Chapter

Bleeding in Patients with Antiphospholipid Antibodies

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Abstract

The antiphospholipid antibodies (aPL) are commonly associated with thrombotic events and obstetric complications. However, apart from the bleeding complications of antithrombotic therapy, the acquired coagulopathy caused by the aPL, particularly by lupus anticoagulant and anticardiolipin antibodies, might be occasionally manifested as a hemorrhagic syndrome with various clinical severity. Bleeding symptoms vary from mild (mucocutaneous) up to life-threatening (gastrointestinal, intracranial). The bleeding may be the first manifestation of aPL or appear concomitantly with thrombosis. The underlying hemostatic changes include thrombocytopenia, platelet function disorders, and coagulation factor inhibitors or deficiencies, namely prothrombin, FVII, FVIII, FX, and FXI. Thrombocytopenia is the most common finding, seen in up to 53% of patients with aPL, although it is usually mild to moderate and associated with significant bleeding only in a minority of cases. Of interest, patients with severe thrombocytopenia appear to be less likely to suffer from thrombotic events. The involved pathophysiological mechanisms are heterogeneous. Non-neutralizing antibodies against coagulation factors resulting in increased clearance, specific antibodies against platelet membrane glycoproteins, increasing platelet activation and aggregation with subsequent consumption, and immune-mediated platelet clearance are among those identified. Immunosuppression, preferably with corticosteroids, represents the first-choice therapeutic approach. Plasmapheresis is efficient in the case of catastrophic antiphospholipid syndrome. Antithrombotic therapy can be challenging, but its administration should continue as much as possible.

Keywords: hemorrhage, antiphospholipid antibodies, thrombocytopenia, acquired prothrombin deficiency, acquired coagulation factor deficiencies, coagulation factor inhibitors

1. Introduction

The antiphospholipid syndrome (APS) is an acquired autoimmune disorder, defined by the combination of generally accepted laboratory and clinical criteria [1]. The latest laboratory criteria include repeated (at least 12 weeks apart) positive testing for at least 1 of 3 selected antiphospholipid antibodies (aPL): lupus anticoagulant (LA), anticardiolipin (aCL), anti-beta2-glycoprotein I (anti-B2GPI) antibodies. Clinical criteria emphasize the arterial and venous thromboembolic and pregnancy-related (recurrent miscarriages in the first trimester, fetal death in the second or third trimesters, severe pre-eclampsia requiring delivery of a premature infant before 34 weeks of gestation) events. However, other laboratory

and clinical complications with clear association to aPL, referred to as non-criteria manifestations, have been described. Based on the affected organ system, the clinical non-criteria manifestations divide into several subgroups: cardiovascular, neurologic, skin, renal, hematologic, and other [2, 3]. Hematologic complications include thrombocytopenia, hemolytic anemia, and functional changes or deficiencies of coagulation factors with both thrombotic (acquired resistance to activated protein C, protein S deficiency) or bleeding tendencies. As mentioned above, the association of aPL with thromboembolic events is extensively and well documented. However, the acquired coagulopathy caused by the aPL is complex and

