Kidney and Blood Pressure Research

Review Article

Kidney Blood Press Res 2023;48:666–677
DOI: 10.1159/000529229

Received: May 13, 2022
Accepted: January 7, 2023
Published online: September 21, 2023

Antiphospholipid Syndrome and Kidney Involvement

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Keywords
Antiphospholipid syndrome · Kidney disease · APS nephropathy

Abstract
Background: Antiphospholipid syndrome (APS) is an autoimmune disease characterized by the development of autoantibodies and the impairment of the coagulation system. Knowledge about this syndrome is increasing over time, but kidney involvement, especially APS nephropathy, still represents a challenge for physicians. ***Summary:*** A "two hit" model has been hypothesized to explain APS pathophysiology, and the role played by some factors, such as the complement system, is becoming more and more clear. From a clinical point of view, along with thrombosis in any site and/or obstetric morbidities, that are the hallmarks of APS, a constellation of several other clinical symptoms is related to APS. These symptoms alone are not sufficient to fulfill Sydney criteria for APS and this could potentially lead to omitting some diagnoses. The mainstay of management of APS is antithrombotic therapy, but there are expectations for new drugs that regulate the immune system. APS could affect the kidneys in many ways and among them, APS nephropathy is an intriguing entity that has been overlooked in recent years. Novel studies on APS nephropathy are lacking. ***Key Messages:*** In this review, we discuss what we currently know about APS and its relationship with the kidney, with an eye toward the future perspectives. Multicenter studies on APS nephropathy are necessary in order to develop targeted therapies.

Introduction

Antiphospholipid syndrome (APS) is an autoimmune disease characterized by the development of autoantibodies and the impairment of the coagulation system. APS is considered a rare disease even though its prevalence is very likely underestimated [1].

In 1983, Graham Hughes provided the first detailed description of APS [2]. Earlier observations were made in systemic lupus erythematosus (SLE) patients. These patients often presented with a positive Venereal Disease

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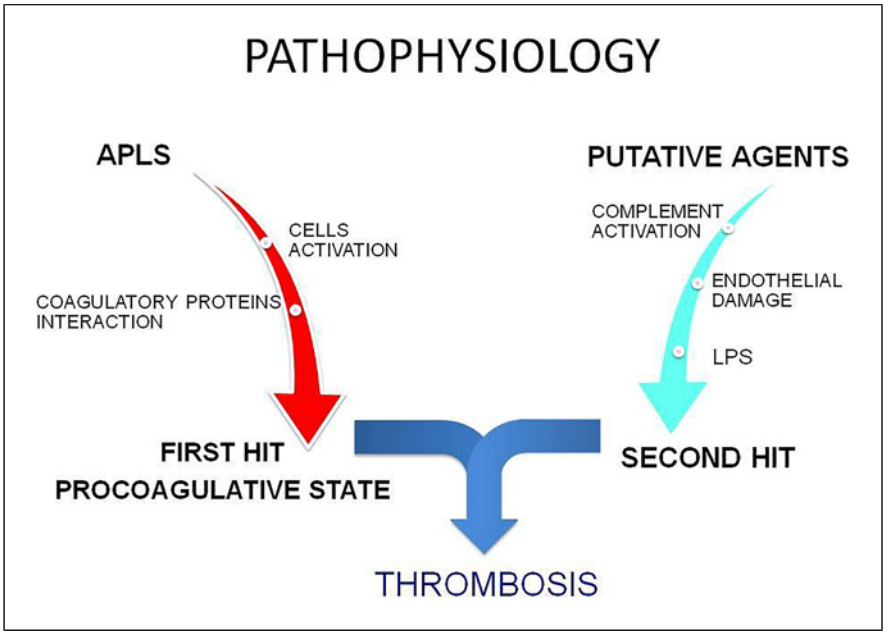

Fig. 1. Pathophysiology of APS – according to the hypothesis of "two hits" aPLs determine a "pro-thrombotic" state by interacting with coagulation proteins and by activating cells. This "first hit" does not imply thrombosis and this explains why some patients present with aPL positivity for a long time before the clinical event. A "second hit," such as damage to endothelial cells, provokes an aberrant response leading to thrombosis.

