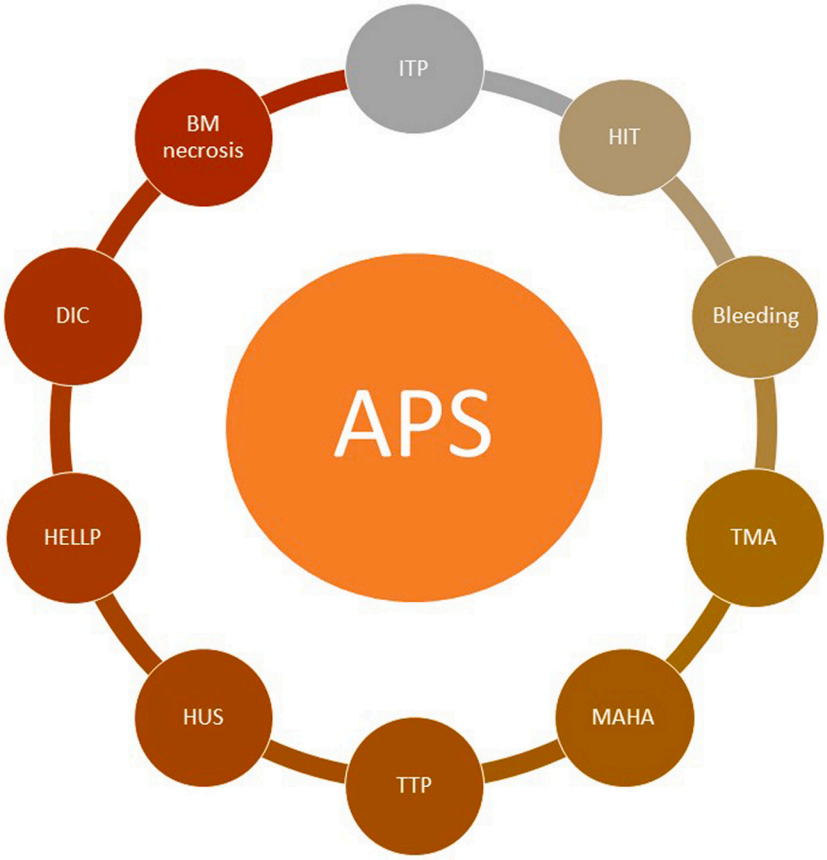

Fig. 1. Summary of the non-criteria hematological manifestations of antiphospholipid syndrome (APS).
APS: Antiphospholipid syndrome; ITP: Immune thrombocytopenia; HIT: Heparin-induced thrombocytopenia; TMA: Thrombotic microangiopathy; MAHA: Microangiopathic hemolytic anemia; TTP: Thrombotic thrombocytopenic purpura; HUS: Hemolytic uremic syndrome; HELLP: hemolysis, elevated liver enzymes, low platelet count; DIC: Disseminated intravascular coagulation; BM necrosis: Bone marrow necrosis.

Table 1
Common receptors and mediators that can lead to thrombocytopenia by interaction with platelets and anti-β2-GPI-β2-GPI complexes.

Receptor or mediator	Result of aPL interaction	Effect on platelets
TLR-2 (Receptor)	Increased protein levels of the activated TLR transduction protein (IL-1 receptor-associated kinase 1) leading to monocyte activation [106]	Accumulation of oxidized phospholipids leading to platelet hyperreactivity and aggregation [107]
TLR-4 (Receptor)	Generation of intracellular signal transduction pathway induces activation of peritoneal macrophages and VECs [108]	Lipopolysaccharide-induced thrombocytopenia and platelet accumulation in the liver and lung [109–111]
Annexin A2 (Receptor)	Cross linking of β2GPI/anti-β2GPI antibodies and anti-annexin A2 antibodies leads to endothelial cell activation [112]	Inhibition of aggregation [113]
Gp Ibα (Receptor)	Activation of platelets releases procoagulant factors [114]	Adherence to thrombin and platelet recruitment to the involved site with subsequent consumption [115]
LRP-8 (Receptor)	Activation of platelets with induction of thomboxane A2 synthesis [116]	Modulate activation in vitro and thrombosis in vivo via apolipoproteins [117]
vWF (Mediator)	Binding causes more release of vWF especially from human umbilical vein endothelial cells providing a nidus for the formation of thrombi [118]	Formation of a reduced number of platelets by megakaryocytes, ectopic release of platelets in the bone marrow, and increased clearance of platelet/vWF complexes [119]
ApoER2' (Receptor)	Increased release of PP2A, a procoagulant [120]	Platelet activation with release of thromboxane A2 [116]
Fcγ-receptor IIa	Increased risk of thrombosis, unclear mechanism [121]	Aggregation via integrin αIIbβ3 activation and P-selectin surface expression [122]

TLR-2: Toll-like receptors 2; TLR-4: Toll-like receptors 4; A-2: Annexin-2; Gp Ibα: Glycoprotein Ibα; LRP-8: Low-density lipoprotein receptor-related protein 8; vWF: von Willebrand Factor; VECs: Vascular endothelial cells; ApoER2': Apolipoprotein E receptor 2'; PP2A: Phosphatase 2A.

factor 4 (PF4) could be released [32]. PF4 can bind to heparan sulfate on endothelial cells, and this complex could trigger the generation of HIT antibodies [32]. The process can definitely be augmented in patients treated with heparin [32]. Conversely, HIT antibodies can lead to the generation of aPL. HIT antibodies cause vascular damage and a configurational change in the membrane phospholipids of endothelial cells which can lead to the production of antibodies to such phospholipids [32]. HIT in APS requires anticoagulation. Non-heparin anticoagulants are recommended [32]. The choice of anticoagulant remains debatable, with case reports supporting the use of direct thrombin inhibitors (bivalirudin) [33].

3. Bleeding

Although thrombosis is a classical clinical manifestation in APS, major bleeding occurs in 10% of patients [34]. The risk of bleeding is increased by certain patient characteristics including renal impairment and old age [35].

APS bleeding can occur inside the organs, such as diffuse alveolar hemorrhage and adrenal hemorrhage. Diffuse alveolar hemorrhage is the result of inflammation and necrosis of the pulmonary circulation with a resulting hemorrhage [36,37]. Despite being very rare in the context of APS [38], the frequency can reach about 10% in CAPS [39]. Some of the proposed mechanisms for diffuse alveolar hemorrhage in APS concentrate on the activation of L-ficolin, an innate protein, which in turn activates the lectin pathway of complement in the lung tissue [40]. In addition, the activation of systemic inflammatory response syndrome can result in cytokine activation leading to acute lung inflammation via increasing neutrophil migration which can result in the loss of the integrity of the alveolar capillary basement membrane, thus permitting subsequent extravasation of red blood cells into the alveoli [37,41]. High-dose corticosteroids are the mainstay of the therapy during the acute period [35]. Cyclophosphamide or rituximab-based regimens have also around 50% remission rates based on case reports and case series [40].