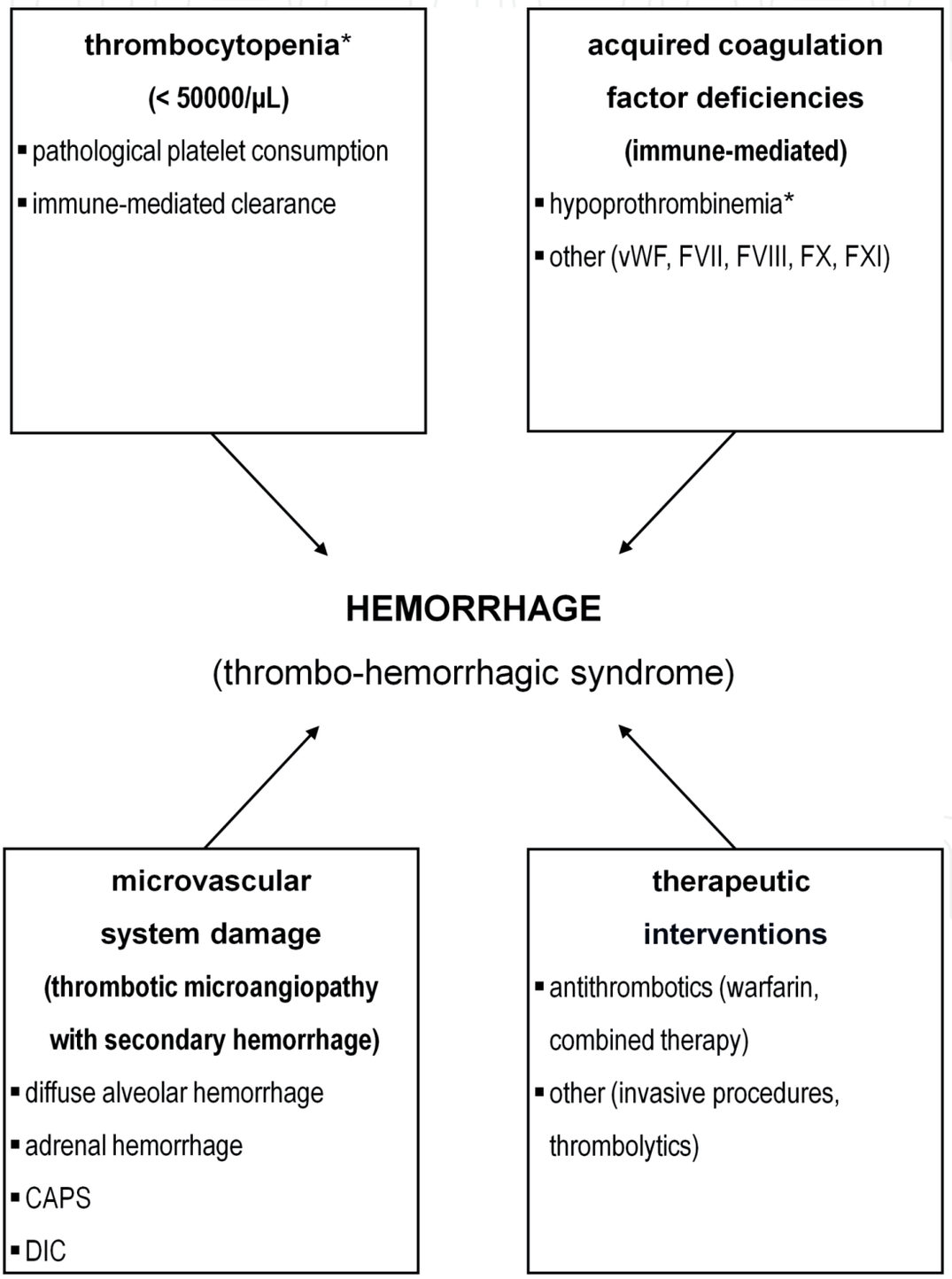

Figure 1.
*Pathomechanisms involved in hemorrhage in aPL patients. CAPS, catastrophic antiphospholipid syndrome; DIC, disseminated intravascular coagulation; F, factor; vWF, von Willebrand factor; * most common pathomechanisms.*

might occasionally manifest as a hemorrhagic event with various clinical severity or combined thrombo-hemorrhagic syndrome. The latter is common in catastrophic APS (CAPS), a rare but often fatal variant with excessive activation of hemostasis, consumption of its components, and micro-thrombotic damage in multiple organs.

aPL can interact with different blood and vascular components and cause hemorrhage through several mechanisms (**Figure 1**) [1]. Firstly, aPL-positive patients frequently develop thrombocytopenia. Secondly, acquired immune-mediated coagulation factor deficiencies, such as hypoprothrombinemia, can appear after the interaction between aPL and coagulation factors.

Thirdly, the microvascular system damage with an extensive thrombotic or inflammatory insult via the monocyte, endothelial, and complement activation can result in secondary bleeding to the affected tissue. Thrombotic microangiopathies (TMAs) such as CAPS, as well as diffuse alveolar hemorrhage (DAH) and adrenal hemorrhage (AH), the pathognomic complications of APS, are representative examples of this pathomechanism. Since the antithrombotic therapy remains a mainstay of management of aPL, the extensive use of antithrombotics, typical for patients afflicted with their presence, can contribute to bleeding events and represents the fourth cause. Severe thrombocytopenia (platelet count lower than 50000/μL) and prothrombin deficiency are the most prominent causes of bleeding [4]. The discussion of the given pathomechanisms follows.

2. Thrombocytopenia in patients with aPL

Though not included in the current diagnostic criteria for APS (Sydney 2012 criteria), thrombocytopenia represents a complication directly linked to aPL [1]. Thrombocytopenia is a frequent finding in aPL-positive patients; it is their most common non-criteria hematologic manifestation. The Euro-Phospholipid project, a large prospective multicenter international study evaluating 1000 European patients with both primary and secondary APS, found thrombocytopenia in 296 (29.6%) of its participants [5]. Other studies focused on the whole population of aPL-positive patients reported comparable incidence, ranging from 20 to 53% [6–10]. Of interest, particular subgroups seem to be more prone to develop thrombocytopenia. Patients with secondary APS associated with systemic lupus erythematosus (SLE) have thrombocytopenia approximately 2-times more often than those with primary APS (reported incidence 40 vs. 21% in the Euro-Phospholipid project) [5]. A low platelet count is more frequent in patients with CAPS [10, 11].

Thrombocytopenia tends to be mild to moderate with the nadir above 50000/μL in most cases. Only a small portion of patients (approximately 10%) develop severe thrombocytopenia, and its occurrence is often associated with other complications, such as TMAs (disseminated intravascular coagulation (DIC), CAPS) [8]. Rapid (within days) progression of thrombocytopenia or its new occurrence in patients with previously normal platelet count can be the first indication of CAPS [11, 12].

