Implications for pathogenesis of patterns of injury in small- and medium-sized-vessel vasculitis

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Systemic vasculitis can be categorized as large-vessel vasculitis, medium-sized-vessel vasculitis, and small-vessel vasculitis based on the predominant vascular distribution of vasculitic lesions **(Figure 1)**.[1] Large-vessel vasculitis is chronic granulomatous arteritis that affects predominantly the aorta, major arteries to the extremities and head, and major visceral arteries. Medium-sized vessel vasculitis is necrotizing arteritis that affects predominantly major visceral arteries. Small-vessel vasculitis is necrotizing polyangiitis that has a predilection for capillaries and venules, but also may affect arterioles, arteries, and even veins.

The chronic granulomatous inflammation of large-vessel vasculitis is pathologically very different from the necrotizing inflammation that is the hallmark of the acute phase of medium-sized-vessel vasculitis and small-vessel vasculitis.[2] This implies that the pathogenesis of large-vessel vasculitis is quite different from the pathogenesis of medium-sized-vessel vasculitis and small-vessel vasculitis. Although medium-sized-vessel vasculitis and small-vessel vasculitis share some pathologic features, for example necrotizing arteritis, there are a number of overt or subtle pathologic features that indicate the engagement of different pathogenic mechanisms in specific categories of vasculitis within these larger groups. In order to shed light on their pathogenesis, this review will compare and contrast the pathologic features of different categories of necrotizing vasculitis.

POLYARTERITIS NODOSA VERSUS KAWASAKI DISEASE

Polyarteritis nodosa and Kawasaki disease are the two major categories of medium-sized-vessel vasculitis.[1,2] In the past, there was confusion about the relationship between polyarteritis nodosa and Kawasaki disease; in fact, the latter was once called infantile polyarteritis nodosa. However, by the late 1970s, polyarteritis nodosa and Kawasaki disease were recognized as separate forms of vasculitis, not only because of different clinical and epidemiologic features but also because of different pathologic features.[3,4] Both categories of vasculitis have acute necrotizing arteritis with inflammatory aneurysm formation; however, Kawasaki disease is clearly distinguished from polyarteritis nodosa by the presence of the mucocutaneous lymph node syndrome in the former but not the latter.[1]

Polyarteritis nodosa was first described by Kussmaul and Maier in 1866.[5] This category was initially used as a waste basket for all types of necrotizing arteritis, and thus would have been the diagnosis often used for patients with Kawasaki disease and necrotizing arteritis with aneurysms prior to Kawasaki's landmark publication in 1967.[6] Many other distinct forms of vasculitis that have a component of necrotizing arteritis also once were included in the polyarteritis nodosa category but now are recognized as pathologically and pathogenically distinct vasculitides. For example, as will be discussed in more detail later, microscopic polyangiitis, Wegener's granulomatosis, and Churg-Strauss syndrome were initially considered to be variants of polyarteritis nodosa but now are recognized as distinct from polyarteritis nodosa.[7]

Hints about pathogenesis of polyarteritis nodosa are more likely to be found in the acute rather than the chronic vascular lesions. Both polyarteritis nodosa and Kawasaki disease arteritis, as well as other forms of necrotizing arteritis, all enter a final common pathway of chronic inflammation and scarring. The transformation of the active acute inflammatory lesions to sclerotic lesions with a predominance of infiltrating T-lymphocytes and macrophages can occur as quickly as one or two weeks after the initiation of injury. Thus, very early lesions must be examined to identify evidence for primary pathogenic events.

Polyarteritis nodosa begins as a segmental necrotizing inflammation of arteries with conspicuous infiltration of neutrophils and monocytes, often with leukocytoclasia, and sometimes with superimposed thrombosis.[2,8,9] This

