Antiphospholipid antibody nephropathy; an updated mini-review

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ABSTRACT

Antiphospholipid antibody nephropathy (APLN) is a rare autoimmune disease that affects the kidneys. It is characterized by the deposition of antiphospholipid antibodies (aPL) in the walls of small blood vessels in the kidneys. These antibodies cause inflammation and damage to the blood vessels, leading to various symptoms, including proteinuria, hematuria, hypertension, and renal failure. Several pathological lesions have been identified in APLN, including thrombotic microangiopathy, glomerular endothelial swelling, and fibrinoid necrosis of glomerular capillaries. Thrombotic microangiopathy is the most common lesion and is characterized by the formation of small blood clots in the vessels of the kidney, which can lead to kidney damage and dysfunction. In addition to these lesions, APLN can also cause damage to the tubules and interstitium of the kidney, leading to tubular atrophy, interstitial fibrosis, and chronic kidney disease. These lesions are thought to be caused by the chronic inflammation and immune response associated with APLN.

Implication for health policy/practice/research/medical education:
Antiphospholipid antibody nephropathy (APLN) is a potentially serious complication of antiphospholipid syndrome (APS), an autoimmune disorder characterized by the presence of antiphospholipid antibodies (aPL) and a predisposition to thrombosis and pregnancy complications. APLN can manifest as a wide range of renal pathologies, including glomerulonephritis, thrombotic microangiopathy, interstitial nephritis, and vasculitis. APLN may be asymptomatic or present with proteinuria, hematuria, hypertension, and/or renal insufficiency. Diagnosis of APLN requires the presence of aPL and renal pathology on biopsy, although the sensitivity and specificity of aPL testing and interpretation of renal biopsy findings can be challenging. Treatment of APLN typically involves anticoagulation with heparin or warfarin, along with immunosuppressive therapy (such as steroids, cyclophosphamide, or rituximab) in severe or refractory disease cases. The prognosis of APLN varies depending on the severity and extent of renal involvement, with some patients experiencing complete remission while others progress to end-stage renal disease.

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Introduction
Antiphospholipid antibody nephropathy (APLN) is a renal small-vessel vasculopathy characterized by acute thrombosis and/or chronic arterial and arteriolar lesions (1,2). APLN is a potentially serious complication of antiphospholipid syndrome (APS), an autoimmune disorder characterized by the presence of antiphospholipid antibodies (aPL) and a predisposition to thrombosis and pregnancy complications (3,4). APLN is defined as the presence of renal pathology in patients with APS, with or without clinical manifestations of renal disease. Diagnosis of APLN requires the presence of aPL and renal pathology on biopsy, although the sensitivity and specificity of aPL testing and interpretation of renal biopsy findings can be challenging (5,6). APLN can coexist with other kidney diseases, such as lupus nephritis, which can further complicate the pathology and clinical presentation (6). Therefore, a comprehensive evaluation, including clinical history, laboratory tests, and kidney biopsy, is essential for accurate diagnosis and appropriate management of APLN (7). Previous studies showed the prevalence of APLN in patients with systemic lupus erythematosus (SLE) varies depending on the population of the studies (6,8). A previous study by Tektonidou et al showed that...

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the prevalence of this disease in SLE patients with aPL was 39.5%, compared to only 4.3% in SLE patients without aPL (9). The study by Gerhardsson et al also demonstrated that the prevalence of APS-associated nephropathy was 14.3% among SLE patients with renal involvement (6).

Recently, efforts have been made to better characterize the APLN for the new APS classification criteria to provide the most accepted terminology for acute and chronic lesions (10). The pathogenesis of this disease is related to the vaso-occlusive lesions, which contribute to the ischemic changes, impaired blood flow, and subsequent damage to the glomerular basement membrane. Vaso-occlusive lesions (renal small-vessel vasculopathy), including total or partial thrombotic microangiopathy, are the most striking features of APLN nephropathy (11,12).

This mini-review emphasized the importance of recognizing APLN as a potential complication of APS and incorporating appropriate diagnostic and therapeutic strategies into clinical management.

Search strategy
For this review, we searched PubMed, Web of Science, EBSCO, Scopus, Google Scholar, Directory of Open Access Journals (DOAJ), and Embase, using different keywords including APLN, autoimmune disease, thrombotic microangiopathy, fibrinoid necrosis, renal biopsy, systemic lupus erythematosus, antiphospholipid antibodies, blood clot, acute kidney injury, vascular occlusion, renal ischemia, interstitial, tubular atrophy and renal vein thrombosis.

Clinical criteria of APLN
The presence of persistently increased titers of aPL, including lupus anticoagulant, antiphospholipid antibodies, and anti-β2 glycoprotein I antibodies is necessary for the diagnosis of APS (13,14). Clinical manifestations of renal involvement are hypertension, acute or chronic renal failure, proteinuria (usually mild, but occasionally nephrotic), and vascular nephropathy syndrome, which refers to the ischemia of the organs (3).

