REVIEW

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Cryptic conspirators: a conversation about thrombocytopenia and antiphospholipid syndrome

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Purpose of review
Although antiphospholipid syndrome (APS) is best known for conveying increased risk of thrombotic events and pregnancy morbidity, thrombocytopenia is also recognized as a common association. In this review, we will explore the relationship between thrombocytopenia and APS, highlighting our evolving understanding – and persistent knowledge gaps – through clinically oriented questions and answers.

Recent findings
A history of thrombocytopenia likely portends a more severe APS phenotype (including increased risk of thrombosis). Although the pathophysiology underlying thrombocytopenia in APS has yet to be definitively revealed, mechanisms that play a role (at least in subsets of patients) include: immune thrombocytopenic purpura/ITP-like autoantibodies against platelet glycoproteins; antiphospholipid antibody (aPL)-mediated platelet activation and consumption; and potentially life threatening thrombotic microangiopathy. Although thrombocytopenia is often 'mild' in APS (and therefore, may not require specific therapy), there are causes of acute-onset thrombocytopenia that mandate emergent work-up and treatment. When APS-related thrombocytopenia does require therapy, the approach must be individualized (requiring an understanding of pathophysiology in the particular APS patient). For patients with ITP-like disease, rituximab is emerging as a popular approach to treatment; in contrast, there are hints that thrombopoietin mimetics may be associated with elevated thrombotic risk.

Summary
Thrombocytopenia is common in APS, and is likely associated with more severe disease. Improved understanding of thrombocytopenia in APS has the potential to improve risk stratification, reveal novel aspects of APS pathophysiology, and lead to treatments that are more individualized and holistic.

Keywords
antiphospholipid, antiphospholipid syndrome, immune thrombocytopenia, thrombocytopenia, thrombosis

INTRODUCTION

Antiphospholipid syndrome (APS) is an autoimmune condition that significantly increases risk of arterial and venous thrombosis, as well as pregnancy complications. This increased risk is mediated at least in part by antiphospholipid antibodies (aPL) themselves, which are most effectively screened for with a functional assay known as the 'lupus anticoagulant.' Although a positive lupus anticoagulant almost certainly portends more risk than other positive tests (which are discussed next), it is susceptible to confounders, such as concomitant anticoagulation, and therefore must be interpreted with caution, especially in hospitalized patients [1]. One can also classify a patient as having APS by antibody-based testing, specifically: IgG/IgM antibeta-2 glycoprotein I or IgG/IgM anticardiolipin. Although aPL are detected in up to one-third of systemic lupus erythematosus (SLE) patients, they can also be found in the absence of a second autoimmune condition (a common situation denoted as primary aPL/APS).

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KEY POINTS

- The cause of thrombocytopenia in APS has not been fully revealed. Both activation-mediated consumption and traditional antiplatelet antibodies (as are seen in idiopathic immune thrombocytopenic purpura) likely contribute in subsets of patients.
- Although based primarily on retrospective data, the balance of evidence suggests that modest thrombocytopenia (50 000 to 100 000/μl) is predictive of increased thrombotic risk in antiphospholipid antibody-positive patients.
- There are a number of serious causes of acute-onset thrombocytopenia in APS that require aggressive and immediate investigation.
- The presence of antiphospholipid antibodies in patients diagnosed with idiopathic immune thrombocytopenic purpura may suggest increased thrombotic risk.
- In an APS patient with severe thrombocytopenia, the approach to both immunosuppression and anticoagulation must be individualized.

According to the most recent classification criteria, definite APS is defined by the presence of either thrombotic or obstetric complications and persistently positive aPL [2] (Table 1).

WHY DISCUSS THROMBOCYTOPENIA AND ANTIPHOSPHOLIPID SYNDROME?

Although thrombotic and obstetric complications are the only clinical events included in the APS classification criteria, there are numerous 'extra-criteria' manifestations commonly observed in APS, including (but not limited to) nephropathy, cardiac valve lesions, neurologic complications (chorea, seizure, cognitive decline), skin manifestations (livedo reticularis, inflammatory skin ulceration), and cytopenias (hemolytic anemia, thrombocytopenia) [3]. Of these, thrombocytopenia is likely the most common, with some APS cohorts demonstrating a higher prevalence of thrombocytopenia than obstetric complications [4,5]. Given this high prevalence, some early attempts at defining APS included thrombocytopenia as a clinical event warranting APS classification [6]. Similarly, there have been more recent calls to consider the inclusion of thrombocytopenia as part of an updated classification strategy for APS [7].