Despite being common, thrombocytopenia alone is not usually responsible for clinically relevant bleeding. For example, in the Italian Registry of aPL, only four patients out of 90 with thrombocytopenia experienced major hemorrhagic events [8]. On the other hand, nor it protects, especially if mild to moderate, from thromboembolism. Notwithstanding, if severe and without CAPS, it can account for a minor protective effect. In the Italian Registry with 360 patients included, severe thrombocytopenia was associated with a significantly lower rate of thrombotic events in comparison to the group with normal platelet count; however, the group with mild thrombocytopenia did not show a significant difference (9 vs. 40 vs. 32%) [8]. A recent study analyzing altogether 305 patients with primary

APS, 51 with thrombocytopenia included, observed a higher rate of thrombotic relapses (29% vs. 19%) during a long (median 11 years) follow-up in the group with thrombocytopenia, though the difference did not reach statistical significance [13]. Despite comparable antithrombotic therapy, no difference in major hemorrhage (4% vs. 3%) was observed between the thrombocytopenic and non-thrombocytopenic group, albeit the significantly higher rate of overall bleeding (17% vs. 8%) was in the thrombocytopenic group. The authors conclude that thrombocytopenia may have a prognostic value in primary APS and help identify high-risk patients for APS-related complications [13].

The evidence concerning the association between thrombocytopenia and other clinical features of APS such as hemolytic anemia, livedo reticularis, skin ulcerations, chorea, and cardiac valve dysfunction is conflicting. Some studies, but not all, observed more frequent occurrence of those symptoms in patients with thrombocytopenia.

The pathogenesis of aPL-related thrombocytopenia is likely heterogeneous. aPL can directly or indirectly via B2GPI interact with several platelet membrane glycoproteins (GP) and phospholipids and thus initiate two processes: 1) pathologically enhanced platelet activation and aggregation after their initial activation or damage with subsequent platelet thrombus formation and platelet consumption; 2) immune-mediated pathological platelet clearance. The interaction with platelets involves the binding of anti-B2GPI via B2GPI to the activated platelet surface or direct interaction of aPL with specific platelet membrane glycoproteins (GPIb/IX, GPIIb/IIIa, GPIV) [14]. Particular subtypes of aPL and their quantity likely play a prominent role in the pathogenesis of thrombocytopenia. Anti–B2GPI antibodies of IgG class, LA, a higher titer of aCL of IgG class, and triple aPL positivity were a more common finding in patients with thrombocytopenia [13, 15, 16]. LA and a high titer of aCL were frequent among patients with severe thrombocytopenia. Since LA is associated with the highest prothrombotic risk among aPL, its higher prevalence in these patients could mitigate the bleeding tendencies and contribute to a relatively low rate of major bleedings.

Other pathomechanisms may occasionally contribute to thrombocytopenia in aPL-positive patients. The association, albeit anecdotal, between aPL and the hemophagocytic syndrome (a hyperinflammatory disorder with pathological phagocytosis of blood cells and their precursors in the bone marrow and other tissues) and bone marrow necrosis was described [17, 18]. These disorders decrease platelets via impairing megakaryopoiesis. Splenomegaly after splenic or portal vein thrombosis leads to increased platelet pooling and redistribution from circulation [7].

It should be emphasized that the etiology of thrombocytopenia in aPL-positive patients can be multifactorial and not exclusively linked to these antibodies. Other diseases can contribute to and further deepen the decrease in platelet count. Coincidence with immune thrombocytopenia (ITP), drug-induced thrombocytopenia with heparin-induced thrombocytopenia included, thrombocytopenia related to infections, TMAs, and pregnancy-related thrombocytopenia have been described [18, 19].

The relationship with ITP seems to be particularly interesting and complex. Patients with ITP are frequently positively tested for aPL, with a reported incidence ranging from 25 to 75% [20]. A recent retrospective study of 159 adult patients with primary and secondary severe ITP (platelet count below 50000/μL) identified aPL in 37 (23.2%), with 14 being triple positive. Triple positivity was associated with a lower platelet count [21]. Clinical implications of the relation between ITP and aPL are still discussed and not clear. The available data regarding the risk of thrombosis and treatment are inconclusive. However, a recent study with altogether 196 patients with primary ITP, 49 aPL-positive included, did observe a significantly

higher risk of thrombotic events. Other monitored characteristics (hemorrhage, response to therapy, clinical course, changes in platelet counts) were comparable [19]. Analogically to the observation in APS, it seems that the risk of thrombosis in patients with concomitant ITP and aPL positivity, particularly in those undergoing therapy with corticosteroids and other immunosuppressive agents, is more prominent than the risk of bleeding.

The diagnostic approach has to consider the possibility of aPL as a sole cause of thrombocytopenia as well as the coincidence of other disorders with aPL, especially TMAs. Since patients with aPL/APS are often anticoagulated and treated with immunosuppressives, heparin-induced thrombocytopenia and infectious causes should be addressed in the diagnostic process.