Adrenal insufficiency due to adrenal hemorrhage in APS has been reported. Around one third of patients with APS developing adrenal hemorrhage are in a catastrophic phase [42]. The triggers for adrenal hemorrhage in APS include surgical procedures, infections, trauma, and warfarin withdrawal [42]. The main mechanism is related to the thrombotic risk. Since there is a limited venous drainage of the adrenal gland by a single vein, there is an increased risk of the development of adrenal vein thrombosis and hemorrhagic infarction [43]. Because of adrenal insufficiency, patients with adrenal hemorrhage should receive intravenous hydrocortisone promptly [35]. Notably, antithrombotic therapy should be maintained as much as possible [35]. Major bleeding can contribute to precipitating CAPS, especially if the anticoagulation is held for a prolonged period of time [35]. The combination of plasma exchange and/or IVIG can be added as a rescue therapy, especially in the setting of CAPS [44].

One of the rare APS-associated entities that can lead to life threatening bleeding complications is lupus anticoagulant-hypoprothrombinemia syndrome (LAHPS), which is characterized by an acquired factor II deficiency in the setting of LAC [45,46]. Non-neutralizing antibodies against prothrombin are the key in the pathogenesis of LAHPS (Fig. 3). The rapid clearance of the antigen-antibody complex by the reticuloendothelial system can cause major life threatening bleeding [47]. Early diagnosis of LAHPS is critical as the complications can be fatal. A high index of suspicion should be maintained with appropriate evaluation of factor II activity when indicated.

Corticosteroids, which tend to decrease the clearance of the prothrombin-antiprothrombin antibody complexes, are the mainstay of treatment in LAHPS [35]. The dilemma lies in the fact that patients with LAHPS are at an increased risk for both thrombosis and bleeding. Therefore, the use of long term anticoagulation is debatable.

4. Thrombotic microangiopathic syndromes

4.1. Thrombotic thrombocytopenic purpura (TTP)

Differentiating between TTP and APS is a clinical challenge. While TTP occurs in the context of occlusive microangiopathy, APS thrombotic complications involve all vessel sizes. The presence of autoantibodies to a disintegrin-like and metalloprotease with thrombospondin type I motif, member 13 (ADAMTS13) is essential for the development of microthrombosis in TTP [48].

Patients with APS can possess antibodies to ADAMTS13, despite that no specific aPL targets ADAMTS13 [48]. Nevertheless, patients with APS can have a decreased renal clearance of von Willebrand factor (vWF) [48]. Therefore, TTP can be induced by aPL. After the development of antibodies against ADAMTS13, a lack of metalloprotease activity within the vasculature, leads to lack of regulation of the clotting cascade and resultant clots within small vessels [49].

Plasmapheresis and steroids should be rapidly administered once TTP, with or without APS, is suspected [50]. In the patient presenting with neurological symptoms and thrombocytopenia, checking both antiphospholipid antibodies and ADAMTS13 activity should be pursued until the entities of CAPS and TTP are excluded [51].

4.2. Hemolytic uremic syndrome (HUS)

Among thrombotic microangiopathic syndromes in adults, HUS has been reported to be the most commonly occurring disorder in the setting

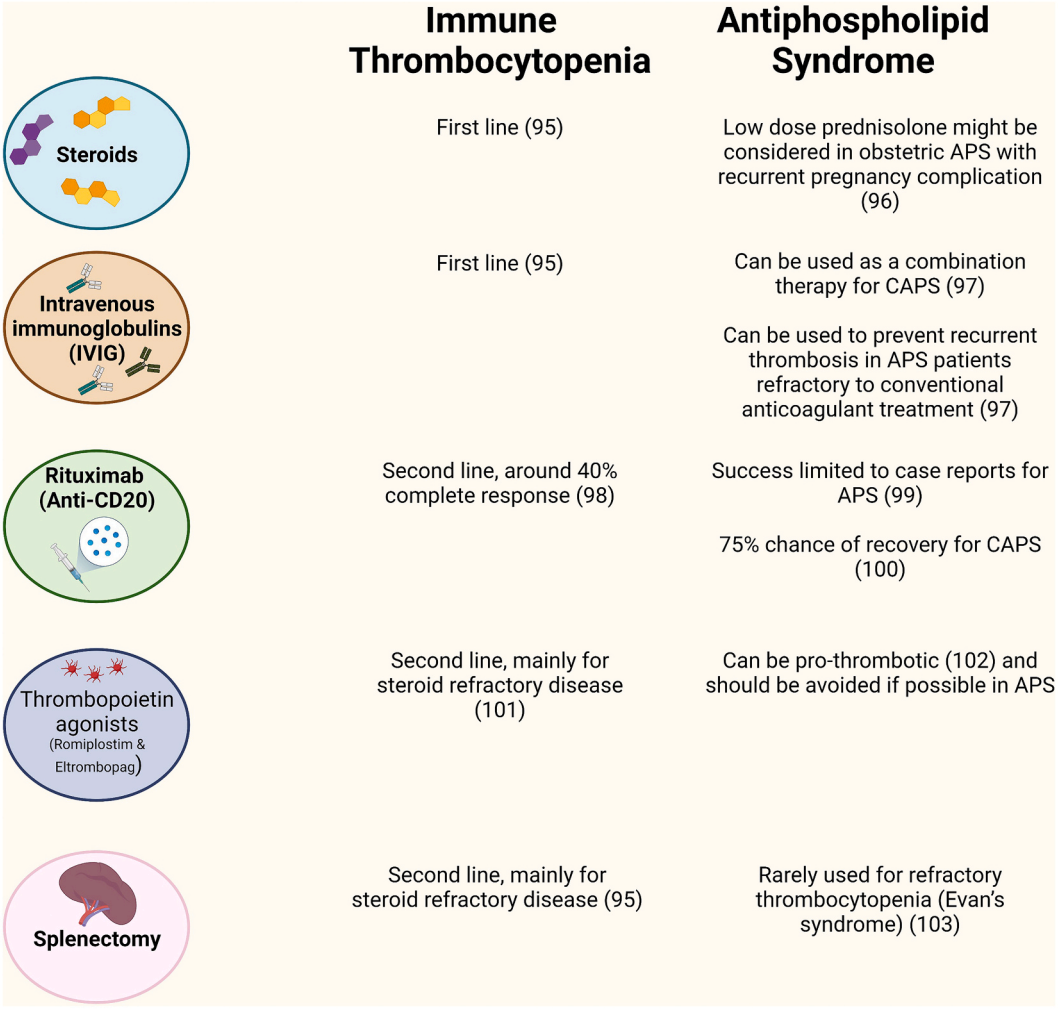

Fig. 2. Summary of the role of common treatments used for immune thrombocytopenia (ITP) and their indications in antiphospholipid syndrome (APS) [95–103]. Created with BioRender®.