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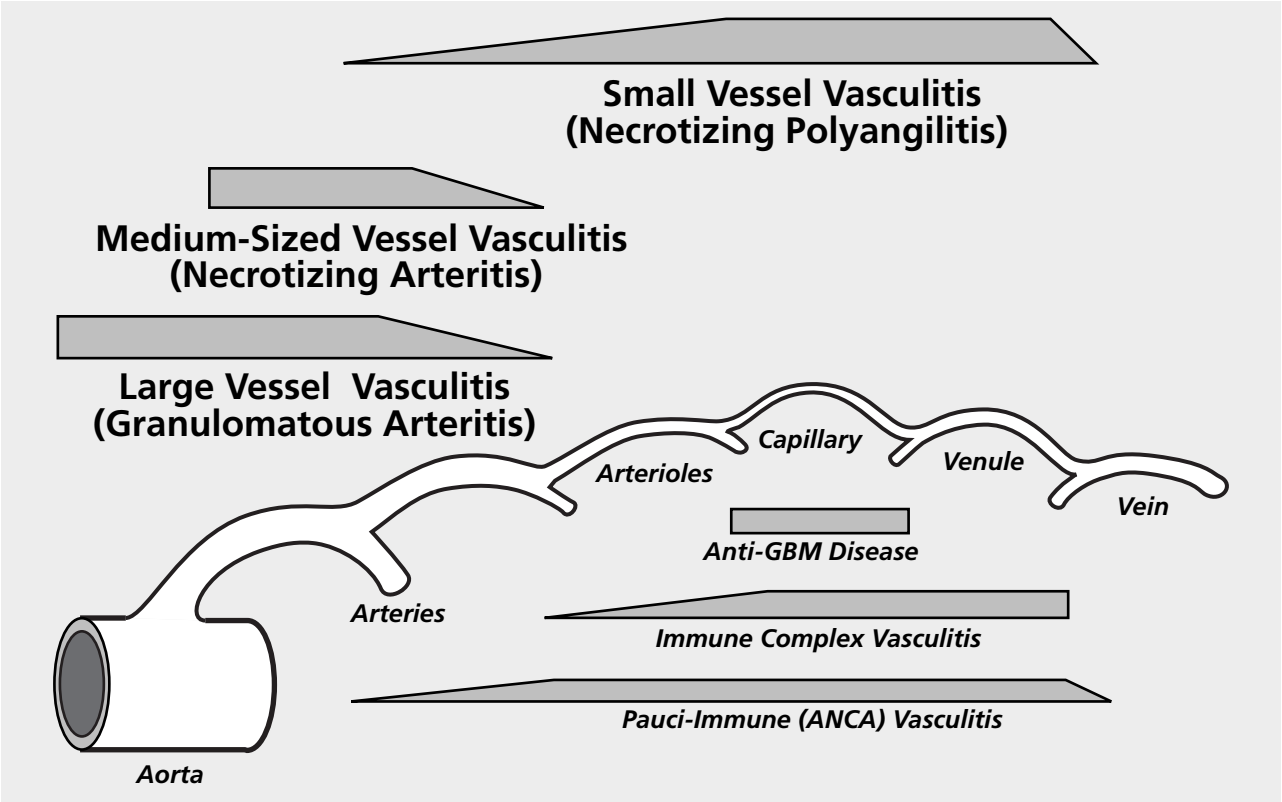

Figure 1. Diagram depicting the predominant vascular distribution of different categories of vasculitis. Note that large-vessel vasculitis, medium-sized-vessel vasculitis and small-vessel vasculitis can all affect arteries; however, only small-vessel vasculitis affects capillaries and venules. Anti-GBM disease, immune complex vasculitis and pauci-immune vasculitis all are types of small-vessel vasculitis, but they have different distributions of vessel involvement because of differences in their pathogenesis.

may progress to extensive circumferential, transmural fibrinoid necrosis **(Figure 2)**. Fibrinoid necrosis is a nonspecific pattern of acute necrotizing injury that is shared by all forms of necrotizing vasculitis.[10] Fibrinoid necrosis is characterized by the accumulation of plasma proteins, including coagulation factors that are converted to fibrin, at sites of tissue destruction. Over time, tissue matrix proteins infiltrate the fibrinous material, and it eventually is completely replaced by collagenous scar. If the necrotizing inflammation causes extensive destruction of the vessel wall and perivascular tissue, inflammatory aneurysms (pseudoaneurysms) will develop.

The histologic features of early lesions of polyarteritis nodosa suggest that focal activation of neutrophils and monocytes at the interface of blood and artery is an early pathogenic event and that leukocyte activation results in transmural infiltration of the artery wall and necrotizing injury. Once the injury enters the wall it may dissect longitudinally along the media or adventitia; thus, at some planes of section it may appear to be arising in the media or adventitia rather than adjacent to the lumen.