Since thrombocytopenia in aPL-positive patients is predominantly mild and without significant bleeding, outside of CAPS, most patients do not require specific treatment. As a general rule, the goal is to maintain the platelet count above 30000/μL – a critical threshold for the development of severe spontaneous bleeding. When immune etiology is behind thrombocytopenia, strategies effective in ITP are preferably used [22, 23]. Corticosteroids, initially in high-dose with gradual tapering, alone or combined with intravenous immunoglobulins (IVIg), represent the first-line treatment. In contrast to ITP, the use of IVIg as a first-line treatment is controversial in aPL-positive patients since their administration is potentially associated with an increased risk of thrombotic events [24]. Other immunosuppressive or immunomodulatory agents or procedures (danazol, chloroquine, dapsone, rituximab, plasmapheresis) or splenectomy can be chosen as alternatives for those with inadequate response. Rituximab seems to be a particularly perspective agent. Though only limited clinical data from a small number of patients are available so far, the response and persisting stable platelet count after rituximab have been observed in a reasonably high number (50–83%) of treated patients [25, 26]. It is important to emphasize that most of the included patients had refractory thrombocytopenia without a satisfactory response to previous treatment modalities. Rituximab was tolerated well with no significant increase in thrombotic risk. Its risk profile in the aPL setting appears to be comparable to ITP [25].

The use of thrombopoietin mimetics (TPOMs) remains controversial due to the conflicting clinical data. There is a general agreement on their effectiveness in increasing platelet count, but safety remains an open issue. Several authors did not observe any increase in the thrombotic events during the administration of TPOMs [27, 28]. Others, including those who analyzed larger patient groups, report a prothrombotic risk associated with this therapy in the a-PL positive subgroup [29–31]. Gonzales et al. found in their retrospective study of 46 patients with thrombocytopenia and various systemic autoimmune disorders, all treated with eltrombopag, that 3 (6.5%) participants suffered from thrombotic events while on treatment. Crucially, 6 out of 46 participants had concurrent APS, and 2 of them (33% of all patients with aPL) were among those with thrombosis [30]. Guitton et al. retrospectively studied 18 patients with thrombocytopenia and SLE treated with romiplostim or eltrombopag; 10 had been diagnosed with concurrent aPL/APS. 5 patients developed thrombosis; 3 of them (30% of all patients with aPL) had APS [31]. These observations suggest a higher thrombotic risk in the aPL-positive group. Though well established in therapy of ITP, the use of TPOMs in aPL-positive patients requires caution and individual evaluation of thrombotic risk. Minimized dosing of TPOMs, aimed to maintain platelet count around 50000/μL, was suggested to decrease thrombotic risk since the thrombotic events are more frequent at platelet count greater than 100000/μL [22].

Except for severe thrombocytopenia, a decrease in platelet count does not fully protect patients with aPL/APS from thromboembolic events, and antithrombotic

prevention or therapy should be continuing as long as possible. However, bleeding risk has to be considered, and an individualized approach is mandatory. In general, full anticoagulation can be given in the setting of platelet count over 50000/μL, and its stopping should be considered seriously in platelet count below 25000/μL. The patients with platelets between these values should be treated individually with anticoagulants in reduced doses. Half-dose low molecular weight heparins (LMWHs) represent the usual first-choice treatment [22].

3. Factor deficiencies associated with aPL

3.1 Hypoprothrombinemia

Acquired deficiency of prothrombin, referred to as lupus anticoagulant hypoprothrombinemia syndrome, is the most known and well defined of all coagulation factor deficiencies associated with aPL. Its precise incidence is unclear, but with the order of magnitude of hundreds of reported cases, it appears to be a rare complication [32, 33]. It typically occurs in the child or adolescent female patients with aPL after viral infections or with systemic immune disorders, most commonly SLE [34]. Adults can be affected as well, albeit less frequently [35]. The preexisting systemic immune disease is not obligatory since cases without were identified; other precipitating conditions include tumors such as lymphomas, particularly with the production of pathological immunoglobulins and drug reactions.

Bleeding severity varies from mild mucocutaneous (epistaxis, ecchymosis), which is the most common, to severe and life-threatening, including localizations such as muscles, genitourinary tract, gastrointestinal tract (GIT), and central nervous system (CNS) [32–38]. A substantial number of patients (up to 50%) have no significant bleeding events and can be even asymptomatic [36]. Concomitant presence of thrombotic events, hemorrhagic-thrombotic syndrome, and CAPS were occasionally described [39–41]. The condition is usually self-limiting when associated with viral infections, whereas it can have a lasting duration or relapses in the presence of autoimmune diseases [36]. Despite the possibility of severe bleeding events, the overall prognosis is good in general, with a reported mortality rate of less than 5%.