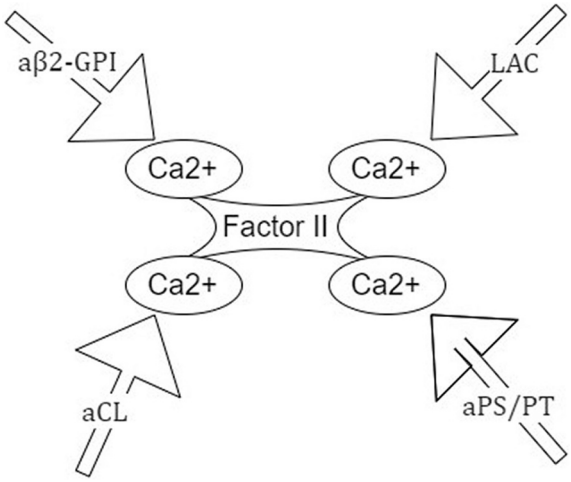

Fig. 3. Proposed mechanism for lupus anticoagulant-hypoprothrombinemia syndrome [104,105].

of aPL [52]. aPL were found in sera of patients with diarrhea-associated adult HUS [53]. Very rarely, aPL can be present in pediatric patients with atypical HUS [54]. Fatality has been reported among APS patients with HUS [52].

Plasma from patients with adult HUS has demonstrated apoptosis of microvascular endothelial cells [55]. Endothelial damage results in widespread release of unusually large vWF multimers ultimately causing platelet aggregation and thrombosis [56]. Relatively recent data suggest that anti-b2GPI antibodies from patients with APS activate complement – an event associated with thrombosis in APS. In addition, most patients with CAPS have underlying complement regulatory gene variants predisposing to increased complement activity, thrombosis, and organ failure [57].

It is important to differentiate between HUS, TTP, and CAPS (Table 2).

Table 2
Similarities and differences between hemolytic uremic syndrome (HUS), thrombotic thrombocytopenic purpura (TTP), and catastrophic antiphospholipid syndrome (CAPS).

Parameters	HUS	TTP	CAPS
Thrombocytopenia	Marked	Marked	Variable (mild to severe)
Schistocytes	Marked	Marked	Rare or absent
aPTT	Normal	Normal	Elevated
aPL	+/−	+/−	Significantly elevated
Plasma activity of ADAMTS 13	Normal	Decreased	Normal
Preceding bacterial infection	+	−	+/−

aPTT: Activated partial thromboplastin time; aPL: Antiphospholipid antibodies; ADAMTS 13: A disintegrin and metalloproteinase with thrombospondin type 1 motif, 13.

4.3. HELLP syndrome (hemolysis, elevated liver enzymes, low platelet count)

Pre-eclampsia complicates around 8% of all pregnancies and is a major contributor to maternal mortality worldwide [58]. HELLP syndrome complicates around 10 to 20% of severe pre-eclampsia cases [58]. Despite the paucity of data, a relationship has been reported between HELLP and aPL, in particular CAPS.

The interplay between aPL and endothelial cells may explain the occurrence with HELLP. Insufficient migration of trophoblast in the spiral arteries associated with aPL have been reported [59]. aPL may reduce the amount of annexin V in the trophoblasts and the production of prostacycline, leading to reduced fibrinolysis and therefore induction of resistance to activated protein C [59]. The resulting hypercoagulable state and placental spiral artery vasculopathy may be associated with pre-eclampsia and HELLP syndrome through a mechanism of placental insufficiency [60].

The presence of aPL in HELLP has been described as a poor prognostic indicator [61]. Certain non-criteria clinical manifestations of APS have been reported in the context of aPL-positive HELLP. For example, APS nephropathy progressing to renal failure requiring dialysis has been described [62].

The treatment protocol of HELLP in the context of positive aPL has not been fully established yet. Symptomatic treatment for hypertension, platelet transfusion, and magnesium sulfate, routinely used in pre-eclampsia, may be useful in aPL positive HELLP [63]. Anticoagulation with oral, intravenous, and subcutaneous anticoagulants has been used [63]. Typically, therapeutic plasma exchange has no benefit in patients with HELLP. The mainstay of therapy for HELLP occurring during pregnancy remains delivery. Therapy with heparin and aspirin may prevent obstetric complications in subsequent pregnancies.

4.4. Other thrombotic microangiopathies

APS leads to noninflammatory occlusion of renal blood vessels which may lead to renal ischemia or thrombotic microangiopathy involving the glomeruli, which are non-overt thrombotic events. Thrombotic microangiopathy is histologically characterized by vessel wall abnormalities leading to microvascular thrombosis. The diagnosis is typically made on a renal biopsy specimen. Patients with APS and thrombotic microangiopathies tend to have higher frequency of arterial events than APS without thrombotic microangiopathies [64]. In CAPS associated with thrombotic microangiopathy, large vessels are typically involved [65]. The pathophysiology of APS-related thrombotic microangiopathy has been linked to complement activation [66]. Patients with thrombotic microangiopathy in the glomeruli or thrombosis in larger vessels should be treated with anticoagulation to avoid irreversible and potentially fatal vascular damage. The use of eculizumab has been reported in the setting of preventing recurrent thrombotic episodes in patients with APS as complement activation is one of the critical mechanisms of thrombosis [67]. While anecdotally beneficial, evidence for eculizumab based on prospective or large retrospective studies is lacking.

5. Autoimmune hemolytic anemia (AIHA)

The clinical significance of the relationship between autoimmune hemolytic anemia (AIHA) and APS or aPL positivity is yet to be established. aPL positivity seems to be associated with an increased risk of AIHA, especially with LAC, IgM aCL, and IgM anti-b2GP1 [68]. Although the mechanism of AIHA in APS remains unclear, the presence of several autoantibodies directed against red blood cell surface cell membrane structures can explain the manifestations [68].

Notably, AIHA has been more reported with secondary APS rather than primary APS [69,70]. Patients with AIHA and positive aPL are at a higher risk of developing systemic lupus erythematosus [71]. Furthermore, these patients are prone to developing myocardial infarctions [71]. Other manifestations that can be seen in AIHA patients with positive aPL, despite being rare, include livedo reticularis, chorea, intrauterine growth restriction, or pregnancy toxemia [71].

6. Other causes of anemia

6.1. Iron deficiency

Comparing a group of APS patients to healthy individuals, iron deficiency was more common among APS [72]. The etiologies of this finding were attributed to significant reduction in folic acid and vitamin C intake as well as malabsorption of iron [72]. The role of reactive oxygen species may also be one explanation for low vitamin C in APS [73].

The assessment of iron deficiency in patients with APS can be challenging. Hyperferritinemia is more common among patients with APS than healthy individuals, especially among patients with CAPS [74]. Therefore, ferritin alone would not be a good indicator of iron deficiency in APS.

6.2. Vitamin B12 deficiency

In line with data data in SLE, hyperhomocysteinemia is present among secondary APS patients [75]. Homocysteine levels were found to be elevated in obstetric and thrombotic APS [76]. Elevation in homocysteine levels has been reported to be associated with an increased risk for a major thromboembolic event in APS [77]. On the contrary, recent pieces of evidence suggest that the rate of thrombotic events, thrombocytopenia, seizures, and livedo reticularis are not significantly different between APS with vitamin B12 deficiency and without vitamin B12 deficiency [78].

7. Special conditions

7.1. Philadelphia-negative myeloproliferative neoplasms

7.1.1. Polycythemia vera (PV) and essential thrombocythemia (ET)

The co-existence of APS or aPL and PV is rarely reported. The pathophysiological basis for such an occurrence remains unknown. The JAK2 V617F mutation, frequently found in PV [79], has been linked to thrombosis via neutrophil extracellular traps (NETs), a mechanism linked to APS [80,81]. Anticoagulation with vitamin K antagonist or direct oral anticoagulants could be considered [82].

