Renal Vascular Complications of Systemic Lupus Erythematosus

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Renal vascular complications are not infrequently encountered in systemic lupus erythematosus (SLE), and their occurrence can have a profound effect on the clinical course and choice of therapy. A variety of histopathologic lesions of the renal vessels as well as a number of distinct clinical syndromes related to vascular damage may occur in SLE. These renal vasculopathies include vascular immune complex deposition, noninflammatory necrotizing vasculopathy, thrombotic microangiopathy, and true renal vasculitis. The clinical syndromes of thrombotic thrombocytopenic purpura (TTP), anticardiolipin syndrome, and renal vein thrombosis (RVT) are also well-documented vascular complications of SLE. Because glomerular pathology is of primary importance in the classification of lupus nephritis, the presence and significance of these vascular lesions are often overlooked. Although the pathogenesis of many of these vascular entities is not fully defined, therapeutic intervention has often been successful. This article reviews their pathology, pathogenesis, epidemiology, and clinical course, as well as the various therapeutic strategies used to treat the vascular complications of SLE.

HISTOPATHOLOGY AND PATHOGENESIS OF LUPUS RENAL ARTERIOPATHIES

In the past, the term "lupus vasculitis" was used indiscriminately and included a variety of arterial lesions involving not only the renal circulation but also the vessels of the upper and lower extremities and the coronary, mesenteric, gallbladder, and cerebral circulations (1-14). Recent studies have pointed out that, with the exception of cutaneous vasculitis, true inflammatory lesions of larger arteries are relatively uncommon in SLE (3,14,15).

In our own experience and that of others (15-22), the pathology of the renal vasculopathies seen in SLE patients may take several morphologically distinct forms: uncomplicated vascular immune deposits, noninflammatory necrotizing vasculopathy, thrombotic microangiopathy, and true vasculitis of the microscopic polyarteritis nodosa (PAN) type.

Vascular Immune Complex Deposits

The most common renal vascular lesion in SLE is immune complex deposition in the walls of arterioles, small arteries, and to a far lesser extent, veins (19,21,23,24). By light microscopy (LM), the vessels usually appear normal. Less commonly, eosinophilic, periodic acid-Schiff–positive, and fuchsinophilic deposits are seen beneath the endothelium or between the cells of the media (19). No thrombosis, necrosis, or inflammatory infiltration of the vessel wall is present, and the lumen is usually not compromised (Figure 1). By immunofluorescence microscopy (IF), the deposits may contain immunoglobulin G (IgG), IgM, IgA, and complement components (Figure 2). By elec-

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Figure 1. Vascular immune deposits thicken the subendothelial basement membranes of multiple small interlobular arteries. The lumen is not significantly narrowed. There is no associated inflammation, necrosis, or thrombosis. Uncomplicated vascular immune deposits. Periodic acid–Schiff, x320.
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Figure 2. By IF, deposits of IgG are detected in the walls of several small arteries. Same biopsy as that shown in Figure 1. Uncomplicated vascular immune deposits. IF, ×400.

electron microscopy (EM), the deposits are electron dense and discrete and often have a granular texture, although occasionally a fingerprint or tactoid substructure is seen (Figures 3–5). They are most commonly located beneath an intact vascular endothelium or within the basement membranes surrounding the medial myocytes (Figure 6). Only rarely are perivas-
Microscopy will help in differentiating hyalinosis from vascular deposits of immune complexes. Differentiation is more difficult when the two diseases are present together.

Noninflammatory Necrotizing Vasculopathy

This type of vasculopathy is much less common than simple vascular immune deposits and may represent a complication of more severe forms of immune complex deposition. It predominantly affects preglomerular arterioles and to a lesser extent the interlobular arteries, frequently in the setting of active, diffuse proliferative lupus glomerulonephritis. This lesion is characterized by necrotizing changes in the vessel wall associated with abundant immune complex deposits, causing significant luminal narrowing or occlusion (16–20,25,26). By LM, smudgy eosinophilic, fuchsinophilic material that stains focally positive for fibrin occupies the lumen and intima, with frequent extension into the media. The endothelium is usually swollen or denuded, with occasional pyknotic nuclear fragments and smudgy degeneration of the medial myocytes (Figure 7). The elastic membrane of the interlobular arteries is usually disrupted. Rarely, a few lymphocytes may be seen in the lumen or intima (16,19). By IF, variable staining for IgG, IgM, IgA, complement components, and fibrin-related antigens is present in the wall and extends to the lumen, (16,19,26) (Figure 8). Ultrastructurally, there is swelling or loss of endothelium, with massive confluent intraluminal and mural deposits of granular electron-dense material, with the combined appearance of insudated proteins, and immune deposits, sometimes associated with tactoids of fibrillar fibrin and platelets. Degenerative changes may be seen in the medial myocytes adjacent to these deposits (16).

