Renal Vascular Lesions in Systemic Lupus Erythematosus

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Systemic lupus erythematosus (SLE) is a relatively common autoimmune disease in the Asian population. The clinical manifestations are diverse, ranging from hematologic disorders, arthritis, skin lesions, nephritis and neurological symptoms. The roles of sex hormone, genetic and environment have been implicated in the etiological factors. The pathogenesis involves the inadequate clearance of autoantigen from apoptosis and the inability of the immune system to delete autoreactive T and B lymphocytes.

Multiple organs can be involved by SLE. The injury is caused by an autoantibody-self antigen reaction resulting in immune complex deposition in tissue. Due to the systemic nature of this process, it is not surprising that blood vessels can be the targets. The majority of SLE vascular lesions occur in the skin in the form of vasculitis. The lesion was found less commonly in other visceral organs. The visceral organs involved by vasculitis include the heart, lung, kidney, gastrointestinal tract and brain. Although the visceral organ involvement is less common than in the skin, it is more associated with morbidity and mortality.

The kidney involvement in SLE or lupus nephritis occurs in 60% of SLE patients in the first 5 years of diagnosis. The predominant pathology is acute glomerulonephritis due to immune complex deposition in the glomeruli. The classification of lupus nephritis is focused on glomerular lesions. The vascular lesions, though proven important prognostic findings, are not included in the lupus nephritis classification. As a result, vascular lesions may not be well-recognized and may be overlooked. In addition, a certain type of lesion prompts clinicians to look for other associated conditions common in SLE patients such as antiphospholipid antibody syndrome (APS). This article reviews pathology of vascular lesions found in the kidneys of SLE patients.

Uncomplicated vascular immune deposits

The lesion may not be detected by light microscopy (LM) or there may be accumulation of eosino-
philic material underneath the endothelium of arterioles and small arteries. Small arteries and arterioles are commonly involved. There is no inflammatory cell infiltrate in the arterial wall. The arterial lumens are not compromised (Fig 1A). The arteries with eosinophilic material are similar to arteries in patients who have hypertension or diabetes. Hypertension is not uncommon in lupus nephritis patients, especially ones with a significant degree of renal fibrosis. Immunostaining is needed to differentiate this lesion from normal vessels or from vessels with changes due to hypertension and diabetes. Staining is to determine whether immunoglobulin G (IgG), IgA, IgM and complement components are present, indicating deposition of immune complex (Fig 1B). Electron microscopy (EM) shows immune complex deposits beneath the endothelium and/or extending between medial myocytes.

The pathogenesis of this lesion is most likely due to the deposition of immune complex, similar to glomerular and tubular lesions. Uncomplicated vascular immune deposits are more common in patients with active lupus nephritis (class III and IV) in which more immune complex is produced. Of note, this type of vascular lesion is frequently seen concurrently with immune complex deposits in tubules.

Fig 2. Noninflammatory necrotizing vasculopathy (lupus vasculopathy). A. The arteriole shows amorphous eosinophilic material replacing most of its wall and extending into the lumen (arrow). There is no inflammatory cell infiltrate (Hematoxylin & Eosin (H&E), x400). B. IgG is detected in the arteriolar wall and lumen (Immunofluorescence IgG, x400).

Fig 3. Thrombotic microangiopathy (TMA). A. In acute form, fibrin thrombi are seen in glomeruli and hilar arterioles (arrows) (Hematoxylin & Eosin (H&E), x400). B. The interlobular artery shows severe narrowing of lumen due to fibrointimal proliferation “onion skin” in chronic TMA. The adjacent glomerulus shows wrinkle due to ischemia (Hematoxylin & Eosin (H&E), x400). C. The glomerular capillary wall in chronic TMA shows widening of lamina rara interna containing electron lucent material (asterisk) (Electron microscopy, x8000).
The lupus nephritis patient with this lesion shows no different renal outcome compared to those without.