As in PV, limited data is present on the occurrence of ET in APS patients. Interestingly, there is a propensity for such patients to have recurrent thrombotic events [82]. One explanation for that is the release of negative charge on platelet phospholipid membranes which allows b2GP1 to bind to such membranes, exposing epitopes for aPL subtypes [83].

An important consideration for a co-existing PV/ET and APS is the bleeding risk as the treatment of PV/ET can be an antiplatelet agent such as aspirin and the treatment of APS is anticoagulation. Additionally, in ET, patients with significant thrombocytosis may develop a clinical picture of acquired von Willebrand syndrome. Bleeding events might include bilateral adrenal hemorrhage and hematuria [82].

7.1.2. Myelofibrosis

The co-occurrence of primary MF and APS is still rarely reported (Table 3). The autoimmune mechanism of MF involving hypocomplementemia hints towards a possible association with APS, especially secondary APS [84]. Autoimmune myelofibrosis is a non-hematologic cause of bone marrow fibrosis, and it typically responds to immunosuppression targeted at treating the underlying autoimmune disorder, specifically APS in this situation. Autoimmune MF has been reported in aPL positive SLE patients treated with glucocorticoids [85,86]. For CAPS, MF has been reported as a long-term fatal outcome

Table 3
Selection of reported cases of antiphospholipid syndrome and reported myelofibrosis in the literature.

Case	MF characteristics	APS characteristics	Outcome
Bregani et al. [123]	Hepatosplenic myeloid metaplasia	aPL, unspecified	NA
Niki et al. [124]	Bone marrow fibrosis and extramedullary hematopoiesis of the spleen.	B2GPI with cerebral infarction	Failure of high dose prednisolone, high dose gamma-globulin, and splenectomy Remission with azathioprine
Katayama et al. [125]	Bone marrow fibrosis	aCL and recurrent splenic infarctions	Recurrent thrombosis Died after 5 years of diagnosis
Breccia et al. [126]	Presence of splenomegaly, anisopoikilocytosis with teardrop erythrocytes, circulating immature myeloid cells, circulating erythroblasts, and presence of clusters of megakaryoblasts in bone marrow section	aCL and LAC with DVT of the leg	Development of paroxysmal cold hemoglobinuria treated with high dose of prednisone

aPL: Antiphospholipid antibodies; aCL: Anticardiolipin antibodies; B2GPI: Anti-β2 glycoprotein 1; LAC: Lupus anticoagulant; DVT: Deep vein thrombosis.

[87]. It may be challenging for the clinician to discern primary MF from autoimmune MF without longitudinal follow-up.

7.2. Leukemias

Antiphospholipid antibodies have been reported in the context of hematological malignancies [88]. Interestingly, patients with chronic myelomonocytic leukemia (CMML) can rarely develop CAPS in the long term [89]. The predisposing mechanism involves a release of aPL by the malignant cells themselves leading to thrombosis [89]. Patients with CMML and positive aPL are prone to multiple thrombotic episodes, and glucocorticoids may be needed as part of the treatment regimen [89]. We mention aPL positivity and clinical APS here in the context of leukemias in an attempt to be as comprehensive as possible. It is difficult to establish a strong association, let alone causality, based on case reports and series.

7.3. Thalassemia

The data on thalassemia and APS is dependent on the serotype of aPL. For example, LAC prevalence ranges from 0 to 25.8% on a single screening test without confirmation among polytransfused thalassemia patients [90]. Intracranial bleeds and cerebral infarctions have been reported as complications [90]. As for aCL, it can be present in transfusion dependent thalassemia patients but at low titers not causing any thrombotic or bleeding complications [91]. Nevertheless, hepatitis C positive thalassemia patients are more likely to be aCL or b2GPI positive but without increased risk of APS complications [91,92].

When compared to transfusion dependent thalassemia, the prevalence of aPL among non-transfusion dependent thalassemia pediatric patients is higher [93]. The reduction of the amount of phosphatidylserine surface exposing the red blood cell by blood transfusions might explain the lower prevalence of aPL in transfusion dependent thalassemia [94].

8. Conclusions and future directions

While thrombosis is the hallmark of APS, the practicing hematologist, rheumatologist, and internist should be mindful of other non-criteria hematological manifestations of the disease. Thrombocytopenia is frequently found in APS and, unless profound, typically requires no intervention. Profound thrombocytopenia, via platelet surface-b2 GPI-aPL interaction, may complicate APS treatment and increase the risk of bleeding. Corticosteroids and IVIG remain the treatment of choice, with consideration of immunosuppressive agents especially rituximab, particularly in the context of CAPS. Heparin-induced thrombocytopenia has been also reported in APS through endothelial damage, with therapeutic options including an array of non-heparin anticoagulants despite the scarcity of prospective data. Bleeding has been also reported in APS and CAPS. Internal organ hemorrhage has been linked to prolonged anticoagulation use in APS. It is important to keep in mind the necessity to hold anticoagulation for the shortest duration possible as prolonged periods off anticoagulation may contribute to precipitating CAPS. Hemolysis in APS can mimic CAPS. Clinical history, cell counts, coagulation profile, and levels of ADAMTS-13 can allow differentiation between CAPS, other TMA, and hemolytic diseases. In a nutshell, the hematological manifestations of APS go beyond thrombosis, may be associated with significant morbidity and mortality, and should be promptly identified to minimize long-term repercussions.

Practice points

- Antiphospholipid syndrome can be complicated by certain non-thrombotic manifestations which have different treatment approaches than thrombosis.
- -When no obvious cause is present, antiphospholipid antibodies can be taken into consideration when assessing thrombocytopenia, autoimmune hemolytic anemia, and microangiopathies.

Research agenda

- Assessing thrombocytopenia as a clinical criterion for the diagnosis of antiphospholipid syndrome.
- Determining and predicting the exact incidence and prevalence of different non-thrombotic manifestations in antiphospholipid syndrome.
- Evaluating the role of antiphospholipid antibodies in Philadelphia-negative myeloproliferative neoplasms and autoimmune hemolytic anemia.