The pathogenesis of this noninflammatory necrotizing vasculopathy is uncertain. Its occurrence in patients with mild or no hypertension, the infrequent presence of hypertensive retinopathy, and the histopathologic findings of vascular immune deposits in addition to fibrin all militate against malignant hypertension as the primary etiologic process. However, it is likely that the superimposition of severe hypertension may exacerbate these vascular lesions (19,26). The presence of abundant electron-dense vascular deposits consisting in part of immunoglobulins and complement strongly suggests immunologic factors in the evolution of these lesions (18,26). Secondary thrombosis might contribute to the damage occurring in these vessels (16,17,19). The fact that such vascular lesions are most common in patients with active proliferative lupus glomerulonephritis also supports a role for immune deposition as a primary process (16–19,26). The possible involve-
Thrombotic Microangiopathy

This type of vasculopathy may involve the renal vessels of lupus patients with TTP or antiphospholipid antibody syndrome or may occur without a recognizable thrombotic systemic process. It is often difficult to distinguish from the noninflammatory necrotizing vasculopathy described above. It also

Figure 6. Granular electron-dense deposits within the basement membrane between the medial myocytes of an interlobular artery. Uncomplicated vascular immune deposits. Electron micrograph, ×5,000.

Figure 7. Noninflammatory necrotizing lupus vasculopathy affecting two arterioles from a patient with diffuse proliferative lupus nephritis. The lumen is occluded by eosinophilic smudgy material with endothelial denudation and pyknotic nuclear debris. Note the absence of leukocytes infiltrating the vessel wall. Hematoxylin and eosin, ×320.
Figure 8. An interlobular artery from the same patient as shown in Figure 7 shows staining of the intraluminal material with antiserum to IgG (a) and fibrin-related antigens (b). The elastic is disrupted. Noninflammatory necrotizing lupus vasculopathy. IF, x400.

Figure 9. Multiple thrombi occlude glomerular capillaries and arterioles. TTP-like syndrome in SLE. Jones methenamine silver, x320.

most commonly affects preglomerular arterioles and small interlobular arteries. Unlike noninflammatory necrotizing vasculopathy, however, it also involves the vascular pole and adjacent glomerular capillaries (22,29–31) (Figures 9 and 10). Histologically, it appears identical to the vascular changes seen in nonlupus patients with hemolytic-uremic syndrome (HUS), TTP, malignant hypertension, scleroderma, and other thrombotic microangiopathies (19,25,31,32). In the acute phase, there is marked luminal narrowing or total occlusion by intraluminal, subendothelial, or medial accumulation of eosinophilic, fuchsinophilic material with staining properties of fibrin (Figure 11), invariably associated with endothelial swelling, denudation, and sometimes fragmented and/or hemolyzed erythrocytes. It is dis-

Figure 10. A large fibrin thrombus obstructs the afferent arteriole as it enters the glomerular tuft. TTP-like syndrome in a patient with WHO Class IV lupus nephritis. Jones methenamine silver, x320.

tinguished from noninflammatory necrotizing vasculopathy, however, by the predominance of fibrin and the absence of discrete immune deposits on IF and EM. Frequently, the media appears thinned and stretched around the expanded intima. There is no leukocyte infiltration of the vessel wall. In the chronic phase, mucoid edema of the intima and/or the "onion skin" type of intimal fibroplasia may occur (25) (Figure 12).

The pathogenesis of thrombotic microangiopathy
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True Renal Vasculitis

This is by far the least frequent renal vascular lesion encountered in SLE. Its morphologic appearance is identical to that of microscopic PAN (19,20,25). This vascular lesion is so uncommon in SLE that some have questioned whether its presence does not represent overlap with PAN rather than a true manifestation of SLE. The vessels affected are usually small and medium-sized arteries, most commonly intralobular arteries. There is prominent inflammatory cell infiltration of the arterial wall by neutrophils and mononuclear leukocytes, affecting the vessel eccentrically or circumferentially. This mural inflammation is accompanied in the acute phase by fibrinoid necrosis, usually most severe in the intima and to a lesser extent in the media (Figure 13). In some biopsies, rupture of the elastic lamellae is seen (21). IF discloses fibrin-related antigens sometimes associated with less intense staining for immunoglobulin and/or complement fractions. Although there are no EM reports of this lesion in SLE patients, the few EM descriptions of necrotizing vasculitis of the PAN type in nonlupus patients have disclosed no electron-dense deposits of the immune type, although fibrin deposition is common (34). Thus, the IF positivity may represent nonspecific trapping of circulating plasma proteins in the damaged arterial wall (35). However, ultrastructural studies are needed to conclusively exclude a role for immune deposits in the pathogenesis of these lesions in the setting of SLE.

The pathogenesis of this rare, true inflammatory vasculitis resembling periarteritis nodosa may involve mechanisms similar to those proposed for vasculitides of the PAN type (35). The fact that intralobular edema of the intima of an interlobular artery (TTP-like syndrome in SLE). Phosphotungstic acid hematoxylin, x320.

in SLE is probably unrelated to immune complex deposition. In lupus patients with these findings on renal biopsy, accelerated hypertension, overlap with scleroderma, TTP-like syndrome, or lupus anticoagulant syndrome should be excluded as possible etiologic factors (vide infra). Sometimes these vascular lesions are identified in the kidneys of patients without a clinically evident thrombotic tendency. The possibility of cyclosporin A nephrotoxicity should also be excluded in patients who have received this therapy for lupus nephritis because this medication has been reported to cause a thrombotic microangiopathy in organ allograft recipients (33).

Figure 11. An arteriole from the same patient as shown in Figure 10 stains positively for fibrin. TTP-like syndrome in a patient with WHO Class IV lupus nephritis. Phosphotungstic acid hematoxylin, x320.

Figure 12. Mucoid edema of the intima of an interlobular artery (TTP-like syndrome in SLE). Phosphotungstic acid hematoxylin, x320.