Despite the high prevalence of thrombocytopenia in APS, there is still much to learn regarding its etiological drivers, prognostic significance, and management strategies. In this review, we will explore these and other clinically relevant issues, attempting whenever possible to focus on the most recent literature. The target audience for this review includes rheumatology clinicians and researchers, and the comments below should especially be viewed in the context of patients seen in the rheumatology clinic. Our goal is that through this review, clinicians and researchers will have a better understanding of what is known about thrombocytopenia in APS and the knowledge gaps that remain to be filled.

HOW COMMON IS THROMBOCYTOPENIA IN ANTIPHOSPHOLIPID SYNDROME?

Estimates for the prevalence of thrombocytopenia in APS range anywhere from 16 to 53% [8]. Variability in these estimates may be attributable to both the definition of thrombocytopenia (typically platelets <100 000/μl, although some studies favor <150 000/μl) and the specific population studied (primary APS, secondary APS, or a combined population). One fairly consistent observation is that

Table 1. Classification criteria for antiphospholipid syndrome

APS is present if one of the clinical criteria and one of the laboratory criteria are met.		
Clinical criteria	Vascular thrombosis	≥1 clinical episode of arterial, venous, or small-vessel thrombosis
	Pregnancy morbidity	(a) ≥1 unexplained death of a morphologically normal fetus at ≥10 weeks of gestation (b) ≥1 premature delivery of a morphologically normal fetus at <34 weeks gestation because of: (i) Severe preeclampsia or eclampsia defined according to standard definition (ii) Recognized features of placental insufficiency (c) ≥3 unexplained consecutive miscarriages at <10 weeks gestation, with maternal and paternal factors (anatomic, hormonal or chromosomal abnormalities) excluded
Laboratory criteria	The presence of antiphospholipid antibodies on ≥2 occasions ≥12 weeks apart (a) Presence of lupus anticoagulant in plasma (b) Medium-to-high-titer anticardiolipin antibodies of IgG or IgM isoforms (c) Medium-to-high-titer antibeta-2 glycoprotein-I (antiβ_2GPI) antibodies of IgG or IgM isoforms	

APS, antiphospholipid syndrome. Data from [2].

thrombocytopenia is more common when APS is secondary to SLE (albeit with the caveat that thrombocytopenia is part of the classification criteria for SLE – but not for APS). Most studies have shown a prevalence of thrombocytopenia in secondary APS that is roughly double than that for primary APS [4,9–11]. Indeed, the recent analysis of a large international cohort documented thrombocytopenia in 28% of patients with secondary APS and 16% with primary aPL/APS [12].

DOES THE PRESENCE OF THROMBOCYTOPENIA IN A PATIENT WITH PRIMARY ANTIPHOSPHOLIPID SYNDROME PREDICT THE EVENTUAL EMERGENCE OF SYSTEMIC LUPUS ERYTHEMATOSUS?

As noted previously, thrombocytopenia is more common when aPLs are associated with SLE. It, therefore, stands to reason that the presence of thrombocytopenia in primary APS might predict the development of SLE. There are only a few retrospective analyses that have investigated this question, with all studies revealing no correlation. The largest of these was published in 2005 and included 128 primary APS patients who were followed for an average of 9 years (in addition to a disease duration of 8 years at study entry) [13]. Over this timeframe, the vast majority of primary APS patients did not progress, with only 8% developing SLE and 5% developing a lupus-like syndrome. Thrombocytopenia did not predict progression in these patients. A more recent study also failed to identify thrombocytopenia as a risk factor for progression to SLE, although the sample size was small [14].

DOES THE PRESENCE OF THROMBOCYTOPENIA PREDICT OTHER ANTIPHOSPHOLIPID SYNDROME COMPLICATIONS?

