Scientific Research Publishing

Open Journal of Internal Medicine, 2020, 10, 112-120
https://www.scirp.org/journal/ojim
ISSN Online: 2162-5980
ISSN Print: 2162-5972

Antiphospholipid Syndrome: Nephrologists' Perspective

Noha Abdou[1], Sabry Abd Allah Shoeib[2], Enas Sobhy Zahran[2]

[1]Shebin El Kom Teaching Hospital, Shebin El Kom, Egypt
[2]Faculty of Medicine, Menoifya University, Monufia, Egypt
Email: dr.nohaabdou30@gmail.com

How to cite this paper: Abdou, N., Shoeib, S.A.A. and Zahran, E.S. (2020) Antiphospholipid Syndrome: Nephrologists' Perspective. *Open Journal of Internal Medicine*, **10**, 112-120.
https://doi.org/10.4236/ojim.2020.102012

Received: February 21, 2020
Accepted: April 4, 2020
Published: April 7, 2020

Abstract

Introduction: Antiphospholipid antibody syndrome is a complex autoimmune disease that can affect all systems of the body and characterized by presence of antiphospholipid antibodies that cause vascular thrombosis and pregnancy complications, kidney involvement is very common in patients with antiphospholipid syndrome and leads to many serious complications. **Objectives**: study the effect of antiphospholipid syndrome on kidneys. **Data Sources:** By searching and reviewing Medline databases (Pub Med and Medscape) and all renal involvement in antiphospholipid syndrome materials available till 2019. **Study Selection:** All studies were independently assessed for inclusion. They were included if they fulfilled the following criteria: 1) published in English language; 2) published in peer-reviewed journals; 3) discussed the involvement of kidney in antiphospholipid syndrome. **Data Extraction:** Data from each eligible study were independently abstracted using a data collection form to capture information related to our concerned study outcomes. If the studies did not fulfill the inclusion criteria, they were excluded. Study quality assessment includes if ethical approval is gained, eligibility criteria specified, adequate information and defined assessment measured. **Data Synthesis:** Structured review with the results tabulated was made for comparison. **Conclusions:** We can conclude that kidney affection in patients with antiphospholipid syndrome has a wide spectrum and variation.

Keywords

Antiphospholipid Syndrome, Kidney, Nephropathy, Thrombosis, aPL

1. Background

Antiphospholipid syndrome [APS] is an autoimmune disorder with thrombus

formation in arteries or veins and pregnancy morbidity are its main characteristic features [1].

It can be a primary condition, or it can be secondary to other autoimmune diseases especially systemic lupus erythromatosus [2].

Thrombotic antiphospholipid syndrome characterized by venous or arterial thrombosis. Catastrophic antiphospholipid syndrome presented with thrombosis involving many organs. Obstetrical antiphospholipid syndrome characterized by recurrent miscarriages, intrauterine growth restriction and severe preeclampsia [1] [3].

The major non-thrombotic manifestations of antiphospholipid syndrome included valvular heart disease, livedo reticularis, antiphospholipid syndrome nephropathy, thrombocytopenia and hemolytic anemia. Antiphospholipid antibodies [aPL] are a heterogeneous group of antibodies directed against anionic phospholipids or protein-phospholipid complexes and are composed of antibodies against cardiolipin, β2-glycoprotein 1 and lupus anticoagulant [4].

A major common target organ in patients with antiphospholipid syndrome is kidney. Both acute and chronic renal insufficiency may occur. In this Review, the role of aPL antibodies in inducing renal disease and the clinical and histological features of APS involving the kidney will be discussed [2].

2. Review of Literature

In patients with APS, any organ could be affected by thrombus formation, therefore, the range of clinical features is extremely wide, the main clinical features are recurrent abortion and venous thromboembolism which can affect any organ but the deep venous thrombosis of the lower limbs is the most common site of venous thrombosis [2].