Laboratory findings include the prolongation of both prothrombin (PT) and activated partial thromboplastin time (aPTT), variably decreased prothrombin activity (about 10–20% on average, although it may be extremely low or unmeasurable) with a proportional decrease of prothrombin antigen. As mentioned above, a deficiency of other coagulation factors might be present. Therefore, their activity should be checked [32]. Positive testing for LA complements the picture. The finding of PT prolongation in an aPL-positive patient should prompt the testing for prothrombin deficiency even if no bleeding is apparent at the time.

The traditional view based on the initial analyses in the 1980s defined the involved antibodies as non-neutralizing, unable to directly inhibit the prothrombin coagulation activity [42]. Cross-reactivity between the aPL and phospholipid epitopes in the prothrombin molecules is a likely explanation. The aPL form prothrombin antigen–antibody complexes, and their subsequent elimination results in the proportional decrease of both prothrombin activity and antigen. If the clearance is extensive enough to lead to a relevant prothrombin decrease with its activity below 20%, bleeding manifestations may occur. However, some researchers provided conflicting evidence with hints on more complex changes of hemostasis. In the recent analysis of a relatively large cohort of 41 patients, Japanese authors did not observe an exact correlation between prothrombin levels, anti-FII antibody quantity, and

bleeding phenotype. They also identify different autoantibodies directed against FVIII besides the anti-prothrombin ones in several patients with the disorder [43]. They confirmed combined coagulation factor deficiencies in a small number of the studied cases as well. Based on this observation and a known heterogeneity of the clinical presentation, it is reasonable to conclude that hypoprothrombinemia is not an isolated change in aPL-positive patients, and a complex evaluation of hemostasis is always required.

The therapeutic approach aims at (1) stopping the active bleeding; (2) eradicating antibodies responsible for prothrombin deficiency; (3) preventing further thromboembolic events [35, 37]. The withdrawal of antithrombotic agents, supplementation of blood components (transfusion of packed red blood cells and fresh frozen plasma), activation of coagulation factor production (vitamin K administration), hemostatic agents (styptics, antifibrinolytics) represent the strategies for bleeding cessation [35]. However, all these approaches can in aPL-positive patients, especially in prolonged use, lead to the increased thrombotic risk. Immunosuppression, with corticosteroids as the first-line choice or other agents (azathioprine, rituximab, cyclophosphamide) and procedures (plasma exchange) as alternatives, leads to antibody eradication. Monotherapy with corticosteroids is efficient in most cases. Measurement of prothrombin levels, whether by clotting, chromogenic or immunologic methods, can be used for the treatment monitoring. Since the risk of thrombosis usually remains significantly increased even in the presence of bleeding and bleeding itself does not protect from thromboembolism, the therapies aimed at bleeding cessation has to be counterweighted by antithrombotic therapy. Both bleeding and thromboembolic risks have to be evaluated carefully in all cases.

3.2 von Willebrand factor deficiency (von Willebrand syndrome)

Few case reports of concurrent acquired von Willebrand syndrome (AWS), an acquired vWF deficiency, with the presence of aPL were described [44–48]. Interestingly, other disorders with well-defined relation to AWS (myeloproliferative neoplasm, aortic valve stenosis, connective tissue diseases such as SLE) were identified in most cases. Therefore, aPL are not regarded as a usual cause of AWS, but rather as a coincidental finding in underlying immune disorders. Some researchers speculated that aPL might modify and counterbalance the bleeding phenotype typical for AWS [44, 48]. Thrombotic event after normalization of vWF was reported [44]. Immunosuppression, the standard treatment of AWS, combined with antithrombotic prevention, was given in reported cases with good clinical outcomes.

3.3 Deficiencies of other coagulation factors

Acquired deficiencies of other clotting factors, namely FVII, FVIII, FX, and FXI, were reported [49–52]. In summary, these deficiencies are extremely rare, and clinical data are limited to case reports or series. Bleeding manifestations are variable, with varying severity. The therapeutic strategies are similar to the approach used in AWS.

4. Bleeding in thrombotic microangiopathies associated with aPL

4.1 Diffuse alveolar hemorrhage

DAH is a severe and life-threatening pulmonary complication of aPL. Inflammatory damage to the pulmonary microcirculation, namely to alveolar

arterioles, capillaries, and venules, with subsequent necrotic changes and secondary hemorrhage, define the disorder [53]. A microscopic pathoanatomical picture typically reveals capillaritis with interstitial neutrophilic infiltrate, thrombi in small muscular pulmonary arteries, myointimal thickening, and the remodeling of the muscular pulmonary arteries and arterioles [53, 54]. The condition is rare and appears in less than 1% of all aPL-positive patients, though it is considerably more frequent and clinically relevant in those with CAPS, affecting 5–10% [54–57]. Both genders are affected, but males constitute approximately 2/3 of cases with primary APS, whereas women dominate the group with APS secondary to SLE [54]. The patients with DAH are more likely to have a higher titer of aPL and suffer from other comorbidities associated with aPL than those without DAH. Cardiac valve disease, pulmonary hypertension, livedo reticularis, skin ulcers, CNS involvement (stroke or seizure), and pregnancy complications are among the reported concomitant disorders [54, 57].