A longstanding question in the APS field is whether thrombocytopenia in APS implies a more severe disease phenotype, and therefore, a greater risk of morbid events. Early work did not demonstrate an association [15], although one study found a link between thrombocytopenia and other extra-criteria manifestations including cardiac valve thickening/dysfunction, epilepsy, chorea, arthritis, livedo reticularis, and skin ulceration [9].

Newer research, however, seems to be telling us something different. For example, a recent study found that the combination of aPL and thrombocytopenia (platelets $<150\,000/\mu l$) increased the risk of future thrombosis two-fold over an average follow-up of 125 months [16▪▪]. Importantly the presence of an associated SLE diagnosis did not impact thrombotic risk [16▪▪]. Another recent study demonstrated similar results in a cohort of 138 patients with aPL; over an average 146 months of follow-up, patients with thrombocytopenia had elevated risk of thrombosis compared with patients without thrombocytopenia (29.4 versus 6.6%) [17]. Furthermore, Radin *et al.* [19▪] recently published a manuscript that utilized a validated APS risk score – adjusted Global APS Score (aGAPSS) [18] – in a group of primary APS patients with or without additional extra-criteria APS manifestations (including thrombocytopenia). The 21% of patients with thrombocytopenia had a higher aGAPSS score than patients with no extra-criteria manifestations (10.6 versus 8.2). In summary, with the addition of recent literature, thrombocytopenia increasingly appears to be predictive of other APS complications. In our opinion, this is among the most pressing issues requiring further, and ideally prospective, interrogation.

WHAT IS THE GENERAL APPROACH TO TREATMENT OF THROMBOCYTOPENIA IN ANTIPHOSPHOLIPID SYNDROME?

When the clinician is confronted with thrombocytopenia in a patient with APS, they might consider an algorithm similar to Fig. 1. In the following sections, we will summarize possible mechanisms of thrombocytopenia and how they may inform therapy decisions.

WHAT IS KNOWN ABOUT THE PATHOPHYSIOLOGY OF THROMBOCYTOPENIA IN ANTIPHOSPHOLIPID SYNDROME?

To our knowledge, there is no consensus explanation as to what drives thrombocytopenia in APS, and we would posit that distinct, overlapping mechanisms are often at play. These may include immune thrombocytopenic purpura/immune thrombocytopenia (ITP)-like autoantibodies against platelet glycoproteins; aPL-mediated platelet activation and consumption; and potentially life-threatening thrombotic microangiopathy. Less common causes of thrombocytopenia in APS include decreased platelet production, increased platelet pooling, and pseudothrombocytopenia (platelet clumping *in vitro*), as discussed in an excellent recent review of the topic [20]. Clinicians may also need to investigate causes of thrombocytopenia not related to APS, including adverse effects of medications, certain atypical infections, and bone-marrow processes.