Kawasaki disease is characterized by the presence of the mucocutaneous lymph node syndrome, which was first described by Kawasaki in 1967.[6] The pathology of Kawasaki disease vasculitis was thoroughly described by the late 1970s.[11-14] The classic gross lesion is the inflammatory arterial aneurysm, often complicated by thrombosis. Although the coronary arteries are the most frequently involved vessels, arteries throughout the body may be involved, such as the iliac and femoral arteries, the renal arteries, arteries to the gut, and even veins. The inflammatory aneurysms are not optimum for studying the etiology and pathogenesis of Kawasaki disease because they occur relatively late in the evolution of acute injury. The earliest lesion, or at least one of the earliest lesions, is the focal accumulation of leukocytes beneath endothelial cells in arteries. These are predominantly monocytes and macrophages with some admixed neutrophils and T lymphocytes.[15,16] As the lesion progresses, there is transmural infiltration by mononuclear leukocytes and progressive edema and smooth muscle cell degeneration in the media **(Figure 3)**. Ultimately, the infiltrates extend completely through the media and into the adventitia. In the adventitia, as with polyarteritis nodosa, the infiltrates sometimes extend longitudinally along vessels. Thus, in some cross sections, the infiltrates appear to be adventitial (perivascular) rather than transmural. The infiltrating cells are predominantly macrophages with admixed T lymphocytes, predominantly CD8 T lymphocytes.[16] Although CD 20–positive B cells are infrequent, IgA-producing plasma cells may be present.[17] As the lesions progress there is more and more destruction of the media, infiltration by leukocytes, and eventually aneurysm formation if the injury is severe enough.

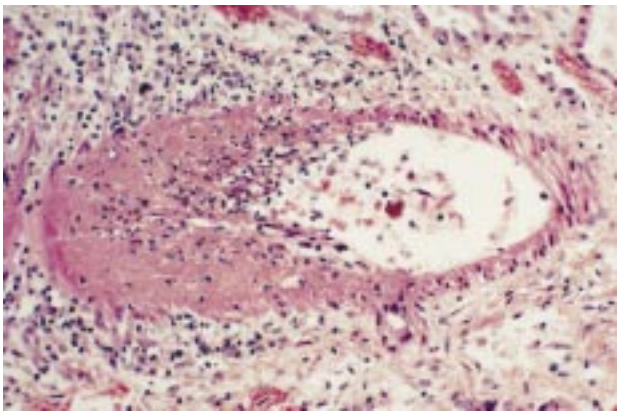

Figure 2. This necrotizing arteritis is consistent with a number of different categories of vasculitis, including polyarteritis nodosa, microscopic polyangiitis, and Wegener's granulomatosis. The wall of the artery on the right is relatively uninvolved, but the wall to the left has been completely replaced by fibrinoid material that contains focal accumulations of neutrophils and monocytes in varying stages of necrosis and apoptosis.

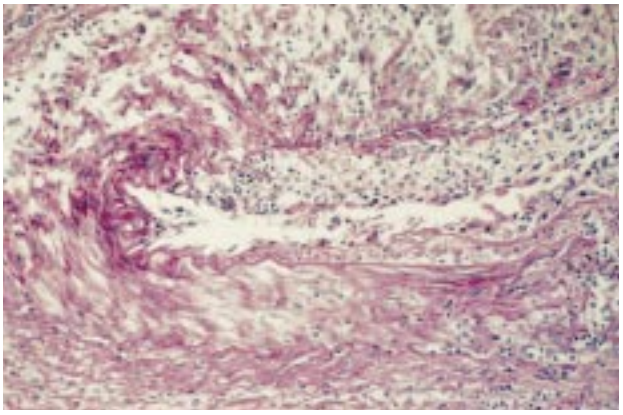

Figure 3. This necrotizing arteritis is from a patient with Kawasaki disease. The intima and muscularis of the upper half of the artery have marked edema with extensive infiltration by mononuclear cells. Note that there are no neutrophils and no fibrinoid necrosis. The different appearance of this arteritis compared to the arteritis in Figure 2 suggests a different pathogenesis.

Thus, the vasculitis of Kawasaki disease shares some pathologic attributes with polyarteritis nodosa; however, it has a number of distinctive characteristics that clearly set it apart, including the association with mucocutaneous lymph node syndrome, a strong predilection for the coronary arteries, and a pattern of inflammation characterized by marked edema and macrophage infiltration and little or no fibrinoid necrosis. This distinctive histology indicates that the pathogenesis of Kawasaki disease arteritis is different from that of polyarteritis nodosa. The numerous macrophages and T lymphocytes and the scarcity of neutrophils suggests that activation of T lymphocytes and monocytes plays a pivotal role in the pathogenesis of Kawasaki disease arteritis. This is supported further by the finding of high levels of monocyte chemoattractant proteins at sites of vasculitis and in the circulation of patients with Kawasaki disease[18] as well as by the presence of activated monocytes in the tissue and circulation.[19]