Figure 13. Necrotizing arteritis of the PAN type affecting an interlobular artery in a patient with diffuse proliferative lupus nephritis. There is concentric inflammation of the vessel wall. The endothelium is focally denuded with fibrinoid necrosis of the intima. Hematoxylin and eosin, x100.
mural immune deposits have not yet been found in these lesions and that they may occur in association with the benign mesangial pattern of lupus nephritis makes a role for immune complex deposition unlikely (20). To date, not enough of these cases have been studied to determine whether circulating antineutrophil cytoplasmic antibodies may play a role (36). Some of these cases are associated with systemic vasculitis, whereas others appear to be limited to the kidney (personal observation).

EPIDEMIOLOGIC CLINICAL FEATURES, AND PROGNOSIS

There are little data regarding the incidence of vascular lesions in lupus patients, their clinical correlates, and their potential reversibility with specific therapy. Major reviews on vasculitis and on renal pathology in SLE make little reference to this issue (37,38). An analysis of the literature on this subject is also made difficult by the failure of many authors to distinguish between the various types of vascular lesions outlined above.

Tsumagari et al. described “vasculitic” lesions in 16 of 100 autopsied SLE patients and other renal vascular lesions in 17 of 80 patients (25). In one series of 88 biopsied SLE patients, Baldwin et al. described 9 patients with necrotizing fibrinoid vasculopathy (26). Recently, a cooperative study of vascular lesions in 285 lupus nephritis patients from 20 Italian centers found lupus vasculopathy in 27 patients (9.5%) and arteriosclerotic lesions in 20 (7.0%) (21). Another study found a much higher incidence of renal vascular lesions in autopsy material from SLE patients (7 of 20) compared with renal biopsies (10 of 200), a discrepancy probably related to sample size, severity and/or duration of SLE, and differences in treatment (17,19). The majority of SLE patients with renal vascular lesions have been young women, with only one study suggesting a higher frequency of such lesions in men (19).

The clinical features associated with renal lupus vasculopathy, defined as fibrinoid necrosis without true inflammation of the vessel wall, are described in a few series of SLE patients. Most authors agree that this lesion adversely affects outcome. In one series, acute severe glomerulonephritis associated with the onset of severe hypertension and a rapid progression to renal failure was present in eight of nine patients with lupus vasculopathy (26). Most of these patients had plasma creatinine values of less than 2 mg/dL when they developed a deterioration in their course. Six progressed to renal failure in fewer than 6 weeks, and the others did so in 4 to 14 months. All patients had hypertension and congestive heart failure, with severe retinopathy present in five of the nine. Thus, this type of renal vasculopathy was associated with abrupt deterioration in the clinical course and an ominous prognosis. In another series of five patients with a similar renal vasculopathy, serum creatinine values ranged from 0.8 to 1.7 mg/dL and proteinuria ranged from 0.8 to 10 g daily, exceeding 3 g in four patients (16). Hypertension was present in four of the five patients, but no blood pressure exceeded 180/110 mm Hg. The pattern of lupus nephritis was diffuse proliferative glomerulonephritis in four patients and mesangial proliferative glomerulonephritis in one patient. In the short period of follow-up, only one patient died with renal failure; this patient also had cardiac and pulmonary disease. In that series, the authors could not distinguish such patients clinically from patients without renal vascular lesions. In a review of 17 cases of “angiitis” involving arterioles and interlobular arteries in SLE patients (18), all patients had underlying diffuse proliferative lupus glomerulonephritis. Nephrotic-range proteinuria was recorded in 50% of these cases. All of the following were more common in patients with “angiitis” than in patients without these vascular lesions: hematuria, urinary casts, increases in the serum creatinine level, hypertension, active serology, and a progressive course to renal failure and/or death.

In a series of 100 autopsy cases, four of the seven patients with “necrotizing arteritis” had accelerated hypertension (diastolic blood pressure, >130 mm Hg) and two others were hypertensive; six of the seven developed renal failure, with four of these six having a rapid progression to uremia (25). Lesions described as “mucinous intimal thickening” were found in nine cases and were associated with hypertension in seven of these (accelerated hypertension in three). Nephrotic syndrome was present in only three of these patients, all of whom eventually developed renal failure. The third vascular lesion described by this group, “onion skinning” of the intima, was identified in two patients, one of whom had hypertension and one of whom developed renal failure. Grishman et al. noted acute “arteritis” much more commonly in their autopsy cases (7 of 20) than in their biopsy cases (10 of 200), suggesting that it carries a worse prognosis (17). In a subsequent study of the vascular lesions in lupus nephritis, Grishman and Venkatachelen noted arterial lesions in the autopsy specimens of 8 of 24 patients who died in the presteroid era and in 5 of 26 who died in the “modern” era (19). These lesions were again identified less frequently in renal biopsy specimens (19 of 276 patients). Most patients with vascular lesions had diffuse proliferative lupus glomerulonephritis, hypertension, and a progressive course to renal failure. Likewise, a recent Italian study found over half of their lupus vasculopathy patients to have diffuse proliferative lupus, and an elevated creatinine and hypertension were
more common in that group than in patients without renal vascular changes (21).

The presence of uncomplicated immune complex deposits in the walls of small renal arteries without inflammation or necrosis is quite common in lupus nephritis, especially in WHO Classes III and IV. These deposits are focally distributed, and although not well studied, they do not appear to affect significantly the clinical course and prognosis.