Research Laboratory (VDRL) test but without clinical evidence of syphilis. They showed prolongation of the phospholipid-dependent coagulation tests [3] and this explains the origin of the term "lupus anticoagulant" (LA), even though clinically, these patients are prone to form clots. The reason why SLE patients tested positive for VDRL was found to be due to the presence of antibodies directed against cardiolipin, a phospholipid that is also an antigen of the VDRL test. Anti-cardiolipin antibodies (aCLs) were thus recognized as specific for APS. Subsequent studies showed that, in many cases, phospholipid binding proteins rather than cardiolipin itself are the antigenic determinants of aCL binding [4]. Thus, the β2-glycoprotein 1 (β2GP-1) was identified among these proteins and this led to the development of the β2GP-1 antibody immunoassay.

Epidemiology and Pathophysiology

APS is usually referred to as the most common form of acquired thrombophilia. Nevertheless, both its frequency in the general population and its occurrence on a worldwide scale are unknown. According to the European definition of rare diseases (prevalence 5 cases/10,000 individuals), APS is currently categorized among them [5]. There have been attempts to look at the prevalence of APS in various parts of the world, with estimates ranging from 20 to 50 cases per 100,000 people [6–10]. When examining patient subgroups, such as young patients with cerebrovascular accidents [11], patients with pregnancy morbidity, or patients with their first unprovoked thrombosis [7], the prevalence of the condition rises [12]. It is worth noting that anti-phospholipid antibodies (aPLs) can be detected more commonly in the general population than APS. Transient and low titer aPLs positivity with no clinical implications has been reported in association with several conditions, such as infections, malignancies, and some medications [13–18]. Therefore, aPL positivity is a mandatory but insufficient step for the development of APS. It is possible to speculate that aPLs create a "pro-thrombotic" state but a "second hit" is needed to break the hemostatic balance promoting thrombosis (Fig. 1) [19]. Currently, this is considered the most likely theory and it is supported by some experimental data. For instance, in animal models the administration of aPLs does not result in spontaneous thrombosis, but if a priming event is provoked, the thrombotic response is much stronger in aPL-positive mice [20–22]. "Real-life" triggers might include infections, inflammatory factors (i.e., concomitant connective tissue diseases), estrogen-containing contraceptives, surgery, and immobility [20].

The "pro-thrombotic" state induced by aPLs has been attributed to their interaction with plasma coagulation regulatory proteins and their ability to activate cells like platelets, endothelial cells, and monocytes [23]. Complement cascade is implicated as well. Compared to healthy mice, those who were deficient in complement factors C3, C5, and C6 showed a reduced thrombotic response following aPL administration and vascular injury [24].

Why aPLs are produced is unknown but infectious agents are suspected to be a possible trigger. It was shown that molecular mimicry between structures of bacteria and β2GP-1 exists [25]. In addition, misfolding of β2GP-1 can also induce autoantibody production [26]. It was demonstrated that binding of β2GP-1 to the surface protein H of *Streptococcus pyogenes* exposes a cryptic epitope (domain 1) through a conformational change, and that mice injected with the protein H-β2GP-1 complex can develop antibodies against this epitope [27]. Finally, a recent study by Müller-Calleja et al. [28] demonstrated a previously unrecognized interaction between endothelial protein C receptor and certain aPLs, with important implications for our understanding of APS pathogenesis. Indeed, this interaction perpetuates a self-maintaining and amplifying signaling loop dependent on crosstalk between the innate immune system and the coagulation pathway [29].

Clinical Manifestations

From a clinical point of view, thrombosis in any site and/or obstetric morbidities is the hallmarks of APS. Thromboses typically do not present considerable evidence of inflammation in the vessel wall and can involve both arteries and veins [30]. Although arterial thrombosis is less common than venous thromboembolism, it is usually more severe. Arterial thrombosis can affect any vessel; the most common sites include: retina, heart, kidney, gut, and cerebral vasculature, causing in this case strokes or transient ischemic attacks [31]. Venous thromboses occur mostly in the lower extremities, but many other sites such as the pelvis, kidney, lung and portal veins, and cerebral sinuses have been reported [32]. Sometimes the term "thrombotic APS" is used to differentiate, on the clinical side, these cases from "obstetric APS" forms.

Besides thrombosis and its manifestations depending on the affected vessel and organ, patients with APS may show clinical manifestations unrelated to thrombosis. Among them, the most common are livedo reticularis, splinter hemorrhages, thrombocytopenia, and cardiac valve abnormalities [33–36].