■ MEDIUM-SIZED-VESSEL VASCULITIS VERSUS SMALL-VESSEL VASCULITIS

As shown in **Figure 1**, a major distinction between medium-sized-vessel vasculitis and small-vessel vasculitis is the predilection of the latter for vessels other than arteries—especially capillaries and venules.[1,7] The arteritis of polyarteritis nodosa is not distinguishable from the arteritis of small-vessel vasculitis by histology alone. In the acute phase, both have fibrinoid necrosis with neutrophil and monocyte infiltration and leukocytoclasia. Polyarteritis nodosa tends to have less leukocyte infiltration and less leukocytoclasia, but this is not consistent enough to be a distinguishing feature. As described earlier, the necrotizing arteritis of Kawasaki disease not only is histologically different from polyarteritis nodosa but also from the necrotizing arteritis of small-vessel vasculitis.

The pathologic feature that most suggests different pathogenic mechanisms in medium-sized-vessel vasculitis versus small-vessel vasculitis is the difference in vascular distribution. Why does medium-sized-vessel vasculitis only affect arteries, and why does small-vessel vasculitis have a preference for capillaries and venules? The answers are unknown; thus any discussion is of necessity speculative. One reasonable conclusion is that the pathogenic events that cause medium-sized vessel vasculitis are operational only in arteries, whereas the pathogenic events that cause small-vessel vasculitis are most effective in very small vessels but occasionally can be accomplished in arteries. Structural or functional differences between small and large vessels, or both, could cause the differences in vascular distribution. Two of many possibilities is that high shear stress is required for the pathogenesis of medium-sized-vessel vasculitis, whereas close physical contact between vessel walls and leukocytes is required for small-vessel vasculitis.

Both polyarteritis nodosa and Kawasaki disease arteritis occur preferentially at arterial branch points.[9,14] For example, Kawasaki disease arteritis in a kidney may involve almost every junction between lobar arteries and arcuate arteries in the absence of any arteritis elsewhere in the kidney.[14] Branch points in arteries are sites of increased sheer stress. Increased sheer stress induces upregulation of endothelial inflammatory factors, such as adhesion molecules (eg, ICAM-1) and proinflammatory transcription factors (eg, NFκB).[20-23] There also are increased numbers of resident macrophages in the intima at sites of sheer stress.[24,25] This is true even in apparently normal arteries. For example, the coronary arteries of over 90% of children under 5 years old have increased numbers of macrophages in the intima of coronary arteries at points of bifurcation.[25] Thus, medium-sized vessel vasculitis may affect only arteries because sheer stress is required to initiate the pathogenic events, for example by producing susceptible foci of activated endothelial cells with underlying macrophages at bifurcation points in arteries. However, there is no proof for this speculation.

TABLE 1
MAJOR CATEGORIES OF VASCULITIS

- Large-vessel vasculitis (chronic granulomatous arteritis)
  - Giant-cell arteritis
  - Takayasu arteritis
- Medium-sized-vessel vasculitis (necrotizing arteritis)
  - Polyarteritis nodosa
  - Kawasaki disease
- Small-vessel vasculitis (necrotizing polyangiitis)
  - Pauci-immune small-vessel vasculitis (ANCA vasculitis)
    - Microscopic polyangiitis
    - Wegener's granulomatosis
    - Churg-Strauss syndrome
    - Drug-induced ANCA vasculitis
  - Immune complex small-vessel vasculitis
    - Henoch-Schönlein purpura
    - Cryoglobulinemic vasculitis
    - Rheumatoid vasculitis
    - Lupus vasculitis
    - Serum sickness vasculitis
    - Infection-induced immune complex vasculitis
    - Drug-induced immune complex vasculitis
    - Hypocomplementemic urticarial vasculitis
    - Behçet's disease
    - Goodpasture's syndrome
  - Paraneoplastic small-vessel vasculitis
  - Inflammatory bowel disease vasculitis
  - Others

Small-vessel vasculitis occurs preferentially in small vessels, especially vessels involved in substantial trafficking of fluid and cells between blood and tissue (eg, dermal venules), blood and urine (glomerular capillaries), or blood and air (pulmonary capillaries). Leukocytes are in close contact with endothelial cells in these small vessels, and the endothelium of these vessels is particularly responsive to proinflammatory signals. Stimulated neutrophils and monocytes are better able to adhere to endothelium in small vessels compared to large vessels once there has been upregulation of leukocyte and endothelial adhesion molecules.[26,27] Adherence is particularly likely if a leukocyte engages adhesion molecules on opposite sides of a vessel, which can only occur in very small vessels.[26] Even within a given microvascular bed, local hemodynamic factors result in some vessels that allow adherence of leukocytes and others that do not.[27] Because leukocyte adherence is probably a prerequisite for vasculitis, this could explain the focal nature of small-vessel vasculitis that is seen pathologically.