Disclosures

Nothing to disclose.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

[1] Lim W. Antiphospholipid syndrome. Hematology Am Soc Hematol Educ Program 2013;2013:675–80.
[2] Miyakis S, Lockshin MD, Atsumi T, Branch DW, Brey RL, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost 2006;4:295–306.
[3] Dabit JY, Valenzuela-Almada MO, Vallejo-Ramos S, Duarte-Garcia A. Epidemiology of antiphospholipid syndrome in the general population. Curr Rheumatol Rep 2022;23:85.
[4] Pregnolato F, Chighizola CB, Encabo S, Shums Z, Norman GL, et al. Anti-phosphatidylserine/prothrombin antibodies: an additional diagnostic marker for APS? Immunol Res 2013;56:432–8.
[5] Bertolaccini ML, Amengual O, Andreoli L, Atsumi T, Chighizola CB, et al. 14th international congress on antiphospholipid antibodies task force. Report on

antiphospholipid syndrome laboratory diagnostics and trends. Autoimmun Rev 2014;13:917–30.
[6] Rodeghiero F, Stasi R, Gernsheimer T, Michel M, Provan D, et al. Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. Blood 2009;113:2386–93.
[7] Bidot CJ, Jy W, Horstman LL, Ahn ER, Jimenez JJ, et al. Antiphospholipid antibodies in immune thrombocytopenic purpura tend to emerge in exacerbation and decline in remission. Br J Haematol 2005;128:366–72.
[8] Harris EN, Gharavi AE, Hegde U, Derue G, Morgan SH, et al. Anticardiolipin antibodies in autoimmune thrombocytopenic purpura. Br J Haematol 1985;59:231–4.
[9] Stasi R, Stipa E, Masi M, Oliva F, Sciarra A, et al. Prevalence and clinical significance of elevated antiphospholipid antibodies in patients with idiopathic thrombocytopenic purpura. Blood 1994;84:4203–8.
[10] Pierrot-Deseilligny Despujol C, Michel M, Khellaf M, Gouault M, Intrator L, et al. Antiphospholipid antibodies in adults with immune thrombocytopenic purpura. Br J Haematol 2008;142:638–43.
[11] Dayama A, Dass J, Mahapatra M, Saxena R. Incidence of antiphospholipid antibodies in patients with immune thrombocytopenia and correlation with treatment with steroids in north Indian population. Clin Appl Thromb Hemost 2017;23:657–62.
[12] Dash S, Marwaha RK, Mohanty S. Lupus anticoagulant in immune thrombocytopenic purpura. Indian J Pediatr 2004;71:505–7.
[13] Hisada R, Kato M, Sugawara E, Fujieda Y, Oku K, et al. Thrombotic risk stratification by platelet count in patients with antiphospholipid antibodies: a longitudinal study. J Thromb Haemost 2017;15:1782–7.
[14] George JN, Woolf SH, Raskob GE, Wasser JS, Aledort LM, et al. Idiopathic thrombocytopenic purpura: a practice guideline developed by explicit methods for the American Society of Hematology. Blood 1996;88:3–40.
[15] Sciascia S, Cuadrado MJ, Sanna G, Murru V, Roccatello D, et al. Thrombotic risk assessment in systemic lupus erythematosus: validation of the global antiphospholipid syndrome score in a prospective cohort. Arthritis Care Res (Hoboken) 2014;66:1915–20.
[16] Radin M, Ugolini-Lopes MR, Sciascia S, Andrade D. Extra-criteria manifestations of antiphospholipid syndrome: risk assessment and management. Semin Arthritis Rheum 2018;48:117–20.
[17] Veneri D, Franchini M, Randon F, Nichele I, Pizzolo G, Ambrosetti A. Thrombocytopenias: a clinical point of view. Blood Transfus 2009;7:75–85.
[18] Cuadrado MJ, Mujic F, Munoz E, Khamashta MA, Hughes GR. Thrombocytopenia in the antiphospholipid syndrome. Ann Rheum Dis 1997;56:194–6.
[19] Demetrio Pablo R, Muñoz P, López-Hoyos M, Calvo V, Riancho L, Martínez-Taboada VM. Thrombocytopenia as a thrombotic risk factor in patients with antiphospholipid antibodies without disease criteria. Med Clin (Barc) 2017;148:394–400.
[20] Chaturvedi S, McCrae KR. Diagnosis and management of the antiphospholipid syndrome. Blood Rev 2017;31:406–17.
[21] Breen KA, Sanchez K, Kirkman N, Seed PT, Parmar K, et al. Endothelial and platelet microparticles in patients with antiphospholipid antibodies. Thromb Res 2015;135:368–74.
[22] Proulle V, Furie RA, Merrill-Skoloff G, Furie BC, Furie B. Platelets are required for enhanced activation of the endothelium and fibrinogen in a mouse thrombosis model of APS. Blood 2014;124:611–22.
[23] Cikrikcioglu MA, Hursitoglu M, Erkal H, Inan B, Ozturk T, et al. Splenomegaly in primary antiphospholipid syndrome without accompanying portal hypertension or comorbidity. Pathophysiol Haemost Thromb 2010;37:104–9.
[24] Avcin T, Jazbec J, Kuhar M, Zupancic M, Rozman B. Evans syndrome associated with antiphospholipid antibodies. J Pediatr Hematol Oncol 2003;25:755–6.
[25] Zarza J, Von Horoch J, Aguayo N, Baez E. Evans syndrome associated with antiphospholipid antibodies in a patient with SARS-COV-2 infection. Hematol Transfus Cell Ther 2020;42:309–12.
[26] Audia S, Grienay N, Mounier M, Michel M, Bonnotte B. Evans' syndrome: from diagnosis to treatment. J Clin Med 2020;9.
[27] Artim-Esen B, Diz-Kucukkaya R, Inanc M. The significance and management of thrombocytopenia in antiphospholipid syndrome. Curr Rheumatol Rep 2015;17:14.
[28] Vreede AP, Bockenstedt PL, McCune WJ, Knight JS. Cryptic conspirators: a conversation about thrombocytopenia and antiphospholipid syndrome. Curr Opin Rheumatol 2019;31:231–40.
[29] Neunert C, Lim W, Crowther M, Cohen A, Solberg Jr L, et al. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. Blood 2011;117:4190–207.
[30] Shibata S, Harpel PC, Gharavi A, Rand J, Fillit H. Autoantibodies to heparin from patients with antiphospholipid antibody syndrome inhibit formation of antithrombin III-thrombin complexes. Blood 1994;83:2532–40.
[31] Pengo V, Biasiolo A, Fior MG. Binding of autoimmune cardiolipin-reactive antibodies to heparin: a mechanism of thrombosis? Thromb Res 1995;78:371–8.
[32] Hoppensteadt DA, Walenga JM. The relationship between the antiphospholipid syndrome and heparin-induced thrombocytopenia. Hematol Oncol Clin North Am 2008;22(1–18):v.