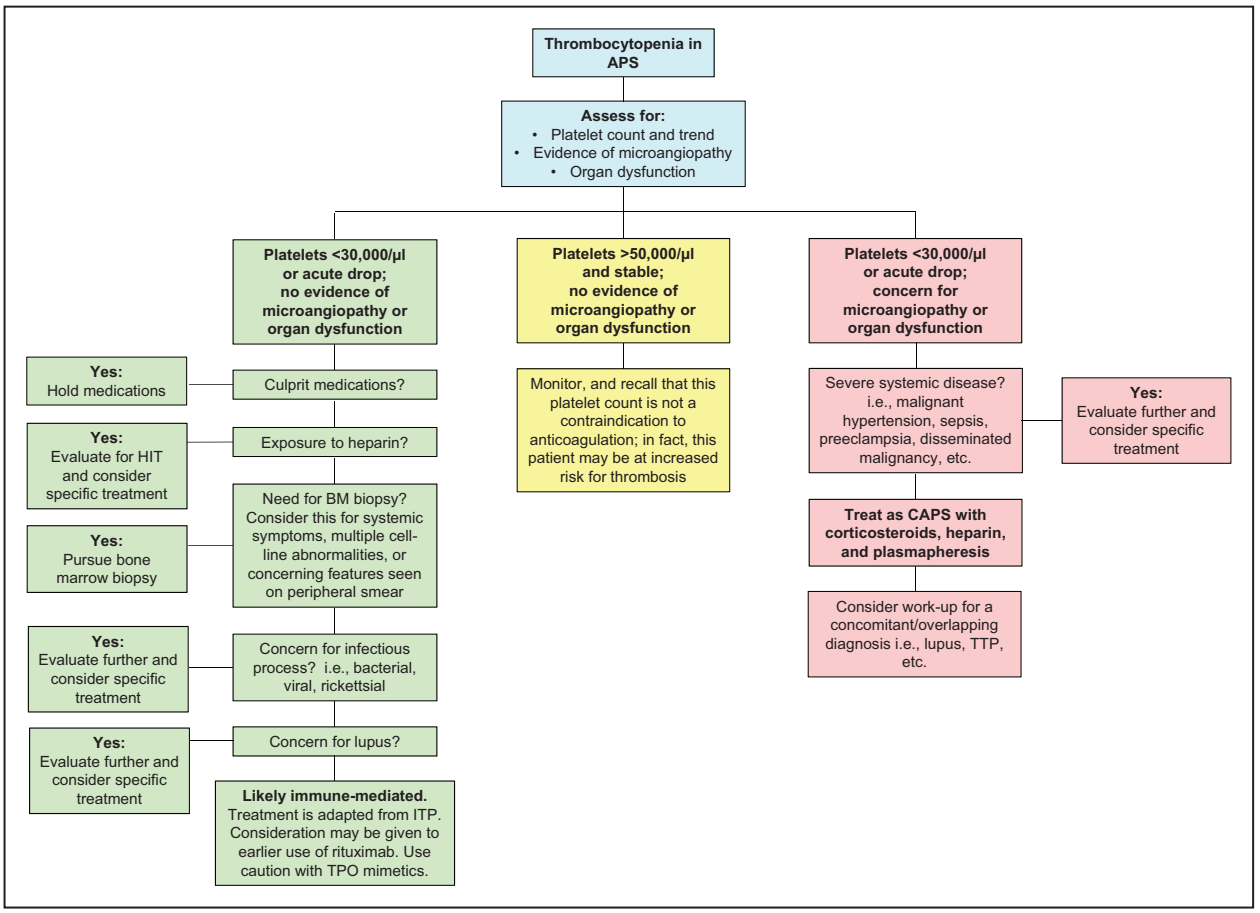

FIGURE 1. Proposed algorithm for a pathogenesis-directed approach to managing thrombocytopenia in antiphospholipid syndrome patients. The yellow path consists of the majority of APS patients with thrombocytopenia, in which no specific therapy is required. The green path highlights a combination of mechanisms of thrombocytopenia, including drug-related causes and immune-mediated pathogenesis. The red/orange path emphasizes acute, life-threatening thrombotic microangiopathies (which may or may not be associated with microangiopathic hemolytic anemia). APS, antiphospholipid syndrome; HIT, heparin-induced thrombocytopenia; BM, bone marrow; ITP, immune thrombocytopenic purpura, TPO, thrombopoietin; CAPS, catastrophic APS; TTP, thrombotic thrombocytopenic purpura.

DO PATIENTS WITH ANTIPHOSPHOLIPID SYNDROME DEVELOP SPECIFIC ANTI-PLATELET ANTIBODIES (AS SEEN IN IMMUNE THROMBOCYTOPENIA)?

One factor undoubtedly contributing to thrombocytopenia in at least some APS patients is the presence of antiplatelet antibodies (similar to those seen in idiopathic ITP). For example, a highly cited 1997 study demonstrated a high prevalence of antiplatelet antibodies in primary APS patients with thrombocytopenia (73%, versus 10% in those without) [21]; the antibodies were similar to those detected in cases of idiopathic ITP – including antibodies against GpIIbIIIa, CD9, GpIaIIa, GpIbIX, and GpIV [21]. Such 'antiglycoprotein' antibodies have been detected in other studies [22,23], which again demonstrated correlation between antibody levels and thrombocytopenia. One particularly interesting article builds a case for a cause of antiplatelet antibodies that is clearly separable from the driver of aPL themselves [24]. In a large cohort of patients with ITP (83% with antiglycoprotein antibodies and 46% with aPL), aPL levels did not correlate with immunosuppressive treatment or subsequent relapse of thrombocytopenia [24]. In contrast, antiglycoprotein antibodies showed a strong correlation with both (one caveat is that this study was published in 1994, and therefore, before the 'rituximab era') [24]. Finally, it should be noted that not every study looking for antiglycoprotein antibodies in APS has revealed a clear association with thrombocytopenia [25], or has even detected antiglycoprotein antibodies at a higher rate than in the general population [26].