Kidney is considered one of the most common site that can be affected in APS, thrombosis occurring at any level within the renal vasculature is the main cause of renal manifestations of APS [2] [3].

Systemic hypertension, renal artery stenosis, renal infarction, antiphospholipid syndrome nephropathy, renal vein thrombosis and allograft vascular thrombosis (**Table 1**) are the renal maifestations of APS [4].

These wide range varieties in clinical manifestations are reflected in the histological findings, which include ischaemic glomeruli and thrombotic lesions, without glomerular or arterial immune deposits on immunofluorescence [5].

The wide spectrum of renal diseases associated with APS, and the impact of APS in end stage renal disease [ESRD] care, increase the importance of including the nephropathy of APS in the classification criteria of definite APS presentation [6].

3. APS Nephropathy

Antiphospholipid syndrome nephropathy [APSN] is an early clinical presentation of APS [6]; APSN refers to the kidney damage caused by vascular lesions (thrombosis) in the glomeruli, arterioles or interlobular arteries in patients with

Table 1. Renal manifestations in antiphospholipid syndrome [4].

Renal involvement	*Prevlance*	*Clinical features*	*Histopathological features*
Renal vein thrombosis	Not recorded	Proteinuria, hematuria, nephrotic syndrome	Thrombosis
Renal artery stenosis/thrombosis	Rare	Hypertension, reduced glomerular filtration rate	Stenosis, more distal than proximal
Primary APS nephropathy	Variable	Hypertension, proteinuria, reduced glomerular filtration rate	Thrombotic microangiopathy, fibrous intimal hyperplasia, membranous glomerulopathy, immune complexes and crescent formation
APS nephropathy and SLE	56% - 67%	Hypertension, proteinuria, hematuria, reduced glomerular filtration rate	Thrombotic microangiopathy, fibrous intimal hyperplasia, membranous glomerulopathy, immune complexes and crescent formation
Catastrophic APS and the kidney	> 50%	Hypertension, proteinuria, reduced glomerular filtration rate	Acute: thrombotic microangiopathy Chronic: fibrous intimal hyperplasia, focal cortical atrophy
CKD and renal transplant	Rare	Reduced glomerular filtration rate, early graft loss	Thrombosis

aPL [5].

It may be acute, the so-called thrombotic microangiopathy [TMA] or chronic, such as arteriosclerosis, fibrous intimal hyperplasia, tubular thyroidization and focal cortical atrophy [5] [6].

Edema, foaming urine, proteinuria & hypertension or a combination of all these are the most prominent symptoms of APS nephropathy [6] [7].

Histological findings in APS nephropathy (**Table 2**) include distinctive microangiopathic features (focal and diffuse) that affect any of the vessels within the intra-renal vasculature, including the glomeruli [8].

4. Renal Vein Thrombosis

Thrombosis of the renal vein has been observed in patients with different types of APS, such as aPL-positive patients with lupus nephritis (those patients have clinical and labratotry manifestations of SLE which are arthritis, positive antinuclear antibody [ANA] test and positive anti double strand DNA test in addition to positive aPL tests) and those with primary APS (those patients have clinical and laboratory manifestatins of APS only) [9].

Renal vein thrombosis can be presented with nephrotic range protinuria, and it sometimes could be the first clinical manifestation of the syndrome [8].

Nephrotic syndrome is found more in patients with secondary APS than in patients with primary APS. The renal vasculature should, therefore, be assessed with Doppler imaging to rule out renal vein thrombosis in aPL-positive patients who develop sudden severe proteinuria or acute impairment of renal function [10].

Other conditions associated with the development of renal vein thrombosis should also be investigated, such as pregnancy and use of oral contraception [10] [11].

Table 2. The main histological features in antiphospholipid syndrome nephropathy [4].