[33] Ibrahim W, Nakia H, Stephen M, Bruce S, Bryan W, William P. A patient with remote heparin-induced thrombocytopenia and antiphospholipid syndrome requiring cardiopulmonary bypass: do current guidelines apply? Semin Cardiothorac Vasc Anesth 2019;23:256–60.
[34] Cervera R, Serrano R, Pons-Estel GJ, Ceberio-Hualde L, Shoenfeld Y, et al. Morbidity and mortality in the antiphospholipid syndrome during a 10-year period: a multicentre prospective study of 1000 patients. Ann Rheum Dis 2015;74:1011–8.
[35] Pazzola G, Zuily S, Erkan D. The challenge of bleeding in antiphospholipid antibody-positive patients. Curr Rheumatol Rep 2015;17:7.
[36] Lara AR, Schwarz MI. Diffuse alveolar hemorrhage. Chest 2010;137:1164–71.
[37] Krause ML, Cartin-Ceba R, Specks U, Peikert T. Update on diffuse alveolar hemorrhage and pulmonary vasculitis. Immunol Allergy Clin North Am 2012;32:587–600.
[38] Stoots SA, Lief L, Erkan D. Clinical insights into diffuse alveolar hemorrhage in antiphospholipid syndrome. Curr Rheumatol Rep 2019;21:56.
[39] Bucciarelli S, Espinosa G, Cervera R, Erkan D, Gomez-Puerta JA, et al. Mortality in the catastrophic antiphospholipid syndrome: causes of death and prognostic factors in a series of 250 patients. Arthritis Rheum 2006;54:2568–76.
[40] Cartin-Ceba R, Peikert T, Ashrani A, Keogh K, Wylam ME, et al. Primary antiphospholipid syndrome-associated diffuse alveolar hemorrhage. Arthritis Care Res (Hoboken) 2014;66:301–10.
[41] Espinosa G, Cervera R, Font J, Asherson RA. The lung in the antiphospholipid syndrome. Ann Rheum Dis 2002;61:195–8.
[42] Ramon I, Mathian A, Bachelot A, Hervier B, Haroche J, et al. Primary adrenal insufficiency due to bilateral adrenal hemorrhage-adrenal infarction in the antiphospholipid syndrome: long-term outcome of 16 patients. J Clin Endocrinol Metab 2013;98:3179–89.
[43] Anson BJ, Cauldwell EW, et al. The blood supply of the kidney, suprarenal gland, and associated structures. Surg Gynecol Obstet 1947;84:313–20.
[44] Espinosa G, Santos E, Cervera R, Piette JC, de la Red G, et al. Adrenal involvement in the antiphospholipid syndrome: clinical and immunologic characteristics of 86 patients. Medicine (Baltimore) 2003;82:106–18.
[45] Mazodier K, Arnaud L, Mathian A, Costedoat-Chalumeau N, Haroche J, et al. Lupus anticoagulant-hypoprothrombinemia syndrome: report of 8 cases and review of the literature. Medicine (Baltimore) 2012;91:251–60.
[46] Reddy S, Friend S, Quintana D, Lockhart EL. Early detection of lupus anticoagulant-hypoprothrombinemia syndrome by rotational thromboelastometry. Blood 2015;126:4699.
[47] Erkan D, Bateman H, Lockshin MD. Lupus anticoagulant-hypoprothrombinemia syndrome associated with systemic lupus erythematosus: report of 2 cases and review of literature. Lupus 1999;8:560–4.
[48] Austin SK, Starke RD, Lawrie AS, Cohen H, Machin SJ, Mackie IJ. The VWF/ADAMTS13 axis in the antiphospholipid syndrome: ADAMTS13 antibodies and ADAMTS13 dysfunction. Br J Haematol 2008;141:536–44.
[49] Hanna RM, Hanna M, Larson B, Lopez EA, Wilson J, Hendifar AJJoO-N. Thrombotic Microangiopathy due to Catastrophic Antiphospholipid Antibody Syndrome Confirmed on Skin Biopsy and Treated with Eculizumab1; 2017. p. e1–7.
[50] Scully M, Hunt BJ, Benjamin S, Liesner R, Rose P, et al. Guidelines on the diagnosis and management of thrombotic thrombocytopenic purpura and other thrombotic microangiopathies. Br J Haematol 2012;158:323–35.
[51] Viner M, Murakhovskaya I. A rare combination of thrombotic thrombocytopenic purpura and antiphospholipid syndrome. Blood Coagul Fibrinolysis 2017;28:411–5.
[52] Espinosa G, Bucciarelli S, Cervera R, Lozano M, Reverter JC, et al. Thrombotic microangiopathic haemolytic anaemia and antiphospholipid antibodies. Ann Rheum Dis 2004;63:730–6.
[53] Ardiles LG, Olavarria F, Elgueta M, Moya P, Mezzano S. Anticardiolipin antibodies in classic pediatric hemolytic-uremic syndrome: a possible pathogenic role. Nephron 1998;78:278–83.
[54] Shiari R, Parvaneh VJ, Dalirani R, Farivar S, Shiva MR. Atypical hemolytic-uremic syndrome associated with antiphospholipid antibodies and antiphospholipid syndrome; a novel presentation. Pediatr Rheumatol 2014;12:P363.
[55] Mitra D, Jaffe EA, Weksler B, Hajjar KA, Soderland C, Laurence JJB, et al. Thrombotic Thrombocytopenic Purpura and Sporadic Hemolytic-Uremic Syndrome Plasmas Induce Apoptosis in Restricted Lineages of Human Microvascular Endothelial Cells89; 1997. p. 1224–34.
[56] Yamazaki S, Taki M, Yasumuro Y, Takayama S, Miyake F, et al. Von Willebrand factor-cleaving protease activity in patients of collagen disease with antiphospholipid antibodies. Rinsho Byori 2002;50:301–7.
[57] Chaturvedi S, Braunstein EM, Yuan X, Yu J, Alexander A, et al. Complement activity and complement regulatory gene mutations are associated with thrombosis in APS and CAPS. Blood 2020;135:239–51.
[58] Coolman M, de Groot CJ, Jaddoe VW, Hofman A, Raat H, Steegers EA. Medical record validation of maternally reported history of preeclampsia. J Clin Epidemiol 2010;63:932–7.
[59] Asherson RA, Pierangeli S, Cervera R. Microangiopathic antiphospholipid-associated syndromes revisited new concepts relating to antiphospholipid antibodies and syndromes. J Rheumatol 2007;34:1793–5.
[60] Steegers EA, von Dadelszen P, Duvekot JJ, Pijnenborg R. Pre-eclampsia. Lancet 2010;376:631–44.
[61] Pécourt M, Yelnik C, Ghesquiere L, Drumez É, Cailliau É, et al. Is the presence of antiphospholipid antibodies a poor prognostic factor for patients with hemolysis, elevated liver enzymes, and low platelet count syndrome? Am J Obstet Gynecol 2021;225(4). 432–432, [225:432.e1-.e7].
[62] Ulander VM, Stefanovic V, Rinta-Kiikka I, Kaaja R. Pregnancy-associated recurrent liver necrosis in patient with antiphospholipid syndrome. Lupus 2006;15:889–91.