IMMUNE COMPLEX SMALL-VESSEL VASCULITIS VERSUS PAUCI-IMMUNE SMALL-VESSEL VASCULITIS

Within the category of small-vessel vasculitis, there are pathologic differences that correlate with different pathogenic events. With respect to vascular distribution, immune complex vasculitis has a more restricted distribution than pauci-immune vasculitis **(Figure 1)**. Pauci-immune vasculitis has a paucity or absence of vessel wall staining for immunoglobulin, and often is associated with anti–neutrophil cytoplasmic autoantibodies (ANCA) in the circulation.[28] Anti–glomerular basement membrane (anti-GBM) disease is a special form of in situ immune complex disease that causes necrotizing vascular injury virtually restricted to glomerular or pulmonary capillaries, or both.

Immune complex vasculitis can be categorized on the basis of clinical and pathologic characteristics into many distinct categories **(Table 1)**. Most immune complex disease has a predilection for glomerular capillaries, dermal venules, and other small vessels, for example arterioles in the intestinal wall. This is the basis for the frequent clinical features of nephritis, purpura, and abdominal pain with many types of immune complex small-vessel vasculitis, for example Henoch-Schönlein purpura, cryoglobulinemic vasculitis, and serum sickness vasculitis.[7] Pauci-immune small-vessel vasculitis, which usually is ANCA small-vessel vasculitis, also has a predilection for capillaries and venules. However, much more often than immune complex vasculitis, it also affects arterioles, arteries, and even veins.[7]

The venulitis and arteritis caused by immune-complex–mediated and pauci-immune small-vessel vasculitis are relatively similar pathologically, although immune complex vasculitis may have identifiable aggregates of immune complexes by light microscopy, especially cryoglobulinemic vasculitis. By immunohistology, immune complex vasculitis has identifiable vessel wall immunoglobulin and complement deposits, whereas, by definition, pauci-immune vasculitis has little or no vessel wall staining for immunoglobulin.[7] The most striking differences in the pathology of immune complex vasculitis versus anti-GBM and ANCA-vasculitis are in the glomerular lesions.[2]

ANCA-vasculitis and anti-GBM disease frequently cause rapidly progressive glomerulonephritis. ANCA-glomerulonephritis and anti-GBM glomerulonephritis are histologically indistinguishable from each other and are characterized in the acute phase by focal segmental lysis of glomerular tufts with disruption of basement membranes and matrix and accumulation of fibrinoid material. Variable numbers of neutrophils and monocytes, often undergoing leukocytoclasia, are seen at the sites of necrosis. As the lesion progresses, over 90% of patients develop crescents in Bowman's spaces as a result of spillage of inflammatory mediators across the ruptured glomerular capillaries, accumulation of macrophages, and proliferation of epithelial cell. Non-necrotic glomerular segments often are remarkably normal histologically. This is in contrast to the immune complex glomerulonephritis that is a component of immune complex vasculitis, such as Henoch-Schönlein purpura or cryoglobulinemic vasculitis. Most immune complex glomerulonephritis has no necrosis or crescent formation, and when crescents are present, they usually affect less than 50% of glomeruli. The localization of immune complexes typically causes glomerular hypercellularity resulting in mesangioproliferative, proliferative, or membranoproliferative glomerulonephritis. Of course, these distinctive differences are most apparent in early lesions. Ultimately, as glomerular inflammatory in-

jury of any type progresses toward resolution or sclerosis, the predominant inflammatory cells are macrophages and T lymphocytes, as is true of any type of chronic inflammation. This can occur relatively quickly. For example, in animal models of necrotizing glomerulonephritis, acute necrotizing lesions with fibrinoid necrosis can transform into sclerotic lesions with no fibrinoid material in less than two weeks.