Obstetric APS is characterized by recurrent miscarriage before 10 weeks of gestation. Maternal morbidities consist of preeclampsia, eclampsia, and placental abruptions [30].

Catastrophic APS (CAPS) is a rare but life-threatening form of APS characterized by clinical evidence of multiple organ involvement (at least three by definition) developing over a short period of time (usually in <1 week) [9]. In about half of patients, CAPS is triggered by an infection. Kidneys are the most commonly involved site (>70% in CAPS) followed by the lungs, brain, heart, and skin. Thrombocytopenia and schistocytes are often present as a sign of microangiopathic thrombosis [37].

Diagnosis

According to the Sydney classification criteria, the diagnosis of APS requires at least one clinical criterion among thrombosis and obstetric morbidities, and the presence of at least one laboratory criterion, confirmed 12 weeks after the first determination (Table 1) [30]. Sometimes patients do not meet the Sydney classification criteria that were developed for research purposes, but the diagnosis of APS remains putative. Besides the clinical manifestations described in the Sydney criteria (the so-called criteria manifestations), APS patients may have, as mentioned above, other symptoms. For instance, a patient with otherwise unexplained thrombocytopenia, heart valve disease, and detectable aPLs might have APS. In any case, differential diagnoses of APS have to be considered, including other causes of arterial and venous thrombosis and recurrent pregnancy loss.

Assays used for the detection of aPLs present some issues such as shortcomings and lack of standardization [19], thus the recommendations by the "Scientific and Standardization Subcommittee on Antiphospholipid Antibodies of the International Society of Thrombosis and Haemostasis" (SSC-ISTH) should be followed [38]. The assays include tests on the coagulation system and immunoassays. LA phenomenon is ascertained by evaluating the ability of aPLs to prolong the phospholipid-dependent clotting time. Two tests, dilute Russell viper venom time and activated partial thromboplastin time, are commonly used for this purpose [38]. Subsequently, confirmatory test is performed to exclude the possibility of a coagulation factor deficiency [39, 40] and to confirm that adding phospholipids to the serum of the patients induces normalization of the clotting time [38]. One of the main shortcomings of these procedures is their sensitivity to anticoagulant therapy [41]. Autoantibodies (aCL and aβ2GP-1) are detected and quantified by solid-phase immunoassays. The presence of either IgG or IgM isotypes is considered diagnostic [42], but thrombosis is more strongly associated with IgG-type antibodies [43]. The SSC-ISTH guidelines define a titer of aCL IgG or IgM and aβ2GP-1 IgG or IgM >40 units as positive [38]. However, in selected patients with an especially high

Table 1. Revised sapporo APS classification criteria (also called the Sydney criteria)

SYDNEY CLASSIFICATION CRITERIA

Clinical criteria One or more of the following is present:	Laboratory criteria The presence of one or more of the following antiphospholipid antibodies (aPLs) on two or more occasions at least 12 weeks apart:
Vascular thrombosis One or more episodes of venous, arterial, or small vessel thrombosis in any tissue or organ, with unequivocal imaging or histologic evidence of thrombosis. Superficial venous thrombosis does not satisfy the criteria for thrombosis for APS.	**IgG and/or IgM anticardiolipin antibodies (aCL)** in moderate or high titer (>40 GPL or MPL units, respectively, or a titer >99th percentile for the testing laboratory), measured by a standardized enzyme-linked immunosorbent assay (ELISA).
Pregnancy morbidity One or more unexplained deaths of a morphologically normal fetus at ≥10 weeks gestation, or one or more premature births of a morphologically normal neonate before 34 weeks gestation because of eclampsia, preeclampsia, or placental insufficiency, or three or more consecutive spontaneous pregnancy losses at <10 weeks gestation, unexplained by chromosomal abnormalities or by maternal anatomic or hormonal causes.	**IgG and/or IgM anti-beta2-glycoprotein (GP)** I >40 GPL or MPL units, respectively, or a titer >99th percentile for the testing laboratory, measured by a standardized ELISA according to recommended procedures.
	Lupus anticoagulant (LA) activity detected according to published guidelines.

APS is present if both clinical and laboratory criteria are fulfilled.

clinical suspicion of APS, it may be appropriate to also consider a borderline titer (between 20 and 39 units) as positive.