[63] Appenzeller S, Souza FH, Silva Wagner, de Souza A, Shoenfeld Y, de Carvalho JF. HELLP syndrome and its relationship with antiphospholipid syndrome and antiphospholipid antibodies. Semin Arthritis Rheum 2011;41:517–23.
[64] Freire de Carvalho J, Brandão Neto R, Skare T. Thrombotic microangiopathy in primary antiphospholipid syndrome is linked to stroke and less deep venous thrombosis. Eur Rev Med Pharmacol Sci 2021;25:7369–74.
[65] Wani AM, Hussain WM, Mejally MA, Ali KS, Raja SH, et al. Catastrophic cerebral antiphospholipid syndrome presenting as cerebral infarction with haemorrhagic transformation after sudden withdrawal of warfarin in a patient with primary antiphospholipid syndrome. BMJ Case Rep 2010;2010.
[66] Chaturvedi S, Brodsky RA, McCrae KR. Complement in the pathophysiology of the antiphospholipid syndrome. Front Immunol 2019;10:449.
[67] Lonze BE, Zachary AA, Magro CM, Desai NM, Orandi BJ, et al. Eculizumab prevents recurrent antiphospholipid antibody syndrome and enables successful renal transplantation. Am J Transplant 2014;14:459–65.
[68] Bernardoff I, Picq A, Loiseau P, Foret T, Dufrost V, et al. Antiphospholipid antibodies and the risk of autoimmune hemolytic anemia in patients with systemic lupus erythematosus: a systematic review and meta-analysis. Autoimmun Rev 2022;21:102913.
[69] Gelman R, Kharouf F, Ishay Y, Gural A. Cold agglutinin-mediated autoimmune hemolytic Anemia in association with antiphospholipid syndrome. Acta Haematol 2021;144:693–7.
[70] Ames PRJ, Merashli M, Bucci T, Pastori D, Pignatelli P, et al. Antiphospholipid antibodies and autoimmune Haemolytic Anaemia: a systematic review and Meta-analysis. Int J Mol Sci 2020;21.
[71] Rottem M, Krause I, Fraser A, Stojanovich L, Rovensky J, Shoenfeld Y. Autoimmune hemolytic anaemia in the antiphospholipid syndrome. Lupus 2006;15:473–7.
[72] Klack K, Monma V, Pelicari K, Appenzeller S, de Carvalho JF. The prevalence of iron deficiency anemia in primary antiphospholipid syndrome: primer antifosfolipid sendromda demir eksikligi anemisinin prevalansi. Turkish J Rheumatol 2013;28. 96+.
[73] Simoncini S, Sapet C, Camoin-Jau L, Bardin N, Harle JR, et al. Role of reactive oxygen species and p38 MAPK in the induction of the pro-adhesive endothelial state mediated by IgG from patients with anti-phospholipid syndrome. Int Immunol 2005;17:489–500.
[74] Agmon-Levin N, Rosario C, Katz BS, Zandman-Goddard G, Meroni P, et al. Ferritin in the antiphospholipid syndrome and its catastrophic variant (cAPS). Lupus 2013;22:1327–35.
[75] Martinez-Berriotxoa A, Ruiz-Irastorza G, Egurbide MV, Rueda M, Aguirre C. Homocysteine, antiphospholipid antibodies and risk of thrombosis in patients with systemic lupus erythematosus. Lupus 2004;13:927–33.
[76] Jiang H, Wang CH, Jiang N, Li J, Wu CY, et al. Clinical characteristics and prognosis of patients with isolated thrombotic vs. obstetric antiphospholipid syndrome: a prospective cohort study. Arthritis Res Ther 2021:23:138.
[77] Avivi I, Lanir N, Hoffman R, Brenner B. Hyperhomocysteinemia is common in patients with antiphospholipid syndrome and may contribute to expression of major thrombotic events. Blood Coagul Fibrinolysis 2002;13:169–72.
[78] Carvalho JF, Shoenfeld Y, Skare TL. Vitamin B12 and primary antiphospholipid syndrome. Lupus 2021;30:1025–6.
[79] Tefferi A, Pardanani A. Myeloproliferative neoplasms: a contemporary review. JAMA Oncol 2015;1:97–105.
[80] Yalavarthi S, Gould TJ, Rao AN, Mazza LF, Morris AE, et al. Release of neutrophil extracellular traps by neutrophils stimulated with antiphospholipid antibodies: a newly identified mechanism of thrombosis in the antiphospholipid syndrome. Arthritis & rheumatology (Hoboken, NJ) 2015;67:2990–3003.
[81] Sayar Z, Moll R, Isenberg D, Cohen H. Thrombotic antiphospholipid syndrome: a practical guide to diagnosis and management. Thromb Res 2021;198:213–21.
[82] Sayar Z, Nallamilli S, Efthymiou M, Lambert J, Cohen H. Coexistent antiphospholipid syndrome and myeloproliferative neoplasm. Lupus 2021;30:1502–8.
[83] de Groot PG, Urbanus RT, Derksen RH. Pathophysiology of thrombotic APS: where do we stand? Lupus 2012;21:704–7.
[84] Del Porto F, Tatarelli C, Di Napoli A, Proietta M. Systemic lupus erythematosus and myelofibrosis: a case report and revision of literature. Leuk Res Rep 2018;9:58–64.
[85] Belfeki N, Shankarasivam G, Declerck D, Diamantis S. Autoimmune myelofibrosis: a rare haematological involvement in systemic lupus erythematosus. BMJ Case Rep 2019;12.
[86] Mertz P, Chalayer E, Amoura Z, Cathebras P, Chiche L, et al. Clinical spectrum and therapeutic management of auto-immune myelofibrosis: a nation-wide study of 30 cases. Haematologica 2021;106:871–4.
[87] Erkan D, Asherson RA, Espinosa G, Cervera R, Font J, et al. Long term outcome of catastrophic antiphospholipid syndrome survivors. Ann Rheum Dis 2003;62:530–3.
[88] Gómez-Puerta JA, Cervera R, Espinosa G, Aguiló S, Bucciarelli S, et al. Antiphospholipid antibodies associated with malignancies: clinical and pathological characteristics of 120 patients. Semin Arthritis Rheum 2006;35:322–32.
[89] Meng J, Chen L, Hou J, Chi H, Wang Z, et al. Probable catastrophic antiphospholipid syndrome secondary to chronic myelomonocytic leukaemia in an adult patient and a mini review. Lupus 2020;29:1287–91.
[90] El Hasbani G, Musallam KM, Uthman I, Cappellini MD, Taher AT. Thalassemia and autoimmune diseases: absence of evidence or evidence of absence? Blood Rev 2022;52:100874.
[91] Kashef S, Karimi M, Amirghofran Z, Ayatollahi M, Pasalar M, et al. Antiphospholipid antibodies and hepatitis C virus infection in Iranian thalassemia major patients. Int J Lab Hematol 2008;30:11–6.
[92] Giordano P, Galli M, Del Vecchio GC, Altomare M, Norbis F, et al. Lupus anticoagulant, anticardiolipin antibodies and hepatitis C virus infection in thalassaemia. Br J Haematol 1998;102:903–6.
[93] Chinsuwan J, Klaihmon P, Kadegasem P, Chuansumrit A, Soisamrong A, et al. High prevalence of antiphospholipid antibodies in children with non-transfusion dependent thalassemia and possible correlations with microparticles. Mediterr J Hematol Infect Dis 2020;12:e2020071.
[94] Atichartakarn V, Chuncharunee S, Chandanamattha P, Likittanasombat K, Aryurachai K. Correction of hypercoagulability and amelioration of pulmonary arterial hypertension by chronic blood transfusion in an asplenic hemoglobin E/beta-thalassemia patient. Blood 2004;103:2844–6.
[95] Neunert C, Terrell DR, Arnold DM, Buchanan G, Cines DB, et al. American Society of Hematology 2019 guidelines for immune thrombocytopenia. Blood Adv 2019;3:3829–66.
[96] Tektonidou MG, Andreoli L, Limper M, Amoura Z, Cervera R, et al. EULAR recommendations for the management of antiphospholipid syndrome in adults. Ann Rheum Dis 2019;78:1296–304.
[97] Tenti S, Cheleschi S, Guidelli GM, Galeazzi M, Fioravanti A. Intravenous immunoglobulins and antiphospholipid syndrome: how, when and why? A review of the literature. Autoimmun Rev 2016;15:226–35.
[98] Arnold DM, Dentali F, Crowther MA, Meyer RM, Cook RJ, et al. Systematic review: efficacy and safety of rituximab for adults with idiopathic thrombocytopenic purpura. Ann Intern Med 2007;146:25–33.
[99] Berman H, Rodríguez-Pintó I, Cervera R, Morel N, Costedoat-Chalumeau N, et al. Rituximab use in the catastrophic antiphospholipid syndrome: descriptive analysis of the CAPS registry patients receiving rituximab. Autoimmun Rev 2013;12:1085–90.
[100] Wang L, Gao Z, Chen XP, Zhang HY, Yang N, et al. Efficacy and safety of thrombopoietin receptor agonists in patients with primary immune thrombocytopenia: a systematic review and meta-analysis. Sci Rep 2016;6:39003.
[101] Vreede AP, Bockenstedt PL, McCune WJ, Knight JS. Cryptic conspirators: a conversation about thrombocytopenia and antiphospholipid syndrome. Curr Opin Rheumatol 2019;31:231–40.
[102] Galindo M, Khamashta MA, Hughes GR. Splenectomy for refractory thrombocytopenia in the antiphospholipid syndrome. Rheumatology (Oxford) 1999;38:848–53.
[103] Sevim E, Willis R, Erkan D. Is there a role for immunosuppression in antiphospholipid syndrome? Hematology Am Soc Hematol Educ Program 2019;2019:426–32.
[104] Bajaj SP, Rapaport SI, Fierer DS, Herbst KD, Schwartz DB. A mechanism for the hypoprothrombinemia of the acquired hypoprothrombinemia-lupus anticoagulant syndrome. Blood 1983;61:684–92.
[105] Pengo V, Zardo L, Cattini MG, Bison E, Pontara E, et al. Prothrombin is responsible for the lupus cofactor phenomenon in a patient with lupus anticoagulant/hypoprothrombinemia syndrome. TH Open 2020;4. e40-e4.
[106] Satta N, Kruithof EK, Fickentscher C, Dunoyer-Geindre S, Boehlen F, et al. Toll-like receptor 2 mediates the activation of human monocytes and endothelial cells by antiphospholipid antibodies. Blood 2011;117:5523–31.
[107] Biswas S, Zimman A, Gao D, Byzova TV, Podrez EA. TLR2 plays a key role in platelet Hyperreactivity and accelerated thrombosis associated with hyperlipidemia. Circ Res 2017;121:951–62.
[108] Xie H, Sheng L, Zhou H, Yan J. The role of TLR4 in pathophysiology of antiphospholipid syndrome-associated thrombosis and pregnancy morbidity. Br J Haematol 2014;164:165–76.
[109] Cognasse F, Hamzeh-Cognasse H, Lafarge S, Delezay O, Pozzetto B, et al. Toll-like receptor 4 ligand can differentially modulate the release of cytokines by human platelets. Br J Haematol 2008;141:84–91.
[110] Aslam R, Speck ER, Kim M, Crow AR, Bang KW, et al. Platelet toll-like receptor expression modulates lipopolysaccharide-induced thrombocytopenia and tumor necrosis factor-alpha production in vivo. Blood 2006;107:637–41.
[111] Cognasse F, Lafarge S, Chavarin P, Acquart S, Garraud O. Lipopolysaccharide induces sCD40L release through human platelets TLR4, but not TLR2 and TLR9. Intensive Care Med 2007;33:382–4.
[112] Cockrell E, Espinola RG, McCrae KR. Annexin A2: biology and relevance to the antiphospholipid syndrome. Lupus 2008;17:943–51.
[113] Zhang Y, Yu G, Wang Y, Zhang J, Wei S, et al. A novel annexin A2 protein with platelet aggregation-inhibiting activity from amphibian Bombina maxima skin. Toxicon 2010;56:458–65.
[114] Zhang W, Gao F, Lu D, Sun N, Yin X, et al. Anti-β2 glycoprotein I antibodies in complex with β2 glycoprotein I induce platelet activation via two receptors: apolipoprotein E receptor 2′ and glycoprotein I bα. Front Med 2016;10:76–84.
[115] Weeterings C, Adelmeijer J, Myles T, de Groot PG, Lisman T. Glycoprotein Ibalpha-mediated platelet adhesion and aggregation to immobilized thrombin under conditions of flow. Arterioscler Thromb Vasc Biol 2006;26:670–5.
[116] Urbanus RT, Pennings MT, Derksen RH, de Groot PG. Platelet activation by dimeric beta2-glycoprotein I requires signaling via both glycoprotein Ibalpha and apolipoprotein E receptor 2′. J Thromb Haemost 2008;6:1405–12.
[117] Robertson JO, Li W, Silverstein RL, Topol EJ, Smith JD. Deficiency of LRP8 in mice is associated with altered platelet function and prolonged time for in vivo thrombosis. Thromb Res 2009;123:644–52.
[118] Huang S, Ninivaggi M, Chayoua W, de Laat B. VWF, platelets and the antiphospholipid syndrome. Int J Mol Sci 2021;22.