DOES THE DETECTION OF ANTIPHOSPHOLIPID ANTIBODIES IMPACT OUTCOMES IN IDIOPATHIC IMMUNE THROMBOCYTOPENIA?

As the presence of aPL ranges from 25 to 73% in ITP (the majority of publications pointing to the low end of that range) [8], there have been numerous recent studies exploring the relationship between aPL and clinical outcomes. For example, one study suggested that the presence of aPL can predict the severity of thrombocytopenia and future need for ITP-focused treatment [27▪]. Although ITP is classically characterized by bleeding events, a paradoxical increased risk of large-vessel thrombosis has also long been recognized [28]. To this end, early research demonstrated a remarkable effect of aPL on thrombotic risk, including a 2001 study in which 60% of ITP patients with aPL experienced a thrombotic event as compared with just 2% of ITP patients without aPL [29]. Similarly, a more recent cohort that consisted of 20% of all discharges from United States hospitals between the years of 2009 and 2014 revealed that the most significant risk factor for thrombosis in ITP was a concurrent APS diagnosis code [30]. In summary, data published to date (all retrospective) suggest a higher thrombotic risk in ITP patients with aPL. Although prospective studies are obviously needed, when a patient with 'ITP' is seen in the rheumatology clinic, consideration should be given to testing for aPL. If nothing else, a positive test will emphasize the need for optimization of other cardiovascular and thrombotic risk factors.

WHAT THERAPIES ARE AVAILABLE FOR ANTIPHOSPHOLIPID SYNDROME PATIENTS WITH IMMUNE-MEDIATED THROMBOCYTOPENIA?

When ITP-like physiology is felt to be at play, therapy is generally started once the platelet count is less than 30 000/μl (expert opinion). For a comprehensive review of this topic, we would refer the reader to the guidelines of the American Society of Hematology [31]. It should be noted that these guidelines do not discuss APS beyond the recommendation that aPL testing not be routinely obtained in patients with idiopathic ITP (as above, we would argue that this rule may be less applicable to the rheumatology clinician).

Given the absence of a specific literature for management of immune thrombocytopenia in APS, treatment recommendations for severe thrombocytopenia have typically been adapted from ITP guidelines as discussed above [31]. First-line treatment classically consists of corticosteroids and/or intravenous immunoglobulin (IVIG). However, as thrombotic events are a potential adverse effect of IVIG [32▪], it is unclear if this therapy should be considered first-line in APS. Although very few studies have specifically investigated the safety of IVIG in APS, a recent case series reported on nine patients with autoimmune disease who received IVIG and developed thromboembolic disease (including two patients with secondary APS) [33▪]. On the basis of relatively good success with rituximab (anti-CD20) in ITP (generally, 60% response rate including 40% of patients developing complete response) [34], there has recently been enthusiasm for its use in the treatment of thrombocytopenia in APS. Indeed, some case series have found rituximab to be efficacious in APS (including thrombocytopenia) [35]. A phase II study that investigated rituximab for non-criteria APS manifestations in aPL-positive patients included four patients with thrombocytopenia, with 50% of patients responding [36]. A more recent study documented six primary APS patients with severe refractory thrombocytopenia, five of whom had a persistent complete response [37▪▪]. Overall, rituximab appears to be relatively well tolerated and effective in APS, with risks and response rates in line with what has been documented for idiopathic ITP.