Immune complexes are thought to mediate vasculitis by activating leukocytes and endogenous glomerular cells to cause inflammatory injury and cell proliferation. Anti-GBM antibodies complexed with collagen in the walls of glomerular and pulmonary capillaries could activate neutrophils and monocytes as the leukocyte surface projections come in contact with these complexes through the fenestrations that are present in glomerular and pulmonary endothelial cells, possibly by Fc receptor or complement receptor engagement. ANCA may first activate neutrophils and monocytes in the circulation by interacting with proteinase-3 or myeloperoxidase on the surface or in the microenvironment around the cells.[29] This could be through Fc receptor engagement or through direct binding to the targets on the cell surface. Activation of leukocytes in the circulation would first cause injury to endothelial cells. This is supported by pathologic findings by electron microscopy indicating that the earliest vascular lesion of pauci-immune small-vessel vasculitis is endothelial injury with subendothelial accumulation of fibrin[30,31] and intravascular lysis of leukocytes.[30]

Something about the pathogenesis of immune complex localization in glomeruli causes predominantly endocapillary cell proliferation and influx of leukocytes without extensive necrosis, whereas something about the pathogenesis of anti-GBM and ANCA disease causes severe necrotizing injury to glomerular capillaries and other small vessels with marked lysis of collagenous matrix material. The basis for this is unknown. However, the remarkable degree of local cell death and lysis of matrix material suggests that major amounts of cytotoxic and proteolytic enzymes are released or activated in a very confined space. One likely mechanism would involve release of oxygen metabolites and enzymes from activated neutrophils and monocytes that were able to act locally but were effectively neutralized beyond the site of injury. The oxidants, in addition to being cytotoxic, would provide a local shield against anti-proteinases and also would activate matrix metalloproteinases. Serine proteinases would neutralize tissue inhibitors of metalloproteinases.[32] Serine proteinases (eg, elastase and proteinase 3) and metalloproteinases (eg, collagenase and gelatinase) would then be able to cause unfettered lysis of vessel wall matrix at the site of leukocyte activation, but the mediators of this injury would be neutralized by antioxidants and antiproteinases away from the site.[32]

In summary, in anti-GBM and ANCA vasculitis, the pathologic finding of focal, very lytic necrotizing injury suggests very effective local activation of neutrophils and monocytes with release of oxidants and proteases that are neutralized beyond the site of injury. The predilection for small vessels suggests that some element of the pathogenesis, most likely adhesions between leukocytes and endothelial cells, is dependent on close proximity of leukocytes to endothelial cells.

ANCA-vasculitis is accompanied by necrotizing granulomatous inflammation in patients with Wegener's granulomatosis and Churg-Strauss syndrome.[1,7] This inflammation does not look like the inflammation that results primarily from T-lymphocyte induced granulomatous inflammation. In the acute phase, there is no dense accumulation of lymphocytes and macrophages, but rather there is a very lytic process with zones of necrosis containing numerous neutrophils and monocytes undergoing apoptosis and necrosis. A few multinucleated giant cells are scattered within the inflamed tissue. This ANCA-associated necrotizing granulomatous inflammation could be caused by ANCA-induced activation of neutrophils and monocytes within extravascular interstitial tissue via mechanisms similar to those that cause activation in vessels. This would not occur with anti-GBM disease or immune complex disease, because the pathogenic complexes between antibodies and antigens are located exclusively or predominantly in vessel walls rather than in the interstitium. In patients with circulating ANCA, these autoantibodies would be in the interstitial fluid as well as the blood. If ANCA can activate neutrophils and monocytes in blood vessels, they should be able to activate them in interstitial tissue. Activation in the vessels would cause necrotizing vasculitis. Activation in the tissue would cause necrotizing tissue inflammation. The pathologic appearance of acute extravascular tissue injury in Wegener's granulomatosis and Churg-Strauss syndrome are consistent with extensive activation of neutrophils and monocytes in extravascular tissue.

■ SUMMARY

The different pathologic features of different types of necrotizing vasculitis indicate that there are different pathogenic mechanisms causing the injury. The pathogenic mechanisms for medium-sized-vessel vasculitis are most effective at causing injury in arteries and are not effective at causing injury in smaller vessels. The predilection of medium-sized-vessel vasculitis for bifurcations may relate to the increased expression of adhesion molecules and increased numbers of intimal macrophages at these sites. The preferential involvement of small vessels by small-vessel vasculitis may relate to the requirement for close apposition between leukocytes and endothelial cells for the pathogenic mechanisms to be operational. The pathology of the necrotizing vasculitis of Kawasaki disease is most consistent with a primary role for monocytes/macrophages and T lymphocytes in the acute injury. The pathology of the necrotizing vasculitis of polyarteritis nodosa and small-vessel vasculitis, including ANCA-vasculitis, is most consistent with a primary role for neutrophils and monocytes in the acute injury.

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