Among the renal vascular lesions occurring in SLE, true inflammatory vasculitis is the least common. A number of experienced nephrologists with extensive experience with lupus nephritis have only rarely seen inflammatory vasculitic lesions resembling PAN in SLE biopsies or autopsies (personal communication). This form of vasculitis was observed by Appel et al. in only 1 (1.8%) of 56, by Grishman et al. in only 1 (0.3%) of 326 (19,20), and by Banfi et al. in only 8 (2.8%) of 285 cases (21). In the Italian study (21), many of the patients also had marked elevation of their serum creatinines and two thirds had hypertension. In that study, patients with lupus vasculopathy or true vasculitis (5-yr renal survivals, 68 and 80%) had a less favorable renal survival than did lupus nephritis patients without vascular lesions (5-yr renal survival, 90%) (21). Thus, although some features vary from series to series, in general, SLE patients with renal vascular lesions are likely to have underlying proliferative glomerular lesions, hypertension, and renal insufficiency. Many have a progressive course to renal failure and a worse survival than do patients without vascular lesions.

**THERAPY**

Precise therapy for the renal "vasculopathic" lesions of SLE remains undefined. For some of the

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**TABLE 1. Renal Vascular Lesions in SLE**

<table>
<thead>
<tr>
<th>Morphologic Categories</th>
<th>Uncomplicated vascular immune deposits</th>
<th>Noninflammatory necrotizing vasculopathy</th>
<th>Thrombotic microangiopathy</th>
<th>True renal vasculitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Thrombotic Syndromes</td>
<td>TTP</td>
<td>Antiphospholipid antibody syndrome</td>
<td>RVT</td>
<td></td>
</tr>
</tbody>
</table>

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**TABLE 2. Pathology of renal vascular lesions in SLE**

<table>
<thead>
<tr>
<th>Vessels Involved</th>
<th>Deposits</th>
<th>Vessel Necrosis</th>
<th>Mural Inflammation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arteries</td>
<td>++</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Arterioles</td>
<td>+</td>
<td>++</td>
<td>0</td>
</tr>
<tr>
<td>Veins</td>
<td>+</td>
<td>++</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>IgG, IgM, IgA, C3, C1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

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**TABLE 3. Clinical features of renal vasculopathies in SLE**

<table>
<thead>
<tr>
<th>Frequency</th>
<th>WHO Class</th>
<th>Hypertension</th>
<th>Renal Insufficiency</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histopathologic Lesion</td>
<td>All, Mostly III, IV</td>
<td>0</td>
<td>0</td>
<td>Good</td>
</tr>
<tr>
<td>Uncomplicated vascular immune deposits</td>
<td>++/++</td>
<td>All</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Noninflammatory necrotizing vasculopathy</td>
<td>++</td>
<td>Mostly IV</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Thrombotic microangiopathy</td>
<td>++</td>
<td>All</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>True renal vasculitis</td>
<td>++/++</td>
<td>All</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Clinical Syndromes</td>
<td>All</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>TTP</td>
<td>++</td>
<td>All</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Antiphospholipid syndrome</td>
<td>++</td>
<td>All</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Renal vein thrombosis</td>
<td>++</td>
<td>V</td>
<td>0</td>
<td>+</td>
</tr>
</tbody>
</table>

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* See footnote to Table 2.
renal vascular lesions that carry a poor prognosis, aggressive methods of treatment appear to be justified. If immune deposition underlies their pathogenesis, then methods that will reduce the formation and deposition of immune complexes such as corticosteroids, cytotoxic drugs, and perhaps plasmapheresis may be rational. Likewise, control of blood pressure is reasonable, regardless of the magnitude of its contribution to the pathogenesis of the various renal lesions. In some patients, all of these measures have been tried but with limited evidence of benefit. Although antiplatelet or anticoagulant therapy may have a role in some patients with prominent microthrombosis, proof of their efficacy is also lacking. In addition, the potential risks of anticoagulation are increased in this hypertensive population. Indeed, it is unclear whether the noninflammatory necrotizing vasculopathy requires any treatment other than control of the hypertension and standard management for the immunologic disease process. Cases of true arteritis would be best treated as a renal vasculitis, and most clinicians would opt for cytotoxic therapy with or without corticosteroids (35).

Even in early studies, renal arterial necrotizing lesions were listed among the active lesions of lupus nephritis, i.e., those lesions that should be considered progressive unless adequately treated (39). Although some later studies included necrotizing angiitis in a renal histologic activity index (40), more recent formulations of histologic activity indices of lupus nephritis used for prognostic considerations have not included vascular lesions (41). Investigators now recognize that the presence in lupus nephritis of arteriopathies characterized by necrosis, thrombosis, and/or inflammation is often associated with the most severe forms of glomerulonephritis and a significantly worse prognosis. It should be noted that the involvement of the small renal arteries also confers a worse prognosis in other glomerular diseases such as IgA nephropathy and HUS (42-44).

THROMBOTIC SYNDROMES IN SLE

Three thrombotic vascular syndromes can be associated with SLE: a TTP-like syndrome, the antiphospholipid syndrome, and RVT. Because of their relative frequency and complex pathogenesis, these syndromes are discussed separately below.