Although thrombopoietin (TPO) mimetics are Food and Drug Administration (FDA)-approved for steroid-refractory ITP, they have not been systematically studied in APS patients [38]. Early case reports and case series describing the use of TPO mimetics in SLE patients (including APS patients) largely showed that these agents were effective and without significant risk [39–45]; however, this was not universally seen [46]. More recently, several reports have noted potential thrombotic risk of these agents in SLE and particularly APS patients [47–50,51▪▪]; two of these series, in particular, showed remarkably high rates of thrombotic complications in APS patients (33–60%) [50,51▪▪]. As the majority of thrombotic complications in these cases occurred at platelet counts greater than 100 000/μl, one can postulate that this risk may be minimized by dosing the TPO mimetics to maintain platelet counts around 50 000/μl. In summary, although TPO mimetics have excellent efficacy and are cost-effective (as compared with rituximab), caution should be exercised with use of these agents in the setting of aPL (especially in patients not receiving anticoagulation) until we have a better understanding of their risk/benefit profile. We have attempted to summarize the data available to date in Table 2.

Other medications that have been described (largely in the context of case reports) to improve platelet counts in APS include aspirin [52], warfarin

Table 2. Overview of case control or case series studies that have investigated use of thrombopoietin mimetics in patients with autoimmune disease

Study	Type of study	Number of patients	Autoimmune Disease	TPO mimetic	Response rate	Thrombotic Adverse Event		
						Type of thrombotic complication	Time of event after starting TPO (months)	Plt count at event ($\times 10^3/\mu l$) mean, range
Alkaabi *et al.* [39], 2012	CR	1	SLE (with aPL)	Eltrombopag, then Romiplostim	100%	None	N/A	N/A
Gudbrandsdottir *et al.* [40], 2012	CR	1	SLE	Not provided	0%	None	N/A	N/A
Tomov *et al.* [46], 2013	CR	1	SLE (with aPL)	Romiplostim	100%	Renal thrombotic microangiopathy	1.5	60
Magnano *et al.* [41], 2014	CS	2	SLE (one with aPL)	Eltrombopag (1), Romiplostim (1)	100%	None	N/A	N/A
Scheinberg *et al.* [42], 2014	CR	1	SLE	Eltrombopag	100%	None	N/A	N/A
Maroun *et al.* [43], 2015	CS	3	SLE (one patient with aPL)	Eltrombopag	100%	None	N/A	N/A
Moreno Martinez *et al.* [44], 2016	CR	1	SLE	Eltrombopag	100%	None	N/A	N/A
LaMoreaux *et al.* [47], 2016	CS	2	One with SLE and aPL one with aPL	Romiplostim	100%	100%: Possible CAPS Arterial thrombus	1–3	134, 111–156
Borrell *et al.* [48], 2016	CR	1	SLE	Romiplostim	100%	DVT	3	177
Boulon *et al.* [49], 2016	CR	1	APS	Eltrombopag	100%	Pulmonary embolism (therapeutic on warfarin)	1	119
Gonzalez-Lopez *et al.* [50], 2017	RC	46	SLE (13), Evans syndrome (8), APS (6), Sjogren's syndrome (4), Rheumatoid arthritis (3), autoimmune hepatitis (2), primary biliary cirrhosis (2), psoriatic arthritis (1), Graves-Basedow disease (1), inflammatory bowel disease (1)	Eltrombopag	63%	6.5% of total (33% of APS patients): Superficial phlebitis (1), pulmonary embolism (1), ischemic stroke (1)	Not provided	Not provided
Guitton *et al.* [51▪▪], 2018	RC	18	SLE (five with APS and five with aPL)	Romiplostim (33%), Eltrombopag (28%), both sequentially (39%)	94%	28% of total (60% of APS patients): Myocardial infarction (2), stroke (1), intracranial sinus thrombosis (1), CAPS (1)	1–7	260, 94–484
Lusa and Carlson [45], 2018	CS	4	SLE (one with APS and one with aPL)	Romiplostim	75%	None	N/A	N/A

aPL, antiphospholipid antibody; APS, antiphospholipid syndrome; CR, case report; CS, case series; RC, retrospective cohort; SLE, systemic lupus erythematosus.