The type and number of positive tests is very important as well. There is sound evidence that patients with more than one positive test, and particularly those who are triple-positive for LA, aCL, and aβ2GP-1 (either IgG or IgM), show the strongest association with APS [44, 45].

Management

Thrombotic APS is treated with secondary thromboprophylaxis based on vitamin K antagonists (VKA) [46]. In venous thromboembolic events, a distinction between provoked or unprovoked events may be applied. Provoking factors, such as the use of estrogen-containing medication, nephrotic syndrome,

or immobility, can precipitate thrombosis. In these cases, a transient course of anticoagulation (3–6 months) may be prescribed. In unprovoked venous thrombosis and arterial thrombosis, indefinite anticoagulation therapy with VKA is recommended. In fact, evidence supports the notion that there is a high rate of recurrent thromboembolism in individuals with APS who discontinue anticoagulation [47, 48]. Some authors suggest that in case of arterial thrombosis standard anticoagulation may be insufficient [49], but the right dosage of anticoagulation is still disputed. Studies show no benefit in patients treated with higher intensity treatment, i.e., a target INR of 3–4 [50]. Several experts suggest adding low-dose acetylsalicylic acid to standard VKA in these cases [51, 52]. The European Alliance of Associations for Rheumatology (EULAR) guidelines recommend taking into account the overall individual risk of bleeding when choosing the best option [53].

A pragmatic tool, the "global antiphospholipid syndrome score" (GAPSS), was developed by Sciascia et al. [54–56] to help manage APS. The GAPSS includes conventional cardiovascular risk factors along with APS features to assess the patient's overall thrombotic risk, and it was validated in aPL patients, with and without SLE, and in external cohorts.

The role of direct oral anticoagulants for the management of APS patients is controversial since trials showed a worse outcome in these patients [57, 58]. Currently, direct oral anticoagulants are limited to patients who cannot tolerate warfarin or low molecular weight heparin and thus otherwise would not be treated.

Prescribing drugs for primary prophylaxis of thrombosis is a delicate issue. In theory, all patients with thrombotic APS are treated to avoid recurrent thrombotic events. However, it is reasonable to assume that every patient with APS has been for some time in the past just an individual with aPL positivity without clinical symptoms. Therefore, in patients with a high-risk profile, such as those with triple positivity or additional cardiovascular risk factors, primary thromboprophylaxis may be justified [59].

Since APS is an autoimmune disorder the role of immunomodulatory agents has been investigated. Some reports support the use of Rituximab in challenging cases of APS [60, 61]. Rituximab showed efficacy mainly on "non-criteria" manifestations of APS (i.e., thrombocytopenia, skin ulcers, and cognitive dysfunction) but had limited effect on aPL titers [62]. Steroid and cytotoxic therapies may alter aPL titers but do not seem to reduce the risk of thrombosis [63]. Therefore, these agents do not avoid the need for antithrombotic therapies. Promising data were recently reported regarding belimumab and its ability to lower or even negativize aPL titers [64, 65], but further studies have to address its clinical utility.

Treatment should be promptly initiated in the setting of CAPS due to the high-mortality rate of this condition [66]. Management is based on anticoagulants, systemic high-dose glucocorticoids, and plasma exchange or intravenous immunoglobulins. Rituximab and eculizumab may also be effective in some cases [67–70].

APS and the Kidney

Kidney Disease in APS

APS can affect the kidneys in many ways. If vascular thrombosis involves the renal artery or one of its main branches, the consequence is renal infarction [71–73]. Renal infarction is a rare manifestation of APS and causes flank pain, hypertension, and a variable degree of kidney function worsening depending on the extension of the ischemia [74, 75]. Besides in situ thrombosis, renal infarction may also be the consequence of arterial emboli from an upstream lesion [76]. APS should be suspected in any young patient with kidney infarction and without other risk factors for thrombosis [77].

Hypertension is a common clinical manifestation of APS, not only in the setting of renal infarction but it can also be due to stenosis of the renal arteries and to APS nephropathy (APSN). Renal artery stenosis induces the activation of the renin-angiotensin system. A study performed by magnetic resonance angiography in aPL-positive patients with poorly controlled hypertension showed that 26% of patients had renal artery stenosis. Two patterns of stenotic lesions can be found: stenosis in the mid-portion of the renal artery (more frequent) that is distinct from both fibromuscular dysplasia and atherosclerosis, and periostial stenosis that resembles an atherosclerotic lesion [78]. Anticoagulation therapy has been beneficial in these cases [79]. Arterial hypertension is a well-recognized risk factor for thrombosis in APS patients, so a vicious circle in this setting is sustained. Therefore, hypertension management is crucial in these patients [80].