TTP Syndrome

TTP is a syndrome characterized by the pentad of fever, thrombocytopenia, microangiopathic hemolytic anemia, fluctuating neurologic symptoms, and renal involvement (45). TTP shares many features with SLE, and the two diseases were commonly mistaken for each other before the advent of accurate diagnostic laboratory tests. Despite some overlap of symptoms between these two distinct entities, both diseases have been well documented to occur simultaneously in a small number of patients. The interrelationship of SLE, an immunologic disease, and TTP, a disease of coagulation, raises intriguing questions about their pathogenesis. Recent studies on SLE patients with antiphospholipid antibodies may help elucidate the basis of this interrelationship.

The true incidence of a TTP-like syndrome in SLE patients is unknown because of the varying criteria for the diagnosis of TTP and SLE in different centers in the past. Levine and Shearn found evidence of SLE in 23% of 151 cases of TTP (46). That study, however, was based solely on clinical features, a positive LE prep, and postmortem pathologic findings. In another study, 13 of 271 patients with TTP had clinical findings suggestive of SLE and 7 had positive LE preps (47). Other cases in the older literature have also failed to document adequately the coexistence of these two disease processes (46,48-51). Rothfield noted the association of TTP and SLE in only 2 of 433 patients with SLE (52). Thus, only a small number of SLE patients have experienced the full pentad of TTP-like symptoms (22,31,34). On the other hand, glomerular microthrombi resembling those of TTP were found in 35 of 103 SLE renal biopsies, occasionally in association with profound thrombocytopenia (53). Although those patients would hardly qualify as having true TTP, it is certainly possible that they have a kidney-limited form of the disease process. Likewise, some patients with lupus "vasculitis" share many renal histopathologic findings with TTP (16). Other workers have also noted a clinical picture resembling TTP or HUS in their SLE patients with vasculopathic lesions (17-19). A recent Italian collaborative study found 8% of lupus nephritis patients to have HUS/TTP-like lesions (21). Many if not most of the above studies lack data on the presence of anticardiolipin or other antiphospholipid antibodies (vide infra).

The clinical features of TTP are those of a multisystem disease due to the microthrombotic occlusion of small vessels in many organs (45). The diagnosis of SLE may precede, be concurrent with, or follow the diagnosis of TTP (22,29-31,48,49,54,55). SLE may be either clinically and serologically active or inactive at the onset of active TTP (22,29-31,54,55). In SLE patients, symptoms related to the TTP-like syndrome have included fever, malaise, petechial and purpuric skin lesions, abdominal pain and tenderness, jaundice, and gastrointestinal bleeding (29-31,55). Neurologic involvement has included headache, reduced consciousness, disorientation, combativeness, seizures, transient pareses, nerve palsies, and coma. Renal involvement by the TTP-like process has ranged from asymptomatic urinary find-
ings, to mild reduction in the GFR, to acute renal failure requiring dialysis (30,31,55). Hypertension has been mild or absent in the majority of cases (29,31,48,49,55). However, in one study of 24 cases of HUS/TTP-like syndrome in lupus nephritis, there was a marked elevation of the mean serum creatinine, proteinuria averaged 3 g daily, and over 90% of the patients were hypertensive (21). Most well-documented cases have had clear evidence of the microangiopathic process on examination of peripheral blood smears, and the thrombocytopenia is usually profound, often less than 20,000/mm³. Other coagulation studies have been normal (prothrombin time, partial thromboplastin time, fibrin degradation products), excluding a diagnosis of disseminated intravascular coagulation. Although some patients have been shown to have altered coagulation studies because of the presence of the lupus circulating anticoagulant (22), the lupus anticoagulant is absent in most patients (31).

Only a limited number of studies have described the histopathology of TTP-like lesions in patients with well-documented SLE. Oen et al. described the course of a 17-year-old girl with SLE and TTP whose renal biopsy showed glomerular changes of SLE but also marked congestion of the glomeruli and occlusion of some glomerular capillaries by fibrin thrombi (29). Cecere et al. described abundant microthrombi in the arterioles and capillaries of the kidneys, as well as in many other organs at autopsy (30). Magil et al. described a case with underlying diffuse proliferative lupus glomerulonephritis with arteriolar thromboses and intimal proliferative changes, narrowing the lumen of the interlobular arteries and arterioles (22). On EM, the glomeruli showed not only scattered subendothelial and mesangial deposits, but also widening of the subendothelial space by electron-lucent flocculent and fibrillar material. Gelfand et al. found one of their patients to have only mesangial sclerosis without proliferative or necrotizing glomerular features; however, the small arteries and arterioles showed fibromucoid thickening of the intima and recent thrombi extending into the glomerular capillaries (31). These thrombi stained positive for fibrin by both the phoshphotungstic acid hematoxylin and picro-Mallory (Lendrum) stains. The second patient described by those authors had a renal biopsy performed when the TTP was inactive. The biopsy showed no recent thrombi, but the small arteries and arterioles displayed severe fibromuscular thickening of the intima. Banfi et al. described intimal proliferative changes with mucoid edema and luminal narrowing in the interlobular arteries and arterioles, as well as arteriolar thrombosis, in their 24 patients. In 15 of these patients, glomeruli showed ischemic changes, and in 10, glomerular thrombi were observed (21).