[53], danazol [54], chloroquine [55], and dapsone [56]. Splenectomy [57,58] and plasmapheresis [59] have also been reported. It is notable that some medications recently approved for ITP have yet to be characterized in the context of APS. For example, fostamatinib, a biologic therapy-targeting spleen tyrosine kinase [60], was approved in 2018 for the treatment of idiopathic ITP. Physicians will need to continue to follow the ITP literature, and pay close attention to any thrombotic-risk signal that emerges in that population.

WHAT CAN WE LEARN ABOUT THROMBOCYTOPENIA IN ANTIPHOSPHOLIPID SYNDROME FROM HEPARIN-INDUCED THROMBOCYTOPENIA?

Beyond antiglycoprotein antibodies, there is likely a role for aPL themselves in the pathophysiology of thrombocytopenia. Indeed, an emerging concept is that there may be parallels between thrombocytopenia in APS and that seen in heparin-induced thrombocytopenia (HIT). HIT is an acquired autoantibody-mediated condition associated – like APS – with increased thrombotic risk. In HIT, complexes of platelet factor 4 (PF4), heparin, and anti-PF4 antibodies engage the platelet surface where they both trigger platelet activation (via FcγRIIa), and 'label' platelets for removal by phagocytic cells in the spleen. A recent study by Gollomp *et al.* [61▪▪] characterized large-vein thrombosis in a mouse model of HIT, and suggested a previously unknown role for neutrophil–platelet crosstalk in HIT pathophysiology. First, the authors demonstrated PF4/anti-PF4 complexes were able to engage the surface of neutrophils (similar to the surface of platelets) and trigger neutrophil activation, adhesion, and extracellular trap (NET) release in FcγRIIa-dependent fashion [61▪▪]. NETs – extracellular tangles of chromatin and granule-derived proteins – subsequently formed complexes with PF4/anti-PF4 (potentially taking the place of heparin in the complex), leading to NET stabilization and thrombus propagation [61▪▪]. Interestingly, inhibition of both neutrophil adhesion and NET release were highly effective strategies for mitigating thrombosis in the HIT model [61▪▪]. Given reports of β_2GPI/antiβ_2GPI engagement with platelets [62,63], neutrophils [64,65], and even PF4 itself [66,67] – as well as striking similarities between the aforementioned HIT model and recently described models of APS [68,69]—one can postulate that crosstalk between platelets, neutrophils, NETs, and possibly even PF4 may play a role in the pathophysiology of both thrombosis and thrombocytopenia in APS.

IS HEPARIN-INDUCED THROMBOCYTOPENIA MORE COMMON IN PATIENTS WITH ANTIPHOSPHOLIPID SYNDROME?

As APS patients are exposed relatively frequently to heparin, HIT needs to be considered when such patients have an acute drop in the platelet count. At least one study showed a frequent co-occurrence of aPL and the pathogenic antibody in HIT (anti-PF4) [70], albeit with no follow-up functional assays performed. Additionally, a single-center case–control study found that autoimmune conditions (including APS) are commonly associated with HIT (55.9% of HIT patients compared with 10.8% of controls) [71▪].

HOW SHOULD ONE APPROACH ACUTE, LIFE-THREATENING THROMBOCYTOPENIA IN ANTIPHOSPHOLIPID SYNDROME?

Thrombotic microangiopathies can be directly or indirectly associated with APS and require prompt recognition owing to their highly associated morbidity and mortality. Thrombocytopenia in these diseases is driven by thrombosis-related platelet consumption or, more rarely, bone marrow infarction. APS-related microangiopathies include CAPS (catastrophic antiphospholipid syndrome), HELLP (hemolysis, elevated liver enzymes and low platelets), and TTP (thrombotic thrombocytopenic purpura). Other possibilities to consider in selected patients include severe infection, malignant hypertension, and disseminated intravascular coagulation. We will briefly summarize some of these potential diseases below.

CAPS is a life-threatening form of APS reflecting a microvascular thrombotic storm afflicting multiple organs simultaneously [72]. In one large series of CAPS patients, thrombocytopenia was detected in 65% of cases (whereas schistocytes were only detected in 22%) [73]. In a recent study, the time course of thrombocytopenia in six patients with APS who developed CAPS was described [74▪]. All events were associated with platelet counts less than 100 000/μl (the majority <50 000/μl) and demonstrated a daily, step-wise decrease for 7 days preceding the clear recognition of CAPS manifestations – hinting that platelet activation and consumption may be integral to the emergence of CAPS, and that progressive thrombocytopenia must be carefully monitored in a patient with APS.