**Noninflammatory necrotizing vasculopathy**

Also known as lupus vasculopathy. The lesion is more common in proliferative forms of lupus nephritis (class III, IV), however, it is much less common than uncomplicated vascular immune deposits. LM shows granular eosinophilic deposits in the intima and media of arterioles and interlobular arteries (Fig 2A). The arteries are occasionally compromised due to the deposits extending into the lumens. There is no or few inflammatory cell infiltrates. Immunostaining shows positive staining with IgG, IgA, IgM, complement components and fibrin-related antigen in varying degrees (Fig 2B). Ultrastructurally, there are immune complex deposits, sometimes with fibrin tactoids and platelets in the vessel wall. The endothelium may be denuded and the myocytes may show degenerative changes in areas adjacent to the immune complex.

There is immune complex deposition in arterial walls similar to uncomplicated vascular immune deposits. In contrast to the latter lesion, a thrombotic process is evident by the presence of fibrin-related products. The injury to the vessel is more severe. Severe hypertension is frequently found, but it is not regarded as the cause of this lesion. There were a number of patients with this lesion without hypertension. Lupus vasculopathy is associated with elevated serum creatinine, hypertension and progression to end stage renal disease.

**Thrombotic microangiopathy (TMA)**

In the acute phase, this lesion is characterized by the presence of fibrin thrombi in glomerular capillaries, arterioles and sometimes interlobular arteries (Fig 3A). The fibrin thrombi often extend into media resulting in an amorphous, eosinophilic appearance of the arterial walls. There are no or few inflammatory cell infiltrates. This finding bears great similarity to the finding in lupus vasculopathy. In contrast to this lesion, lupus vasculopathy seldom shows thrombosis in glomeruli or vascular poles. With glomerular and arterial lumen occlusion, the renal parenchyma shows ischemic changes.

The arterial lesions in the chronic phase show organization and recanalization (fibroblast proliferation and capillary formation within thrombus). Many arteries may show thickening of the walls due to proliferation of intimal cells. This change results in severe narrowing of the lumens. The intima shows mucoid appearance with fibrointimal proliferation ‘onion skin’ (Fig 3B). This arterial lesion can be seen in patients with accelerated or malignant hypertension. The glomerular capillary walls show splitting or duplication. There may be mesangiolysis (disintegration of the mesangium). Fibrin thrombi may still be evident. These lesions reflect glomerular cell injury which can be caused by various etiologic agents. Immunostaining shows positive staining for fibrin-related antigen and may show positive IgM and C3. However, unlike lupus vasculopathy, IgG is negative and the immune complex is not seen by EM in the arterioles and arteries. Therefore, immunostaining and/or EM are crucial in differentiating TMA from lupus vasculopathy. There is widening of the lamina rara interna of the glomerular basement membrane with new basement membrane formation and subendothelial electron-lucent flocculent material (Fig 3C).

TMA is a pathological term characterized by the above description. It can occur in many conditions and can be renal limited or systemic. Its incidence was 8% in a large study. The clinical syndromes associated with TMA include hemolytic uremic syndrome/thrombotic thrombocytopenic purpura (HUS/TTP), antiphospholipid antibody syndrome (APS), systemic sclerosis and malignant hypertension. The finding of TMA in renal biopsy with lupus nephritis could indicate the possible co-existence of these syndromes. However, TMA can occur in lupus nephritis without other associated conditions or systemic involvement.