Most of these changes are similar to those found in patients with TTP or HUS without SLE. The pathophysiology of idiopathic TTP remains unclear. Possible inciting etiologic factors have included infection, abnormal endothelial function, genetic predisposition, and autoimmune disease (45). Virtually all theories, however, suggest a key role for vascular endothelial damage and microthrombosis. The presence of abnormal platelet aggregating factors and the deficiency of factors that prevent coagulation have been documented in some patients with TTP (45,56,57). Defective processing of very large Factor VIII:vWF multimers after secretion by endothelial cells, lack of a prostacyclin releasing factor, and deficiency of an immunoglobulin that inactivates platelet aggregation have all been identified in at least some patients with TTP. The pathogenesis of TTP-like syndromes in the setting of SLE is no less obscure. Although an primary immunologic stimulus for the initiation of vascular endothelial damage is an attractive hypothesis, some patients have been serologically inactive at the onset of their TTP. Moreover, the rarity of this occurrence in the vast majority of patients with very active SLE makes the theory of a nonspecific immunologic stimulus less likely. Conceivably, the onset of microthrombosis in the glomerular capillaries (53) might trigger more widespread systemic thromboses. However, the low incidence of TTP relative to the frequent histologic detection of glomerular capillary microthrombi in patients with active SLE nephritis argues against this mechanism (53). The lupus circulating anticoagulant has been documented in rare cases of the TTP-like syndrome in SLE patients (22), but the majority of patients lack this abnormal immunoglobulin. Moreover, many patients with high-titer antiphospholipid antibodies (whether anticardiolipin or lupus anticoagulant) will have elevated activated partial thromboplastin times, which are normal in TTP. Because SLE patients with TTP appear to respond to the same therapeutic maneuvers as patients with idiopathic TTP (vide infra), it is likely that once the initiating mechanism has been triggered the subsequent events leading to microthromboses are similar in the two populations.

The 5-yr renal survival of lupus nephritis patients with HUS/TTP-like lesions has been shown to be less favorable than that of lupus nephritis patients without renal vascular changes (21,45). Until recently, therapy for idiopathic TTP has included treatment with steroids, antiplatelet agents, heparin, and splenectomy in some cases (45). These forms of treatment were often associated with a high mortality rate. Recently, the use of plasma exchange and plasma infusion therapy has been associated with markedly improved survival (58,59). It is unclear whether such improved survival is related to current therapeutic interventions or to better supportive care (45). In rare
patients with SLE and the TTP-like syndrome, the use of heparin and antiplatelet agents has been successful (55). Plasma infusion and/or exchange therapy have likewise resulted in dramatic benefits in anecdotal reports (29,31). Such treatment has resulted in the resolution of profound neurologic depression and the reversal of renal failure requiring dialysis (31). The exact nature, quantity, and frequency of the plasma product to be infused are not well defined, and controlled trials are lacking. Serologic SLE abnormalities should also be corrected with steroids and/or cytotoxic agents, whereas plasma infusion therapy is directed at the TTP-like lesions. The role of plasma exchange and plasmapheresis versus that of isolated plasma infusion is unsettled. It appears that the latter is equally effective if renal function is adequate to prevent volume overload.

Antiphospholipid Antibody Syndrome

Many patients with SLE produce autoantibodies against certain phospholipids. These autoantibodies may be detected by assays against the phospholipid cardiolipin (anticardiolipin antibodies), by interference with coagulation assays (the lupus anticoagulant, which interferes with the phospholipid component of the prothrombin activator complex), by biologic false-positive tests for syphilis (false-positive VDRL), or by other specific assays measuring antiphospholipid antibodies (ELISA) (60–64). In a review of data from 21 studies on the prevalence of the lupus anticoagulant in SLE patients, 34% of all 1,111 patients were found to have this antibody and 28% of over 500 unselected SLE patients in consecutive series had the antibody (63). In that review, 44% of 815 SLE patients had anticardiolipin antibodies as did 42% of almost 500 unselected patients in consecutive series. The name lupus anticoagulant is a misnomer, because most patients with antiphospholipid antibodies are predisposed to thrombotic events rather than to bleeding. These patients will have a high incidence of arterial and venous thromboses, spontaneous abortions, neurologic disorders, and thrombocytopenia (61–64). A high titer of IgG anticardiolipin antibody by ELISA has been correlated in some studies with a greater tendency to thrombotic events. However, neither the titer of antiphospholipid antibodies nor the frequency of thrombotic events correlate well with either SLE clinical or serologic activity (61,62). Although SLE patients with antiphospholipid antibodies may have thromboses of large renal vessels, microthrombi of glomerular capillaries have now been well documented in several series (22,53,65–67). The role of antiphospholipid antibody has been more difficult to establish in glomerular capillary thrombosis than in large-vessel thrombosis because glomerular lesions characterized by endothelial injury and necrosis are also common in active forms of lupus nephritis not associated with these antibodies (53).

In a review of over 100 biopsied SLE patients, Kant et al. found glomerular capillary thrombosis in 34 biopsies (53). Although only 7 patients had an identifiable lupus anticoagulant, 31 patients had active proliferative lupus nephritis (WHO Class III or IV). Subsequent studies by that group of investigators documented the presence of renal thromboses in 14 of 18 SLE patients with the circulating lupus anticoagulant (68,69). Recent studies of lupus patients have confirmed the association between intraglomerular thrombi and serum IgG antiphospholipid antibodies (70,71). In one series of 33 SLE patients with the lupus anticoagulant, 5 had histologic evidence of renal thrombotic microangiopathy (70). That study found no correlation between the presence of the microangiopathy and the class of lupus nephritis, hypertension, proteinuria, or renal function (70).