[119] Bury L, Malara A, Momi S, Petito E, Balduini A, Gresele P. Mechanisms of thrombocytopenia in platelet-type von Willebrand disease. Haematologica 2019; 104:1473–81.
[120] Sacharidou A, Chambliss KL, Ulrich V, Salmon JE, Shen YM, et al. Antiphospholipid antibodies induce thrombosis by PP2A activation via apoER2-Dab2-SHC1 complex formation in endothelium. Blood 2018;131:2097–110.
[121] Hollerbach A, Müller-Calleja N, Ritter S, Häuser F, Canisius A, et al. Platelet activation by antiphospholipid antibodies depends on epitope specificity and is prevented by mTOR inhibitors. Thromb Haemost 2019;119:1147–53.
[122] Qiao J, Al-Tamimi M, Baker RI, Andrews RK, Gardiner EE. The platelet fc receptor, FcγRIIa. Immunol Rev 2015;268:241–52.
[123] Bregani ER, Corneo G, Pogliani EM. Antiphospholipid antibodies and splenic thrombosis in a patient with idiopathic myelofibrosis (antiphospholipid antibodies and thrombosis). Haematologica 1992;77:516–7.
[124] Niki T, Kawamura Y. Hematological remission of primary myelofibrosis with antiphospholipid antibody following treatment of azathioprine. Rinsho Ketsueki 1995;36:141–6.
[125] Katayama T, Masuoka H, Nishiwaki K, Ogasawara Y, Ohtsubo H, Kobayashi M. Primary myelofibrosis with fatal mesenteric arterial thromboembolism caused by antiphospholipid syndrome. Rinsho Ketsueki 1999;40:646–51.
[126] Breccia M, D'Elia GM, Girelli G, Vaglio S, Gentilini F, et al. Paroxysmal cold haemoglobinuria as a tardive complication of idiopathic myelofibrosis. Eur J Haematol 2004;73:304–6.