Antiphospholipid antibody syndrome (APS) is well-recognized as a major complication in SLE patients. The syndrome is characterized by recurrent thrombosis in various organs and the presence of antiphospholipid antibodies (aPL). These antibodies include anticardiolipin, anti-β2 microglobulin and lupus anticoagulant. Anticardiolipin and lupus anticoagulant were found in 44% and 34% of SLE patients, respectively. Approximately one third of these patients developed APS. The clinical manifestation is the result of vascular occlusion in the arterial and/or venous system including fetal loss (due to thrombosis in placental vessels), deep vein thrombosis and cerebral infarcts. Involvement of the kidney is fairly common and can occur in both intra-renal vessels and renal arteries. The intrarenal lesions are termed antiphospholipid syndrome nephropathy (APSN). The clinical manifestation is variable, depending on the degree and size of the occluded vessels and can vary from asymptomatic hematuria/proteinuria to acute renal failure. It was found in 32% of lupus nephritis patients who had renal biopsies in western population, concurring with the data from Thai patients (34%).

aPL can be formed in SLE patients by the autoimmune mechanism similar to other auto-antibodies. Of note, aPL can be found in both normal persons and patients with APS but without SLE or other autoimmune diseases (primary APS). The mechanism by which aPL promotes thrombosis is still unclear. One of the proposed hypotheses is that the antibodies can activate endothelium by binding to β2 microglobulin.
on the endothelial surface resulting in increased expression of adhesion molecules, secretion of cytokine and prostacyclin. These processes turn the endothelium from a normal into a prothrombotic state. The second hypothesis indicates a cross reaction of aPL with oxidized low-density lipoprotein (LDL) in macrophages, leading to macrophage activation and damage to the endothelium. The last hypothesis points to the interference of aPL with the normal coagulation process. The binding of β2 microglobulin, a natural anticoagulant, with aPL creates a prothrombotic environment.17

APSN has been associated with poor renal outcome regardless of the class of lupus nephritis.18 Detection of this lesion in a renal biopsy is not only providing clinicians with an important prognostic indicator, but also directs treatment towards anticoagulation. There was evidence that treatment with anticoagulant such as aspirin and warfarin may prevent thrombosis in patients with APS.19

Renal vasculitis

The lesion is the rarest among the 4 types. The common vessels involved are the small and medium-sized arteries. The interlobular arteries are the most common targets. This is true vasculitis. The arterial walls are destroyed by inflammatory cell infiltrate and fibrinoid necrosis (Fig 4). Immunostaining shows positivity with fibrin-related antigen, and with IgG, IgM and complement factor C3 in varying degrees. Immune complex deposits were observed in some, but not all cases. The histologic findings are identical to those in other vasculitic diseases, namely polyarteritis nodosa and pauci-immune glomerulonephritis. The pathogenesis of lupus vasculitis is most likely not limited to a single mechanism. The presence of immune complex deposits indicates the usual SLE disease process similar to a glomerular lesion. However, a number of SLE patients with this type of vasculitis may have superimposed pauci-immune glomerulonephritis. Antineutrophil cytoplasmic antibody (ANCA), the antibody responsible for the pathogenesis of pauci-immune glomerulonephritis, has been found in 37% of patients with lupus nephritis.19 The possibility of superimposed pauci-immune glomerulonephritis should be considered when the amount of immune complex is disproportionate to the severity of glomerular injury and vasculitis. The glomeruli may show no or scant endocapillary proliferation and subendothelial immune complex deposits while crescents and fibrinoid necrosis are prominent.20

Renal vasculitis can occur in any class of lupus nephritis though more common in proliferative class III and IV.7 The findings of this lesion in lupus nephritis not only indicates poor renal outcome and the need for more aggressive immunosuppressive treatment, it also prompts the clinician to look for other superimposed vasculitic diseases.

CONCLUSION

In addition to recognize vascular lesions in renal biopsy with lupus nephritis, the pathologists must be able to classify the lesions into the appropriate type. The four well-recognized vascular lesions in lupus nephritis are uncomplicated vascular immune deposits, noninflammatory necrotizing vasculopathy, thrombotic microangiopathy and renal vasculitis. Endothelial injury plays a central role in the pathogenesis and can be the result of various etiologies ranging from immune complex deposition per se or to other superimposed conditions. Different types of lesion implicate different prognosis, treatment strategy and possible different underlying pathogenesis.

REFERENCES