Several pathomechanisms are likely to participate in the damage of the alveolar structures in DAH in aPL-positive patients. aPL-mediated activation of endothelial cells, resulting in the increased expression of tissue factor, platelet, and complement activation with C5a-mediated neutrophil recruitment and the subsequent lung tissue injury is likely behind thrombi formation in the pulmonary microcirculation. aPL-induced systemic inflammatory response syndrome with the excessive cytokine activation (e. g. tumor necrosis factor-α, interleukin-1, interleukin-6, interleukin-18, macrophage migration inhibitory factor) as well as L-ficolin-induced lung injury and interstitial neutrophilic infiltration lead to the loss of the integrity of the alveolar-capillary basement membrane. Disruption of alveolar structure and its veins through the combination of inflammation and thrombosis result in the extravasation of red blood cells into the alveoli [58].

The usual clinical presentation of DAH includes fever, chest pain, cough with hemoptysis, and dyspnea with the signs of hypoxemic respiratory failure [4]. However, not all symptoms, including hemoptysis, need to be present in every case. The symptoms are not specific and appear in other pulmonary diseases such as pulmonary embolism, pneumonia, and pulmonary edema. The complex differential diagnostics is of utmost importance. Laboratory and complementary tests are critical for the distinction of DAH. Anemia, aPL positivity, high diffusing capacity for carbon monoxide in pulmonary function tests, patchy or perihilar opacities on the chest X-ray and signs of hemorrhage, ground-glass infiltrates, and reticular interstitial opacities on pulmonary CT scans belong to the typical findings. Bronchoscopy with bronchoalveolar lavage and biopsy can document alveolar hemorrhage, exclude infections, and provide biological material for cytologic and histologic evaluation. Lung biopsy remains the gold standard for the definitive diagnosis, albeit the patient's condition and benefit–risk ratio should be evaluated before the procedure. As mentioned above, DAH is quite frequently associated with CAPS. Treating physicians should actively search for its signs in all cases.

Immune suppression remains the mainstay of the therapy. High-dose corticosteroids are the preferred initial treatment. The use of other immunosuppressives remains without a clear consensus due to the rarity of the condition and limited clinical data. However, available clinical data support the combined immune suppression (corticosteroids plus another immunosuppressive agent) over monotherapy with corticosteroids. The combined therapy seems to improve the clinical outcome and rate of long-term remission. Cyclophosphamide and rituximab have been showing encouraging results, whereas mycophenolate mofetil and azathioprine seem to be less effective [4]. Other therapeutic modalities that could be beneficial, especially in the presence of underlying CAPS, include plasma exchange and IVIg.

4.2 Adrenal hemorrhage

AH is a potentially devastating complication of aPL due to the resulting adrenal insufficiency. AH represents an infrequent cause of adrenal insufficiency, and besides aPL, it can be caused by other disorders, namely adrenal tumors and anatomical malformations, infections, and bleeding disorders (thrombocytopenia, heparin exposure) [59]. AH is a rare complication of aPL with its prevalence not precisely established. However, a significant proportion - one third - of affected patients have CAPS. The incidence in this subgroup is thus relatively high, between 10 to 16% [56]. A provoking moment usually initiates aPL-induced AH. Trauma, invasive procedures, infections, and warfarin withdrawal have been identified as such moments [60].

The main pathomechanism in aPL-induced AH, supported by the autopsy evidence, is multiple thromboses in the adrenal plexus leading to the secondary hemorrhage and destruction of the adrenal cortex. Due to its unique vascular anatomy (complex arterial system with three supplying arteries, rich vascular plexus in the zona reticularis, single drainage vein), the adrenal gland is prone to develop intraparenchymal hemorrhage in a case of venous obstruction. Vasculitis has not been found in aPL-induced AH [61].

AH usually manifests with back pain. Symptoms related to acute adrenal insufficiency (hypotension, malaise, fever, altered mental status, gastrointestinal symptoms including nausea, vomiting, and diarrhea) complement the clinical picture. Apart from the chronic adrenal insufficiency, skin hyperpigmentation is not present in the aPL-induced AH [59].

Laboratory tests and radiological imagining studies are critical for the confirmation of AH. Decreased cortisol levels and the lack of increase in cortisol levels after an adrenocorticotropic hormone stimulation test represent a typical laboratory finding. Abdominal contrast CT is the standard imagining method. However, CT has its limits, and if performed in the early phases of the bleeding, it may be falsely negative. A repeated CT scan is a must in the case of high clinical suspicion despite an initial negative result. Abdominal magnetic resonance is an alternative imagining method with the best imaging of the adrenal glands [62]. If the laboratory and imaging studies are inconclusive, adrenal biopsy remains the definitive diagnostic procedure. However, it is a high-risk procedure in terms of bleeding, and the risk–benefit ratio has to be evaluated individually. As a general rule, adrenal biopsy should be avoided in aPL-positive patients.