Renal morphologic lesions of APLN
Acute lesions like thrombotic microangiopathy were found in some aPLN patients, while chronic lesions like focal cortical atrophy and fibrous intimal hyperplasia were found in others. Understanding the various pathologic lesions associated with APLN is crucial for diagnosing and managing this condition. In APLN, the pathologic lesions primarily affect the small blood vessels within the kidneys (1,15). The common pathologic lesions found in APLN include thrombotic microangiopathy. This pathologic feature is characterized by the formation of blood clots within the kidney’s small blood vessels. It can lead to ischemia and tissue damage, resulting in various clinical manifestations, including hematuria, proteinuria, and acute kidney injury (16). In some cases, aPL can cause inflammation and damage to the renal arteries. This can result in vascular occlusion, fibrosis, and narrowing of the blood vessels, impairing blood flow to the kidneys. APLN can also involve larger arteries within the kidney.

The most common arterial lesion seen in APLN is fibrous intimal hyperplasia, which refers to the thickening and narrowing of the arterial walls due to excessive growth of smooth muscle cells and collagen deposition. This arterial remodeling can impair blood flow and contribute to renal ischemia (3,17). Moreover, immune complex deposition, endothelial cell damage, and inflammation can lead to glomerular basement membrane thickening, mesangial expansion, and the formation of cellular crescents (18,19). APLN can also result in interstitial inflammation and fibrosis. Inflammation within the interstitial space can cause tubular injury and dysfunction, which may progress to fibrosis over time (3,20). Furthermore, tubular atrophy, loss of brush border, and tubular basement membrane thickening are commonly observed (1,3). In some cases, APLN may also affect veins within the kidney. The most characteristic venous lesion observed is thrombosis, which refers to the formation of blood clots within veins. Renal vein thrombosis can further compromise blood flow and lead to renal infarction (21,22). The combination of these pathologic lesions results in progressive kidney damage and dysfunction in APLN patients. The severity of these lesions varies among individuals, and the extent of kidney involvement can range from mild to severe (23,24).

Diagnosis of APS nephropathy
The diagnosis of APS nephropathy requires the fulfillment of the histological and clinical criteria. The specificity, positive predictive value, and negative predictive value of APS nephropathy for detecting APS are reported to be 96%, 85%, and 87%, respectively. Further research and validation of the histological criteria for APS nephropathy are still needed (1,25).

Treatment of APS nephropathy
The treatment of APS nephropathy involves a combination of medications and lifestyle modifications. The primary goals of treatment are to prevent further kidney damage, manage symptoms, and reduce the risk of complications (26). Since APS is characterized by abnormal blood clotting, anticoagulant medications such as warfarin or heparin may be prescribed to prevent the formation of blood clots in the kidneys and other organs (27). Accordingly, in cases where there is evidence of inflammation and immune system involvement, immunosuppressive drugs like corticosteroids or cyclophosphamide may be used...
to suppress the immune response and reduce kidney inflammation (28). Moreover, high blood pressure can worsen kidney damage in APS nephropathy. Medications like ACE inhibitors or angiotensin receptor blockers (ARBs) may be prescribed to control blood pressure and protect the kidneys from further damage (29). In addition, adopting a healthy lifestyle can help manage APS nephropathy. This includes maintaining a balanced diet low in salt, exercising regularly, quitting smoking if applicable, limiting alcohol consumption, and managing stress levels (30). Besides, Regular check-ups with a healthcare provider are essential to monitor kidney function, blood pressure levels, and overall health. Blood tests may be done to assess kidney function and monitor anticoagulation therapy effectiveness (31). Additionally, it is needed to identify new therapeutic targets for APLN, such as agents that can reduce inflammation and oxidative stress in the kidneys. We also recommend that clinicians consider the screening of high-risk patients for aPL, and monitoring kidney function closely in those who test positive is needed (14,32). Moreover, rheumatologists and nephrologists should work closely to develop an individualized treatment plan based on their specific conditions and needs for cases with APS nephropathy.

Conclusion
Acute thrombosis and/or chronic arterial and arteriolar lesions in the renal small vessels are characteristic features of antiphospholipid antibody nephropathy. Treatment of APLN typically involves anticoagulation. Treatment of APLN typically involves anticoagulation with heparin or warfarin, along with immunosuppressive therapy (such as steroids, cyclophosphamide, or rituximab) in severe or refractory disease cases. However, further research is needed to fully understand the underlying mechanisms and clinical implications of glomerular basement membrane wrinkling in APS nephropathy.

Authors’ contribution
Conceptualization: Narges Ansari.
Data curation: Mansour Salesi & Narges Ansari.
Investigation: Narges Ansari.
Resources: Narges Ansari.
Supervision: Narges Ansari.
Validation: Mansour Salesi and Narges Ansari.
Visualization: Mansour Salesi and Narges Ansari.
Writing-original draft: Narges Ansari.
Writing-review and editing: Narges Ansari.

Declaration of generative AI and AI-assisted tools in the writing process
During the preparation of this work, the authors utilized ChatGPT—a chatbot developed by OpenAI—to refine grammar points and language style in writing. Subsequently, the authors thoroughly reviewed and edited the content as necessary, assuming full responsibility for the publication’s content.

Conflicts of interest
The authors declare that they have no competing interests.

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