Venous thrombosis can be clinically silent or it can cause sudden flank pain and proteinuria (often in the nephrotic range) if thrombosis is acute and complete [81]. Renal vein thrombosis can complicate renal transplantation and affect outcomes [82].

In addition to large vessels thrombosis, damage to the smaller vessels and to the glomeruli has been described and defined as APSN. APSN is a non-inflammatory and not immune complex-mediated disease that will be discussed in detail.

Lastly, APS has detrimental effects in patients on hemodialysis and in those with kidney transplant. Recurrent

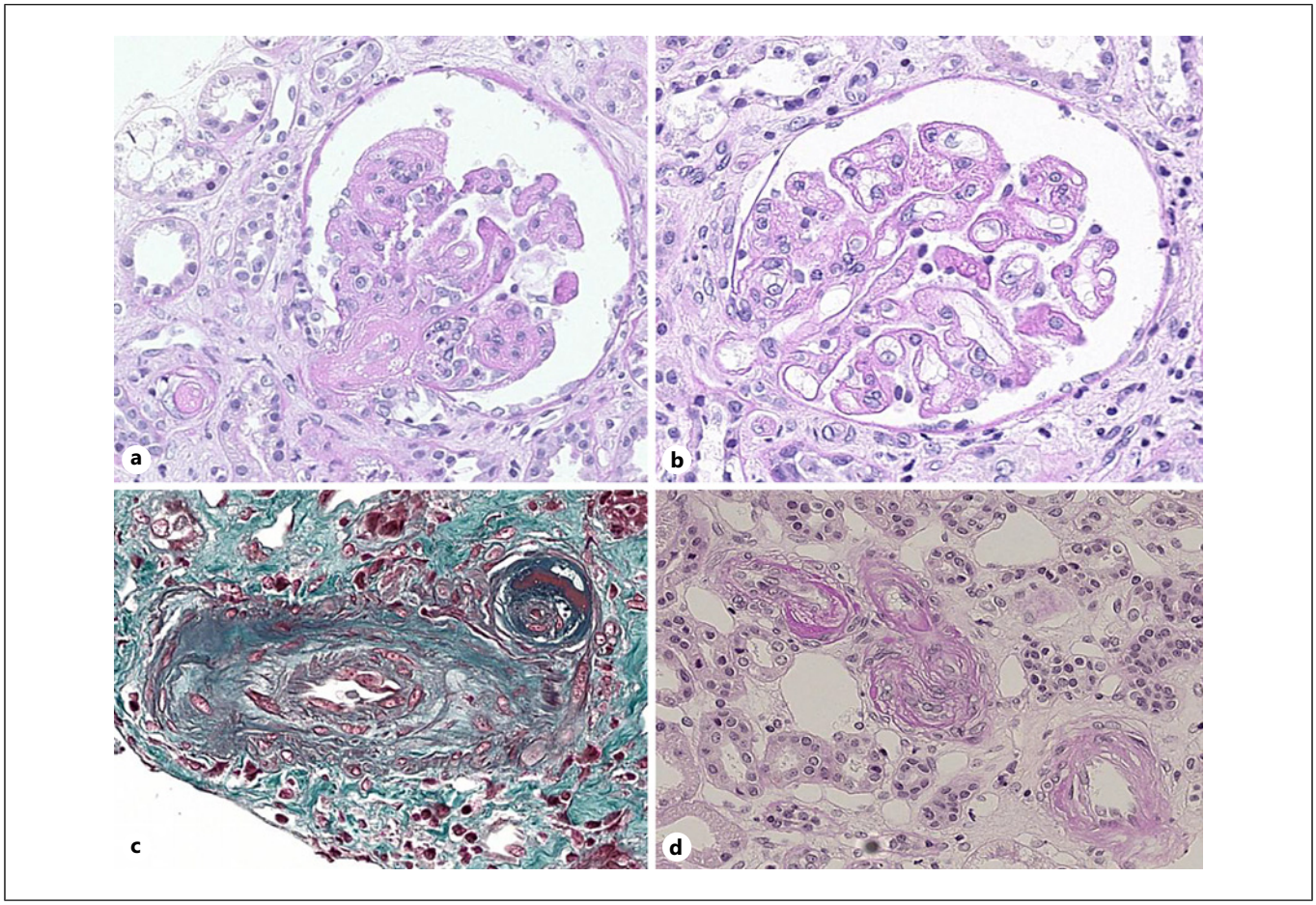

Fig. 2. Kidney biopsy. **a** (Periodic acid-Schiff stain) Afferent arterial thrombosis with ischemic collapse of the tuft. **b** (Periodic acid-Schiff stain) GBM with double contour appearance. **c** (Masson's Trichrome stain) intimal fibrosis and subendothelial mucoid degeneration in a small artery (subacute TMA). **d** (Periodic acid-Schiff stain) fibrous intima hyperplasia in arterioles and small arteries with endothelial enlargement and luminal reduction.

vascular access thrombosis has been described in the hemodialysis population with APS [83, 84]. Furthermore, a high prevalence of aPL has been reported in the hemodialysis population [85], even though the clinical relevance of this finding is unclear. In kidney transplanted patients, aPL positivity is an ominous prognostic factor for graft survival [86], and APS patients may lose their graft because of thrombotic complications [87].

APS Nephropathy

Pathology and Clinical Aspects

In the early nineties, Amigo et al. [88] provided the first description of vascular damage in the kidney biopsies of 5 APS patients that did not present any signs of SLE. Thrombotic microangiopathy (TMA) was the main finding in all those patients, along with other vascular changes. Typical features of lupus nephritis, such as immune-complex deposits, crescents, and hematoxylin bodies, were not reported. Hence, these vascular lesions were unrelated to SLE and were further characterized by a seminal work by Nochy and coworkers in 1999 [89]. They evaluated the kidney biopsies of 16 patients with APS but without SLE. They confirmed the presence of non-inflammatory vascular lesions, in particular TMA and fibrous intimal hyperplasia (FIH) (Fig. 2). Acute TMA is characterized by fibrin thrombi containing fragmented blood cells in both small vessels and glomeruli, along with subendothelial edema. These pathological changes are not exclusive for APS, as acute TMA can occur in many other conditions. In more advanced stages, a double-layer and wrinkled aspect of the glomerular basement membrane can be observed. This is caused by the detachment