Some studies indicate a worse prognosis in SLE patients with the circulating lupus anticoagulant and renal biopsy documentation of thrombotic microangiopathy (70). However, in a recent study of 76 patients with lupus nephritis, although the presence of IgG antiphospholipid antibodies was associated with glomerular thromb, there was no correlation with renal histologic pattern or long-term renal function (71).

By contrast, some patients with antiphospholipid antibodies appear to have a severe form of thrombotic microangiopathy, which dominates their clinical presentation. Kincaid-Smith et al. described the renal biopsies of a group of 12 patients with the circulating lupus anticoagulant. Four of the 12 had evidence of SLE (67). The four patients were hypertensive (two with malignant levels of hypertension) and thrombocytopenic, and all had renal insufficiency. Renal biopsy revealed diffuse proliferative lupus nephritis in two patients and mild mesangial lesions in the other two. Regardless of the WHO Class of renal involvement, all had fibrin thromb in the glomeruli, arterioles, and intralobular arteries. On repeat histologic evaluation in two cases, the interlobular arteries showed fibrosis as well as cellular intimal proliferation. D'Agati et al. described two SLE patients as part of a series of three patients with antiphospholipid antibodies and glomerular thromboses (65). Although the clinical features were varied, including asymptomatic proteinuria, the nephrotic syndrome, renal insufficiency, and hypertension, no patient had active SLE. Biopsies again showed thrombi in the glomeruli, arterioles, and interlobular arteries, but no active endocapillary proliferative lupus nephritis (Figure 14). Others have shown similar thrombotic and ischemic changes in small series of patients with SLE (72).
The exact incidence of RVT in SLE patients is unknown. It has occurred in both males and females of all ages. Its predominance in young women reflects the higher prevalence of SLE in this population. Certain SLE patients with the nephrotic syndrome, prior episodes of thrombophlebitis, and antiphospholipid antibodies have a higher incidence of RVT. The association of RVT, the nephrotic syndrome, and SLE was first emphasized in 1976 (74). As in other renal diseases, RVT in SLE appears to be a complication rather than a cause of the nephrotic syndrome. Gil sans et al. prospectively studied 48 nephrotic patients for the development of RVT (88). Although 11 nonnephrotic patients with either idiopathic membranous or membranoproliferative glomerulonephritis were documented to have RVT, none of the 5 nephrotic lupus patients had RVT. The renal biopsy findings in these patients were not described. In a retrospective review of 280 patients with either idiopathic membranous nephropathy or lupus nephritis who had undergone renal biopsy, 11 were found to have RVT, including 3 patients with SLE (77). In that retrospective study, the exact number of SLE patients studied and the number of SLE patients in which venography-angiography was performed are not indicated. In a recent prospective study, 27% of nephrotic SLE patients had RVT in contrast to none of the non-nephrotic SLE control population (80). Unfortunately, many of these studies fail to indicate the histologic pattern of lupus nephritis. Most biopsied nephrotic lupus patients with documented RVT have had a membranous pattern of lupus nephritis (WHO Class V). The incidence of RVT in nephrotic SLE patients with proliferative patterns of lupus nephritis is much lower (74).

Other factors often associated with RVT in SLE patients include a prior history of thrombophlebitis and the presence of antiphospholipid antibodies or the lupus circulating anticoagulant. In a prospective study, 8 of 13 SLE patients with a history of prior thrombophlebitis had RVT, whereas none of 20 SLE patients without previous thromboses had RVT (80). Although there was no higher incidence of the circulating lupus anticoagulant in this population, other studies have noted an association between this abnormal immunoglobulin and venous thrombotic events (60). However, most studies that report high incidences of thrombotic episodes in SLE patients do not indicate a correspondingly high incidence of clinically evident RVT (2,89). In a recent study of 35 patients with a circulating anticoagulant, 8 of whom had clinically significant thrombotic episodes, no patient experienced RVT (89). Thus, thrombophlebitis
and circulating anticoagulant are much less important than the nephrotic syndrome as predisposing factors to RVT in SLE.

The clinical presentation of RVT in SLE patients does not differ from that of RVT in nephrotic patients without SLE. Most patients have the onset of the nephrotic syndrome with heavy proteinuria and hypoalbuminemia before the onset of RVT. Systemic disease activity has been variable, but because most have membranous lupus glomerulopathy, serologic tests are often less active (74). Indeed, some patients with the nephrotic syndrome and apparently "idiopathic" membranous nephropathy, with or without associated RVT, years later developed signs and symptoms of active SLE (75,77). In such patients, renal biopsy findings of (1) mesangial, subendothelial, or tubulointerstitial electron-dense deposits, associated with the dominant epimembranous glomerular deposits and (2) endothelial tubuloreticular inclusions and/or (3) IF findings of glomerular deposits of IgA and C1q (as well as IgG and C3) may have predictive value in identifying those individuals with membranous glomerulopathy who will later develop SLE (90).