Glomeruli	**Light microscopy:**
	Enlarged glomeruli
	normal glomerular cellularity
	increased number of capillary loops
	diffusely thickened capillary walls
	double contours of glomerular basement membrane
	cellular interposition between the glomerular basement
	membrane and endothelial cells central mesangiolysis
	Immunofluorescence:
	Negative (no immune complex deposites)
	Electron microscopy:
	Lucent flocculent material between the endothelial cells of glomerular capillary and the glomerularbasement membrane
Tubules	Atrophied Thyroidization
Interstitium	Fibrosis
Intrarenal	**Grade 1:**
Vessels	Endothelial swelling
	mild fibrous arterial intimal thickening
	and/or mild patchy arteriolar hyalinosis
	Grade 2:
	Moderate fibrous arterial intimal thickening
	or moderate arteriolar hyalinosis
	Grade 3:
	Severe occlusive intimal thickening, thrombosis

Renal vein thrombosis can complicate renal transplantation and affect outcomes, and these patients should receive special attention due to the increased risk of vaso-occlusive events. Contrast-enhanced CT and magnetic resonance angiography are valid tools to confirm renal vein thrombosis [12].

5. Renal Infarction

Renal infarction might be associated with APS. In situ thrombosis, emboli from an upstream arterial lesion or a heart valve lesion can result in thrombotic events occurring in small diameter intraparenchymal vessels leading to renal infarction [12] [13].

Symptoms at presentation of renal infarction include pain, hypertension (often severe) and impairment of renal function, and it might be one of the first features of APS. Multiple, often serious, thrombotic episodes have been described in some patients, mostly localized in the renal cortex [11] [12] [13].

The most frequently observed histological findings are ischaemic features at the level of the glomerulus, tubular atrophy and interstitial fibrosis [4].

Although renal infarction is not a classic clinical manifestation of APS, aPL

testing should be performed in young people who present with this disorder to tailor treatment if necessary, aPL tests Laboratory criteria for definite antiphospholipid syndrome include one coagulation test, lupus anticoagulant (LAC), and two immunological assays to detect antiphospholipid antibodies (aPL), that is, anticardiolipin antibodies (aCL) immunoglobulin G (IgG) and IgM isotypes and anti-β2-glycoprotein I (aβ2GPI) antibodies IgG and IgM isotypes those tests should be repeated after 3 months to confirm the diagnosis [14].

Withdrawal of drugs, such as hydroxychloroquine, is potentially related to this rare complication [15].

6. Arterial Hypertension

Hypertension is associated with aPL and frequently presents with coexisting livedo reticularis. Arterial hypertension affects many patients with primary and secondary APS and has been proposed as a sensitive sign of potential renal involvement [11].

The high rate of hypertension is suggested to be due to severe vascular lesions, including fibrous intimal hyperplasia (in most of the cases), arteriosclerosis, arterial and arteriolar fibrous and fibrocellular occlusions and TMA [4] [5] [11].

Many cases of malignant hypertension associated with aPL are described. Of note, systemic hypertension has been reported as a strong risk factor for thrombosis in patients with aPL, which suggests that careful blood pressure control is needed in these patients [10].

Control of arterial hypertension and anticoagulation when necessary are thought to prevent progression to end-stage renal disease and future thrombosis [13].

7. Effects on Lupus Nephritis

Prognosis and renal outcomes in patients with lupus nephritis is affected with APS, Lupus anticoagulant and IgG antibodies against cardiolipin were more prevalent in these patients than in those without APS and they correlated with mortality [9].

A strong association between aPL and poor prognosis was also observed. Even after multivariate adjustment, the aPL remained associated with poor renal outcomes, high plasma creatinine levels at presentation and high chronicity index scores. These findings seem to support the role of aPL as an independent risk factor of chronic impairment of renal function in patients with SLE [9] [10].

Serial kidney biopsy findings analysis are required for diagnosis, the first biopsy sample mostly shows acute thrombotic features such as fibrin thrombi in interlobular arteries and glomerular arterioles, the second or third biopsy specimens mostly shows chronic forma, such as fibrous intimal hyperplasia, arteriolar occlusions, focal cortical atrophy or sclerotic features [11].