of the endothelial layer and the infiltration of mesangial cells [90]. Sometimes, along with global ischemic collapse of some glomeruli, segmentally sclerotic glomerular lesions that resemble idiopathic focal segmental glomerulosclerosis can be observed [91]. FIH is characterized by hyperplastic changes due to cells proliferation (mainly intimal myofibroblasts) that can hesitate in an "onion-skin" arrangement. Sometimes the vessel lumina, obstructed by fibrous tissue, can be recanalized with endothelialized channels, quite a typical finding.

Along with vascular damage, Nochy et al. [89] also reported focal cortical atrophy, a consequence of chronic blood flow reduction, and the "thyroidization" of the tubular component. These features are included in the Sydney criteria, even though they are nonspecific for APSN [30].

In patients with CAPS, similar pathological findings can be observed [92]. Tektonidou et al. [93] performed a study on six CAPS patients who underwent kidney biopsy, comparing their pathological findings to those of 23 patients with APS and SLE, and 8 with APS alone. No significant differences were found in these 3 groups. All CAPS patients presented with acute TMA that was massive compared to controls. This study was proof of concept that aPLs are implicated in the pathogenesis of TMA in these settings.

On clinical grounds, arterial hypertension is the most common manifestation of APSN. Over 90% of patients in the Nochy study were hypertensive and this was shown to be related to renin overproduction as a consequence of vascular damage [89]. Mild proteinuria and slowly progressive kidney function deterioration are the other renal manifestations. Since hypertension is very common in chronic kidney disease (CKD) patients, both as a cause and a consequence of CKD, the clinical picture of APSN is nonspecific. Slow kidney function worsening and mild proteinuria may induce clinicians to hesitate to perform kidney biopsy, in consideration of the impaired coagulation system. Furthermore, pathological changes are not pathognomonic, and they need to be framed within the clinical picture. For all these reasons, APSN, which is a rare disease, is probably underdiagnosed.