Clinical management has two goals: 1) to provide substitution of adrenal hormones, especially glucocorticoids; 2) to prevent further complications of aPL, namely thromboembolism. Since CAPS is a frequent finding in aPL-positive patients with AH, antithrombotics should be administered as long as possible despite hemorrhage. If their withdrawal is necessary, usually due to the extensive bleeding, the restart should be as soon as possible. The clinical experience stresses the critical importance of antithrombotic therapy. The study with aPL-positive patients and AH observed concurrent thrombotic events during the acute phase in 7 (43%) out of 16 participants. Five of 7 patients with confirmed thrombosis were diagnosed with CAPS [60]. Apart from the glucocorticoid substitution due to adrenal insufficiency, immunosuppressives are not a standard part of treatment since the available evidence does not confirm an effect on the clinical outcome [61]. However, their addition, alone or in combination with IVIg and plasma exchange, can be beneficial in the presence of CAPS.

The long-term prognosis of AH is relatively favorable after the acute phase, especially if antithrombotics are uninterrupted. In a review of 62 patients with AH

followed for a mean of 25 (2–60) months, 90% (32 out of 35) of anticoagulated patients survived. Interestingly, overall mortality in the study reached 36% (25 out of 69 participants) [61]. Adrenal dysfunction is irreversible in most cases, although occasional recovery remains possible.

4.3 Catastrophic antiphospholipid syndrome

CAPS represents the most severe and potentially fatal variant of APS. It is characterized by excessive activation of hemostasis, rapid, multiple, and progressive thrombotic events, typically affecting small vessels, resulting in acute multiple organ dysfunction (usually kidneys, lungs, CNS, heart, skin) and TMAs [63]. Fortunately, CAPS is a relatively infrequent complication, affecting approximately 1% of patients with APS [2]. CAPS is the first manifestation of previously unrecognized or newly formed aPL in up to 50% of patients [10]. However, it can be the complication of preexisting and known aPL or APS as well. Its onset is usually - in about 2/3 of cases - related to precipitating factors such as infections, malignancies, trauma, invasive procedures, activation of underlying autoimmune disease, pregnancy complications, certain medications (oral contraceptives), and withdrawal or inadequate antithrombotic therapy. Pathological complement activation plays a critical role in its development [64].

Thromboembolic events and their complications dominate the clinical picture. Bleeding is typically secondary to the initial thromboembolism, although rarely can be among the initial clinical manifestations [65, 66]. The etiology of hemorrhage in CAPS is complex. It involves thrombocytopenia secondary to excessive platelet activation and consumption, consumption of coagulation factors, endothelial damage and dysfunction, thrombocytopenic thrombotic purpura (TTP)-like hemostatic changes, and development of DIC [67, 68]. Thrombocytopenia is a dominant change in CAPS, affecting up to 40% of patients with the complication. Thrombocytopenia, mainly if it manifests as the acute drop in platelet count in patients with aPL/APS and previously normal platelets, can be the first sign of impeding CAPS and precede the full clinical picture of CAPS for several days [11]. TTP-like changes frequently accompany thrombocytopenia [68]. Clinical presentation of hemorrhage is variable, with every organ system being a possible target. Life-threatening hemorrhage, including bleeding in the CNS and GIT, can occur [65, 66]. As mentioned before, DAH and AH are relatively frequent complications of CAPS.

The therapeutic approach is aggressive with several goals: 1) to suppress the immune system and production of aPL; 2) to prevent and treat thromboembolic events; 3) treat the underlying or provoking disorder. The combined immunosuppressive and immunomodulatory therapy (corticosteroids, IVIg, plasma exchange) together with full anticoagulation (preferably with heparin or LMWHs in the acute phase with the transition to warfarin) represents the initial therapeutic step [63]. Cyclophosphamide is the preferred immunosuppression in patients with underlying SLE. Rituximab and eculizumab are novel therapeutic possibilities that seem to be efficient in patients with predominant hematologic or microthromboangiopathic manifestations or resistant to first-line treatment [63, 69, 70]. Despite aggressive treatment and novel agents, the prognosis remains unfavorable in a significant number of cases, with a mortality rate reaching up to 40% [2]. The individual assessment of thrombotic and bleeding risk is an indispensable part of therapeutic management. The continuation of antithrombotic therapy is preferred over its tapering or withdrawal. Its continuation has to be considered even in the presence of hemorrhage.

5. Bleeding associated with antithrombotic agents

Bleeding events, particularly those involving the CNS and GIT, are regarded as potentially serious, but the expected adverse events of antithrombotic therapy. The incidence of major bleeding ranges from 3 to 6 per 100 person-years depending on the anticoagulant. It is high for patients on warfarin in particular [71]. The incidence of bleeding on antiplatelet therapy is generally lower, 3 to 4 per 1000 person-years [72]. The risk increases with the intensity of treatment or concomitant use of several agents. The combination of the anticoagulant with antiplatelet agent increases the risk of bleeding approximately 1.5 to 2-fold in comparison to anticoagulant therapy alone [73].