The prevalence of crescents, sclerosis and glomerular necrosis is higher in SLE patients with APS nephropathy than in those without APS nephropathy that in-

crease the association between aPL and glomerular thrombosis with poor renal outcomes [12].

Hypertension and raised creatinine levels are found more in patients with aPL than those without aPL, and were mostly associated with thrombosis (mainly arterial) during follow-up monitoring [11] [12].

Differentiation between patients who have lupus nephritis (immunecomplex disease) and patients who have impaired kidney function related to aPL (thrombotic events) is very important to guide treatment [16] [17].

Immunosuppressive therapy is useful to treat lupus nephritis, whereas in patients with APS who have APS nephropathy lesions on renal biopsy, additional anticoagulation might be required [16] [17] [18].

In summary, the early recognition of suggestive renal disease in patients with APS is crucial, and treatment should be started immediately and kidney biopsy should be considered as early as possible [16].

8. End-Stage Disease and Transplantation

Positive tests for aPL are found among patients with end stage renal disease than in general population, aPL does not relate to demographic features, such as age or sex, or to dialysis factors, including the duration of dialysis or the type of membrane used [16].

Some studies report that both lupus anticoagulant and antibodies against cardiolipin increase the risk of vascular access thrombosis, but this association has been confirmed only for lupus anticoagulant. End-stage renal disease is a rare complication of primary APS and only a few studies have investigated this relationship [13] [16].

Several studies investigating the clinical relevance of aPL in patients who underwent renal transplantation, these studies demonstrated that the risk of graft failure and thrombosis at any site within the renal vasculature increases in patients with positive aPL[16].

Overall, the role of aPL in transplant recipient still a matter of debate, however, strict control of cardiovascular risk factors should be intensified in these patients if aPL are detected in order to reduce the risks of morbidity and transplant failure [16].

9. Catastrophic APS

A very severe variant of classic APS is called catastrophic APS, and is characterized by acute multiple organ failure, evidence of multiple small vessel occlusions on histopathology and usually a high titre of aPL [17].

Less than 1% of all patients with APS could develop this serious condition; kidney involvement is a prominent clinical feature of catastrophic APS [18].

Ischemia of the bowels, lungs, heart and brain are most frequent, but rarely has adrenal, testicular, splenic, pancreatic or skin involvement been described [16] [17].

TMA is characteristic and leads to symptoms related to multiorgan failure, precipitating factors of catastrophic APS are infections, surgical procedures, withdrawal of anticoagulant therapy and the use of oral contraceptives [18].

10. Treatment

At the present time, anticoagulation stills the central focus of thrombosis treatment and prevention in APS, heparin is used for treatment of acute thrombosis, the standard treatment for prevention of arterial and venous thrombosis is warfarin with INR target of 2.0 - 3.0 [19].

Treatment of patients with recurrent thrombosis needs a combination of warfarin therapy with or without low-dose aspirin, hydroxychloroquine, and/or a statin drug, a higher INR target of 3.0 - 4.0 is needed in those patients [20].

Renal artery stenosis treated by antihypertensive agents, antiplatelet drugs or anticoagulants [20].

Corticosteroids, hydroxycloroquine and some immunosuppressive agents are reported to reduce aPL titres [21] [22].

Treatment of patients with catastrophic APS is very difficult and needs a combination of anticoagulants and corticosteroids plus intravenous immunoglobulin, and/or plasma exchange [19].

New oral anticoagulants, such as dabigatran and rivaroxaban, are available and could be used, but still under clinical trials [22].

11. Discussion

Antiphospholipid syndrome is an autoimmune prothrombotic disorder related to the presence of antiphospholipid antibodies that affects many systems of the body and results in thrombus formation [1].

Many variants of the syndrome can be found includes primary APS, secondary APS, seronegative APS and catastrophic APS which is the most serious condition resulting in acute multiorgan dysfunction and often failure, with more than 50% mortality [5].