As above, schistocytes and frank evidence of hemolytic anemia are only detected in one out of four CAPS patients [73]. In contrast, both HELLP and TTP are more likely to express a strong pattern of microangiopathic hemolytic anemia (MAHA). HELLP – which is considered to be on the spectrum of preeclampsia – is characterized by elevated blood

pressure and proteinuria (i.e. signs of preeclampsia), as well as hemolysis, a microangiopathic blood smear, elevated liver enzymes, and a low platelet count. As compared with the general population, APS patients likely experience HELLP earlier in pregnancy, and with a higher degree of severity [75].

TTP is driven by deficiency or inactivation of ADAMTS-13, a metalloproteinase that cleaves von Willebrand factor (vWF). In TTP, abnormally large vWF multimers drive platelet aggregation in small vessels, resulting in end-organ damage and platelet consumption. A review of the literature reveals that definitive TTP is relatively uncommon in primary APS, with less than 10 case reports published [76–78]. Having said that, there has been an interesting body of work exploring the association of APS and ADAMTS-13, with several studies demonstrating no association [78,79]. A few studies, however, have found low ADAMTS-13 activity in APS patients [80,81], possibly mediated by antibeta-2 glycoprotein I antibodies directly antagonizing ADAMTS-13 activity [82▪].

Clinical manifestations significantly overlap between these conditions, likely due to a related pathophysiology that includes a prominent and pathogenic role for complement activation [83]. We would direct readers to prior excellent review articles to assist with diagnosis [72,84,85]. From a practical perspective, we would argue that the clinician should not be overly concerned about nomenclature (i.e., CAPS versus HELLP versus TTP). In a patient with known APS who develops organ failure concerning for a thrombotic microangiopathy, traditional treatment for CAPS will likely be required – typically with the combination of corticosteroids, heparin, and plasmapheresis, as we and others have summarized [72,86].

HOW SHOULD ONE HANDLE ANTICOAGULATION IN AN ANTIPHOSPHOLIPID SYNDROME PATIENT WITH THROMBOCYTOPENIA?

In this difficult situation, treatment recommendations are based upon expert opinion or extrapolated from the cancer literature. Both bleeding and thrombotic risk need to be weighed before starting anticoagulation. In all cases, shared decision-making is essential, and treatment must be individualized. Generally, most experts feel that full anticoagulation can be provided in the setting of platelet counts greater than 50 000/μl. Unfortunately, as controlled studies of anticoagulants almost always exclude patients with platelet counts less than 50 000/μl, there is minimal prospective evidence to guide recommendations. A reasonable approach can be extrapolated from one institution's anticoagulation guidelines for thrombocytopenic cancer patients with history of VTE [87▪]. According to this protocol, full-dose enoxaparin is provided for platelet counts greater than 50 000/μl, half-dose enoxaparin for platelet counts between 25 000 and 50 000/μl, and no anticoagulation for platelet counts less than 25 000/μl [87▪]. Over 2 years of study, there were no recurrent thrombotic events or major bleeding episodes [87▪]. How the thrombotic risk of these patients compares with patients with aPL is of course hard to quantify; however, in the absence of additional evidence, our opinion is that this protocol would be reasonable to institute for APS inpatients with thrombocytopenia (while once again emphasizing the need for an individualized assessment).

CONCLUSION

Although APS is best known for its association with thrombotic events and pregnancy morbidity, thrombocytopenia is a common (perhaps the most common) 'extra-criteria' manifestation. Until the pathophysiology is better defined, the approach to when and how to treat will need to remain individualized. Furthermore, with the balance of evidence pointing to thrombocytopenia as a predictor of a more severe APS phenotype, we feel strongly that the cryptic conspirators of thrombocytopenia and APS warrant further investigation in animal models and prospective patient cohorts.

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Conflicts of interest

There are no conflicts of interest.

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Papers of particular interest, published within the annual period of review, have been highlighted as:
- ▪ of special interest
- ▪▪ of outstanding interest

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