APSN in SLE

In 1981, Kant et al. [94] had already identified that LA positivity in SLE patients correlates with renal TMA and that this finding is unrelated to the severity of lupus nephritis. In the following years, D'Agati et al. [95] found TMA in the renal biopsies of 3 patients with different types of APS (with and without SLE), suggesting that TMA was not related to necrotizing lesions of SLE.

In 2002, Daugas et al. [96] evaluated the renal biopsies from a large French cohort of SLE patients looking for vascular lesions consistent with APSN. They found APSN in 63% of patients with an established diagnosis of APS and also in 22% of patients with aPLs alone. These results were confirmed by another study that found a prevalence of APSN of 40% in SLE aPL-positive patients, versus only 4% of the aPL-negative group [97].

APSN is rarely the only pathological finding in patients with SLE. In fact, lupus nephritis is often present without an association with any histological class [98, 99]. Although in recent years the interest in vascular lesions in lupus nephritis has grown, these lesions are still overlooked when they occur with immune-complex-mediated lesions, and this may lead to an underestimation of the actual prevalence of APSN in these patients. Nonetheless, renal TMA carries the worst outcome among the various forms of lupus nephritis vascular damage and requires thorough evaluation [100–104]. This is consistent with the results of a study performed by Moroni and colleagues on 111 patients with lupus nephritis followed up for over 15 years, which showed that aPL-positive patients carried the worst kidney outcome [98].

Management

There are no specific treatments available for APSN to date. The use of renin angiotension aldosterone system blockers is widely accepted since these patients are frequently hypertensive with high renin angiotension aldosterone system activity [89]. Furthermore, a study found that in SLE patients with APSN, these drugs exerted a beneficial effect on CKD progression, beyond their effects on proteinuria and hypertension [105].

As regards anticoagulation therapy, it is still unclear whether it has any beneficial effects on APSN. A recent retrospective study evaluated renal outcomes in patients with APSN without concomitant lupus nephritis. APSN was shown to have poor renal prognosis, with an end-stage stage renal disease-free survival at 5 years of 80%, despite the population of this study was relatively young (average age 40 years). Patients on anticoagulation therapy did not show any benefit on renal outcomes [106]. However, another recent study found that anticoagulation therapy improved kidney outcomes in SLE patients with TMA [107]. In clinical practice, while APS patients should nonetheless be treated with anticoagulants, the question arises around SLE patients with aPLs and APSN but without thrombotic events. For these patients, anticoagulants cannot be recommended, even though they can be

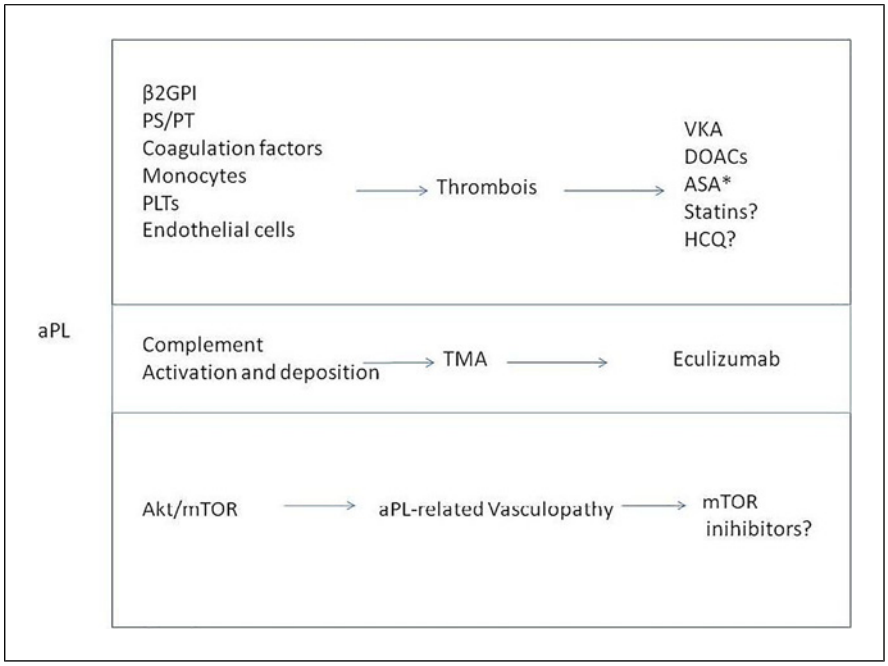

Fig. 3. Hypothesis of a different treatment for each APS pattern. * as thromboprophylaxis or associated with VKA. β2GP-1, β2-glycoprotein 1; PS/PT, phosphatidylserine/prothrombin; PLTs, platelets, VKA: vitamin K antagonist, DOACs, direct oral anticoagulants; ASA, acetylsalicylic acid; HCQ, hydroxychloroquine.

useful in selected cases. In our opinion, another reasonable option in some of these cases is prophylaxis with low-dose aspirin.