Vascular thrombosis and pregnancy morbidity are the two clinical hallmarks of APS and used as main clinical criteria for diagnosis of APS syndrome alongside laboratory criteria that represented in the form of presence of one of the main antibody (LAC, aCL, or aβ2-GPI) diagnosis of the antiphospholipid syndrome should also involve the other non-criteria clinical manifestations of APS that includes other systems of the body [14].

Laboratory tests should be repeated after 3 months of being positive to confirm the diagnosis of APS. Patients with triple and double positivity of aPL tests is accompanied by highest rate of vascular thrombosis and pregnancy morbidity, some patients may have clinical manifestations of APS but negative to aPL tests [4].

Anticoagulation is the main drug for treatment and prevention of thrmbosis in APS [21].

Renal disease is present in 8% to 10% of patients with APS, renal manifestations of APS results mainly from thrombosis occurring at any level within the renal vasculature, the renal manifestations of APS involve systemic hypertension, renal artery stenosis, renal infarction, APSN, renal vein thrombosis and increased allograft vascular thrombosis [9].

Early testing for aPL should be considered in patients with any of these manifestations [10].

Kidney biopsy has an important role in the treatment and diagnosis of these patients for distinguishing between renal failures in SLE due to nephritis from that due to APS as the treatment for each one of them are different [19].

12. Conclusion

The kidney is a major target organ in primary and secondary APS. Renal involvement is a well-recognized manifestation of the syndrome and is characterized by thrombosis that can affect any vascular site in the kidneys.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Myakis, S., Lockshin, M.D. and Atsumi, T. (2006) International Consensus Statement on an Update of the Classification Criteria for Definite Antiphospholipid Syndrome. *Journal of Thrombosis and Haemostasis*, **2**, 295-306. https://doi.org/10.1111/j.1538-7836.2006.01753.x

[2] Pons-Estel, G.J., Andreoli, L., *et al*. (2017) The Antiphospholipid Syndrome in Patients with Systemic Lupus Erythematosus. *Journal of Autoimmunity*, **76**, 10-20. https://doi.org/10.1016/j.jaut.2016.10.004

[3] Gracia-Tello, B. and Isenberg, D. (2016) Kidney Disease in Primary Antiphos- pholipid Antibody Syndrome. *Rheumatology*, **56**, 1069-1080. https://doi.org/10.1093/rheumatology/kew307

[4] De Azevedo, F.V.A., *et al*. (2018) Renal Involvement in Antiphospholipid Syndrome. *Rheumatology International*, **38**, 1777-1789. https://doi.org/10.1007/s00296-018-4040-2

[5] Kotb, H.A., *et al*. (2016) Renal Histopathological Changes and Clinical Characteristics of Antiphospholipid Nephropathy in Lupus Nephritis Patients. *Kasr Al Ainy Medical Journal*, **22**, 1-18. https://doi.org/10.4103/1687-4625.182554

[6] Naseeb, F., *et al*. (2015) Histological Features of Antiphospholipid Nephropathy in Patients with Systemic Lupus Erythematosus. *Journal of College of Physicians and Surgeons Pakistan*, **25**, 332-336.

[7] Mezzina, N. and Sinico, R.A. (2015) Antiphospholipid Syndrome and the Renal Involvement. In: *Antiphospholipid Antibody Syndrome*, Springer, Cham, 103-112. https://doi.org/10.1007/978-3-319-11044-8_9

[8] Jordan, N., Chaib, A., Sangle, S., *et al*. (2014) Association of Thrombotic Microangiopathy and Intimal Hyperplasia with Bleeding Post-Renal Biopsy in Antiphospholipid

Antibody-Positive Patients. *Arthritis Care & Research*, **66**, 725-731. https://doi.org/10.1002/acr.22200