The clinical presentation of acute RVT may include flank pain, costovertebral angle tenderness, and gross hematuria (74,75,78,80). However, when RVT is more indolent, the patient may be asymptomatic without urinary sediment changes or increased proteinuria to suggest the diagnosis of RVT (74). In SLE patients, the first manifestations of RVT or inferior vena cava thrombosis may be the symptoms of shortness of breath, dyspnea, and tachypnea associated with pulmonary emboli (74,78). These symptoms are easily mistaken for lupus pleuritis or infectious pneumonia. Oliguria has rarely been noted in the SLE patients with RVT, and usually, there is no significant reduction in the GFR (74). Unilateral renal enlargement, ureteral notching due to engorged collaterals, and pyelocalyceal abnormalities have been observed on the iv urogram in some patients (74,75,77). Other patients have had entirely normal iv urograms despite documented RVT on venography (74,77). In most cases, renal venography has firmly established the diagnosis by demonstrating a filling defect in the renal vein, often extending into the inferior vena cava. Moreover, the usual washout or "streamer" effect of unopacified blood from the renal vein is not seen in patients with RVT (73,74). The use of Doppler ultrasonography and magnetic nuclear resonance imaging in the diagnosis of RVT appears promising, but the incidence of both false-negative and false-positive results remains to be defined. Chronic RVT may be associated with extensive venous collateral circulation, especially on the left side (because of the origin of the left gonadal and adrenal veins from the left renal vein) (81). In complete right RVT, the development of an extensive collateral circulation is usually not found and renal infarction may occur (75,78).

The renal histopathology in SLE patients with RVT reflects both the nature of the underlying histologic pattern of SLE and the chronicity of the RVT. Many SLE patients with the nephrotic syndrome and RVT have not had a renal biopsy at the time of diagnosis of the RVT (79,80,84). The vast majority of those biopsied have the membranous pattern of lupus nephropathy (WHO Class V) (74,75,77,78,82). Although occasional patients have been observed with mesangial or proliferative lesions (WHO Class II, III, or IV) (25,60,81), some of these lacked IF and EM studies necessary to exclude a membranous component (25,60,73,85). In patients with relatively acute RVT, interstitial edema, tubular degeneration, and margination of polymorphonuclear leukocytes in the glomerular and interstitial capillaries have been noted (74). Rarely, thrombi are observed in the glomerular capillaries and in the small, intrarenal venous radicals (75) (Figure 15). No inflammatory changes are present in and around the wall of the thromboosed renal veins. With more chronic RVT, findings include interstitial fibrosis and tubular atrophy out of proportion to the glomerular changes (73,74,81,85). These findings in a patient with membranous glomerulopathy, with or without evidence of SLE, should prompt a search for associated RVT.

The pathogenesis of RVT in SLE is not completely understood. SLE itself is associated with an increased incidence of venous thromboses and thrombophlebitis. In one series of 114 patients fulfilling the American Rheumatism Association criteria for SLE, over 12% had episodes of thrombophlebitis (84). Other series have reported a 5 to 15% incidence of venous thrombosis in SLE (1,82). The cause of these thrombotic events is unclear, but hypotheses have included "slow intravascular coagulation," possibly related to the hypercoagulable state of the nephrotic syndrome, small vessel vasculitis, or venulitis (an hypothesis not well supported by histologic findings), and the presence of antiphospholipid antibodies and other circulating factors promoting coagulation. The lupus "anticoagulant" paradoxically promotes thrombosis rather than causing a bleeding tendency (vide supra), and thromboembolism in patients with antiphospholipid antibodies is well documented (60,89,91).

Clearly, the general occurrence of extrarenal venous thromboses in SLE cannot account for the high frequency of RVT in SLE patients with the nephrotic syndrome. RVT is clearly a consequence rather than a cause of the nephrotic syndrome in the vast majority of cases. The nephrotic syndrome itself is associated with a hypercoagulable state. Factors favoring coagulation in nephrotic patients include increased
levels of Factors V and VIII, fibrinogen, and β-thromboglobulin; reduced levels of the inhibitor of coagulation antithrombin III; defects in the fibrinolytic system; thrombocytosis and increased platelet aggregation (92). Some inhibitory factors such as antithrombin III are lost in the urine in the nephrotic state. Thus, the postglomerular circulation and the renal veins would be expected to have particularly low levels of this protein relative to the systemic venous blood, thereby predisposing to coagulation at this site. The chronic nonselective proteinuria in those glomerular diseases most frequently associated with RVT (idiopathic membranous and idiopathic membranoproliferative glomerulonephritis) would favor such a process.

The course of patients with SLE, the nephrotic syndrome, and RVT has been similar to that of patients with idiopathic membranous nephropathy and RVT. Some patients have had life-threatening pulmonary emboli (74); others have remained asymptomatic. In general, those with total occlusion of the right renal vein have suffered a reduction in GFR and, rarely, renal infarction. Those with partial occlusion, especially of the left renal vein, often have had no decrease in renal function.

Thrombectomy in a limited number of patients has given equivocal results at best (75). Anticoagulation with heparin followed by long-term oral anticoagulation with coumadin for 4 to 6 months has been rewarding (74,86). Adequate anticoagulation has led to recanalization of the renal vein and reduced pulmonary embolic complications (74). Other patients have been treated successfully with streptokinase as well as heparin (60). Some investigators advocate that patients with recurrent RVT and those with persistent severe hypoalbuminemia due to their nephrotic syndrome should be maintained on long-term or permanent anticoagulation therapy.

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REFERENCES

42. Levy M, Gagnadoux MF, Habib R. Pathology of
Renal Vascular Complications of SLE