Immunosuppressive therapy prescribed for lupus nephritis has shown little efficacy on thrombotic events in APS patients, thus a significant effect on APSN is unexpected. Anecdotal data report the effectiveness of rituximab in some cases of APSN [62], while eculizumab and other complement inhibitors may play an important role in managing TMA [108]. Eculizumab has shown to be effective for the treatment and prevention of APS relapses in kidney transplant recipients [109, 110].

It is worth noting that recent studies have suggested that hyperplastic lesions in APS could have a different pathophysiology than thrombosis [111]. In vitro studies showed that aPLs can interact with endothelial cells through m-TOR and that the activation of the m-TOR complex (MTORC 1, 2) stimulates the growth and proliferation of endothelial cells [112]. These data were confirmed in a cohort of CAPS patients who underwent kidney transplantation and received Sirolimus, an m-TOR inhibitor. These patients presented almost no recurrence of hyperplastic changes in their kidney biopsies that otherwise were present in the control group. A recent case report confirmed these promising results in an APS patient [113]. Interestingly, endothelial proliferation in APS is not limited to the kidneys but can be found in other organs [114]. These drugs are appealing in this setting, but their use may be limited by side effects, such as pneumonia and proteinuria.

Considerations

Sydney criteria define APSN as the presence of TMA involving both arterioles and glomerular capillaries associated with one among focal cortical atrophy, FIH with organized thrombi and tubular thyroidization, in the absence of other causes that may justify TMA [30]. APSN is not considered a criteria manifestation of APS. Recently, a committee of experts published a report on a revision process of the Sydney criteria. Regarding APSN, they noticed that in clinical practice pathologists do not report APSN consistently and that there is a wide heterogeneity of vascular lesion definitions. For these reasons, they do not suggest considering APSN as a criteria manifestation of APS [115]. Nevertheless, in 2015 the Task Force that evaluated the specificity of nine "non-criteria" manifestations of APS found that APSN was among the most specific [116].

Recently, our group participated in a multicenter study that evaluated 123 kidney biopsies from aPL-positive patients with APSN [117]. In order to avoid differences in terminology, a common reporting scheme of histological changes was used. This allowed us to collect homogeneous data and to perform a cluster analysis to investigate whether different clusters of renal injuries with diverse prognostic meanings exist. We found that renal TMA, either acute or chronic, was far more frequent in patients with overt APS, while other changes, such as FIH, were less related to systemic thrombotic events. These data indicate that a stricter definition of APSN may enhance its specificity and thus support its inclusion in

the spectrum of APS. This would have considerable diagnostic and therapeutic implications. Furthermore, other patterns of aPL-related damage could be recognized and managed differently (Fig. 3). This is highly desirable in the era of precision medicine. These data also suggest that kidney biopsy is still mandatory to address kidney involvement in patients with aPLs.

Conclusion

APS is a rare disease characterized by autoimmunity and the impairment of the coagulation system. The current management of the syndrome, however, is only centered on counterbalancing the pro-thrombotic status. As the understanding of this syndrome is growing, new drugs have been explored to manage the disease. APSN is a rare and complicated condition, with poor renal prognosis, that sometimes overlaps lupus nephritis and that is often overlooked by clinicians. Consensus on a more detailed definition of APSN would increase the recognition of the disease and promote the collection of homogeneous data worldwide. Ideally, this will pave the way for new therapeutic scenarios.

Acknowledgments

We are grateful to all the Nephrology and Dialysis Unit, Center of Immuno-Rheumatology and Rare Diseases (CMID) staff for their support.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

This publication received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Author Contributions

Conceptualization: Emanuele De Simone and Roberta Fenoglio; resources: Savino Sciascia and Valentina Oddone; writing original draft preparation: Emanuele De Simone and Savino Sciascia; supervision: Dario Roccatello and Antonella Barreca. All authors have read and agreed to the published version of the manuscript.

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