[9] Gordon, C., *et al.* (2017) The British Society for Rheumatology Guideline for the Management of Systemic Lupus Erythematosus in Adults. *Rheumatology*, **57**, 1-45. https://doi.org/10.1093/rheumatology/kex286

[10] Li, C., Wen, Y.B., Li, H., *et al.* (2019) Clinical Outcomes and Clinico-Pathological Correlations in Lupus Nephritis with Kidney Biopsy showing Thrombotic Micro- angiopathy. *The Journal of Rheumatology*, **46**, 1478-1484. https://doi.org/10.3899/jrheum.180773

[11] Majdan, M. (2017) Kidney Involvement in Antiphospholipid Syndrome Current Diagnostic and Management Problems. *Rheumatology*, **55**, 213-214. https://doi.org/10.5114/reum.2017.71626

[12] Marcantoni, C., Emmanuele, C. and Scolari, F. (2016) Renal Involvement in Primary Antiphospholipid Syndrome. *Journal of Nephrology*, **29**, 507-515. https://doi.org/10.1007/s40620-016-0317-2

[13] Bienaimé, F., *et al.* (2017) Antiphospholipid Syndrome and Kidney Disease. *Kidney International*, **91**, 34-44. https://doi.org/10.1016/j.kint.2016.06.026

[14] Pengo, V., Bison, E., Denas, G., *et al.* (2018) Laboratory Diagnostics of Antiphospholipid Syndrome. *Seminars in Thrombosis and Hemostasis*, **44**, 439-444. https://doi.org/10.1055/s-0037-1601331

[15] Horta-Baas, G., Camargo-Coronel, A., Miranda-Hernández, *et al.* (2019) Renal Transplantation in Systemic Lupus Erythematosus: Comparison of Graft Survival with Other Causes of End-Stage Renal Disease. *Reumatología Clínica* (*English Edition*), **15**, 140-145. https://doi.org/10.1016/j.reumae.2018.10.012

[16] Morales, J.M., Serrano, M., *et al.* (2019) Antiphospholipid Syndrome and Renal Allograft Thrombosis. *Transplantation*, **103**, 481-486. https://doi.org/10.1097/TP.0000000000002510

[17] Schultz, M., Wimberly, K. and Guglin, M. (2019) Systemic Lupus and Catastrophic Antiphospholipid Syndrome Manifesting as Cardiogenic Shock. *Lupus*, **28**, 1350-1353. https://doi.org/10.1177/0961203319871099

[18] Tinti, M.G., Carnevale, V., Inglese, M., *et al.* (2019) Eculizumab in Refractory Catastrophic Antiphospholipid Syndrome: A Case Report and Systematic Review of the Literature. *Clinical and Experimental Medicine*, **19**, 281-288. https://doi.org/10.1007/s10238-019-00565-8

[19] Pengo, V. and Denas, G. (2018) Diagnostics and Treatment of Thrombotic Antiphospholipid Syndrome (APS): A Personal Perspective. *Thrombosis Research*, **169**, 35-40. https://doi.org/10.1016/j.thromres.2018.07.011

[20] Abrahams, V.M., Chamley, L.W. and Salmon, J.E. (2017) Emerging Treatment Models in Rheumatology: Antiphospholipid Syndrome and Pregnancy: Pathogenesis to Translation. *Arthritis & Rheumatology*, **69**, 1710-1721. https://doi.org/10.1002/art.40136

[21] Heuser, C. and Branch, W. (2019) Diagnosis and Management of Antiphospholipid Syndrome. *Evidence-Based Obstetrics and Gynecology*, **31**, 325-333. https://doi.org/10.1002/9781119072980.ch31

[22] Tektonidou, M.G., Andreoli, L., Limper, M., *et al.* (2019) EULAR Recommendations for the Management of Antiphospholipid Syndrome in Adults. *Annals of the Rheumatic Diseases*, **78**, 1296-1304. https://doi.org/10.1136/annrheumdis-2019-215213