Since the presence of aPL represents a high-risk thrombophilia, antithrombotics – anticoagulants, antiplatelet agents, or their combination - are administered for a prolonged period, frequently life-long in most aPL-positive patients. The continuous administration of antithrombotic agents is used even in asymptomatic individuals with estimated high prothrombotic risk. Warfarin remains the preferred agent for anticoagulation, with the intent to achieve a higher INR range of 3.0–4.0 in specific clinical situations (recurrent thrombotic events, arterial events) [74].

Based on the current clinical practice and preferred intensity of therapy, aPL-positive patients receiving antithrombotics may seem to have an increased risk of treatment-related bleeding. However, available data show that hemorrhage does not represent the main clinical issue. The mortality rate due to thrombosis and its recurrence remains several times higher than the mortality rate related to bleeding. For example, a review of clinical studies documented 18 deaths related to recurrent thrombosis and only one due to hemorrhage [75]. The analysis of a prospective 10-year follow-up of 1000 patients with APS, performed as a part of the Euro-Phospholipid project, identified 34 deaths attributed to thromboembolism and only 10 to bleeding [76]. Reviews of clinical studies focused on anticoagulant therapy in APS suggest that, if INR on warfarin is within the standard therapeutic range, the major bleeding does not appear to be significantly more frequent in comparison to other patient groups on warfarin and is about 1.5–2.0% per year [77]. If higher INR levels (3.0–4.0) are needed, the risk of bleeding, but predominantly mild, increases significantly, approximately 2 to 2.5 times [77, 78]. As for antiplatelet agents, the rate of bleeding during their prophylactic or therapeutic use appears to be low, and major bleeding is rare [78, 79]. The risk of bleeding increases after invasive procedures, likely due to the use of bridging therapy, the early reintroduction of antithrombotics, and aggressive antithrombotic policies [80, 81]. Then again, thrombotic risk after surgery increases considerably as well despite preventive measures.

Independent predictors of major bleeding include overdose with warfarin (e. g. INR above 4.0), combined antithrombotic therapy, polypharmacy, age over 75 years, history of major bleeding (mostly gastrointestinal), malignancy, uncontrolled arterial hypertension, leukoaraiosis, and patient non-compliance [76–78]. It is critical to evaluate individual bleeding and prothrombotic risk and purposely identify potential risk factors. Caution is especially required when high-intensity anticoagulation or a combination of antithrombotics are indicated.

6. Conclusion

Bleeding is a rare but potentially severe complication of aPL and APS. Its etiology is heterogeneous; aPL-positive patients can develop bleeding due to

thrombocytopenia, acquired coagulation factor deficiencies (predominantly hypoprothrombinemia), TMAs, or the adverse events of antithrombotic therapy (mostly with warfarin). However, thromboembolic events represent the most dangerous complications for aPL-positive patients, and the thrombotic risk remains clinically relevant even in the presence of hemorrhage in the majority of patients.

The management of bleeding is challenging. It is necessary to balance both thrombotic and bleeding stimuli and to continue antithrombotic prevention or therapy for as long as possible. The individual approach is critical for a favorable clinical outcome. Specific treatment can be necessary for eliminating the cause of bleeding and achieving its control. Immunosuppressive agents, especially corticosteroids, are the first-choice treatment for aPL-associated thrombocytopenia, coagulation factor deficiencies, CAPS, and DAH. Other immunosuppressive or immunomodulatory agents can be efficient in case of unsatisfactory clinical response. Rituximab appears to be the most promising alternative. Corticosteroids are also fundamental for the diffuse alveolar hemorrhage, albeit firstly for the correction of consequential adrenal insufficiency. aPL-positive patients receiving antithrombotics should be monitored closely, and their compliance ensured, especially in the scenario with the high-intensity or combined antithrombotic therapy.

Conflict of interest

The authors declare no conflict of interest.

Appendices and Nomenclature

aCL	anticardiolipin antibodies
AH	adrenal hemorrhage
anti-B2GPI	anti-beta2-glycoprotein I antibodies
aPL	antiphospholipid antibodies
APS	antiphospholipid syndrome
aPTT	activated partial thromboplastin time
AWS	acquired von Willebrand syndrome
B2GPI	beta2-glycoprotein I
CAPS	catastrophic antiphospholipid syndrome
CNS	central nervous system
DAH	diffuse alveolar hemorrhage
DIC	disseminated intravascular coagulation
GIT	gastrointestinal tract
ITP	immune thrombocytopenia
IVIg	intravenous immunoglobulin
LA	lupus anticoagulant
LMWHs	low molecular weight heparins
PT	prothrombin time
SLE	systematic lupus erythematosus
TMAs	thrombotic microangiopathies
TPOMs	thrombopoietin mimetics
TTP	thrombocytopenic thrombotic purpura
vWF	von Willebrand factor

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