Cutaneous Vasculitis Update: Diagnostic Criteria, Classification, Epidemiology, Etiology, Pathogenesis, Evaluation and Prognosis

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Abstract: Vasculitis, inflammation of the vessel wall, can result in mural destruction with hemorrhage, aneurysm formation, and infarction, or intimal-medial hyperplasia and subsequent stenosis leading to tissue ischemia. The skin, in part due to its large vascular bed, exposure to cold temperatures, and frequent presence of stasis, is involved in many distinct as well as un-named vasculitic syndromes that vary from localized and self-limited to generalized and life-threatening with multi-organ disease. To exclude mimics of vasculitis, diagnosis of cutaneous vasculitis requires biopsy confirmation where its acute signs (fibrinoid necrosis), chronic signs (endarteritis obliterans), or past signs (acellular scar of healed arteritis) must be recognized and presence of extravascular findings such as patterned fibrosis or collagenolytic granulomas noted. Although vasculitis can be classified by etiology, many cases have no identifiable cause, and a single etiologic agent can elicit several distinct clinicopathologic expressions of vasculitis. Therefore, the classification of cutaneous vasculitis is best approached morphologically by determining vessel size and principal inflammatory response. These histologic patterns roughly correlate with pathogenic mechanisms that, when coupled with direct immunofluorescent examination, anti-neutrophil cytoplasmic antibody (ANCA) status, and findings from work-up for systemic disease, allow for specific diagnosis, and ultimately, more effective therapy. Herein, we review cutaneous vasculitis focusing on diagnostic criteria, classification, epidemiology, etiology, pathogenesis, and evaluation of the cutaneous vasculitis patient.

Key Words: classification, etiology, epidemiology, pathogenesis, direct immunofluorescence, ANCA, systemic vasculitis, localized vasculitis, endarteritis obliterans

Abbreviations

ACR: American College of Rheumatology
AECA: antiendothelial antibodies
ANCA: antineutrophil cytoplasmic antibodies
APS: antiphospholipid antibody syndrome
CHCC: Chapel Hill Consensus Conference
CLA: cutaneous leukocytoclastic angiitis (a.k.a. cutaneous leukocytoclastic vasculitis)
CSS: Churg-Strauss syndrome
CTD: connective tissue disease (collagen vascular disease)
CTDV: CTD associated vasculitis
CV: cryoglobulinemic vasculitis
DIF: direct immunofluorescent studies
GCA: giant cell (temporal) arteritis
HE: hematoxylan and eosin stained tissue sections
HSP: Henoch-Schönlein purpura
IC: immune complexes
LCV: leukocytoclastic vasculitis (a.k.a. hypersensitivity angiitis/cutaneous leukocytoclastic vasculitis)
MPA: microscopic polyangiitis
MPO: myeloperoxidase
PAN: polyarteritis nodosa
PR3: proteinase 3
PSV: primary systemic vasculitis
RA: rheumatoid arthritis
SLE: systemic lupus erythematosus
UV: urticarial vasculitis
WG: Wegener granulomatosis

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Few diseases in clinical medicine cause as much diagnostic and therapeutic consternation as vasculitis.[1–6] Vasculitis is simply inflammation directed at blood vessels identified by histologic examination. When blood vessel inflammation occurs, vessel wall destruction with hemorrhage and aneurysm formation or stenosis due to intimal hyperplasia can occur, both of which may lead to tissue ischemia and infarction. Vasculitis can be a primary process (no known cause or association), or a phenomenon secondary to drug ingestion, infection, or the presence of a systemic disease (eg, rheumatoid arthritis) or to local factor such as trauma. Systemic and localized vasculitis often affects the skin and subcutis, likely due in part to their large vascular bed, hemodynamic factors (eg, stasis in lower extremities), and environmental influences (eg, cold exposure). Frequent skin involvement by vasculitic syndromes, seen as diverse and dynamic patterns of discoloration, swelling, hemorrhage, and/or necrosis, may be their initial and/or most accessible manifestations. Thus, dermatopathologists and dermatologists often become involved in the diagnosis and management of vasculitis.[2,5,7]

Cutaneous vasculitis presents as a mosaic of clinical and histologic findings due to varied pathogenic mechanisms.

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Physical signs of vasculitis include urticaria, purpura, purpuric papules, infiltrated erythema, ulcer, infarct, livedo reticularis, and nodules that affect the skin with varying intensity, depth, and distribution creating a number of named syndromes, for example, erythema induratum (nodular vasculitis), Henoch-Schonlein purpura (HSP), or Wegener granulomatosis (WG). However, in many cases, specific clinical entities do not always correlate exactly with mechanisms and any one patient may have a constellation of morphologic signs that overlaps with another clinical entity thus preventing confident clinical diagnosis.[8,9] A definitive diagnosis of vasculitis requires histologic confirmation in almost all cases because few vasculitic syndromes have pathognomonic clinical, radiographic, and/or laboratory findings.[6,10] However, a biopsy diagnosis of vasculitis cannot stand by itself, as it must be correlated with clinical history, physical and laboratory findings, and/or angiographic features. For instance, a diagnosis of vasculitis restricted to the skin (aka, hypersensitivity vasculitis, cutaneous leukocytoclastic angiitis) requires that the systemic manifestations of vasculitis be sought and found absent.[5] If systemic vasculitis is present, imaging studies can provide a useful means to determine disease extension and activity[10] and serology, such as C-reactive protein and anti-neutrophilic cytoplasmic antibodies (ANCA) levels and type can be used to monitor disease activity and predict mortality risk, respectively.[11,12] In addition, clinical features such as the presence of arthralgias and cryoglobulinemia, and absence of fever can predict a chronic course.[13] Lastly, the histopathologic interpretation for vasculitis is dependent on the type of biopsy, age of the cutaneous lesion sampled, effects of prior treatment and experience of the pathologist. Not only the diagnosis of vasculitis, but also the recognition of the specific type, associated diseases or triggering factors, and monitoring by histology and/or laboratory tests, may be decisive for optimal therapy of vasculitis.

In this first part of this 2-part review, diagnostic criteria, classification, etiology, epidemiology, pathogenesis, and evaluation of patients presenting with cutaneous vasculitis will be discussed. In the second part, specific vasculitic entities, primary and secondary, that can affect the skin will be presented in the context of morphologic and pathophysiologic classification scheme. A primarily morphologic-based scheme is used rather than the etiologic-based one, as it is the most practical method to generate a relevant differential diagnosis when interpreting a skin biopsy showing vasculitis (Fig. 1).

DIAGNOSIS AND CLASSIFICATION OF VASCULITIS

The diagnosis of vasculitis is a medical challenge due to the unknown or incompletely understood etiology and pathogenesis of most vasculitides as well as their protean and overlapping clinicopathologic features.[14,15] For instance, hepatitis C infection can be found in association with several different types of vasculitis such as polyarteritis nodosa (PAN), cryoglobulinemic vasculitis (CV), and hypersensitivity/cutaneous leukocytoclastic angiitis (CLA).[16] (Henceforth, leukocytoclastic vasculitis (LCV) will be used to describe patients with the histologic reaction pattern of small vessel neutrophilic vasculitis with or without systemic disease; the Chapel Hill Consensus Conference (CHCC) term "cutaneous leukocytoclastic angiitis (CLA)" will be used to describe patients with cutaneous LCV without systemic disease.) To efficaciously manage vasculitis, a precise and accurate diagnostic

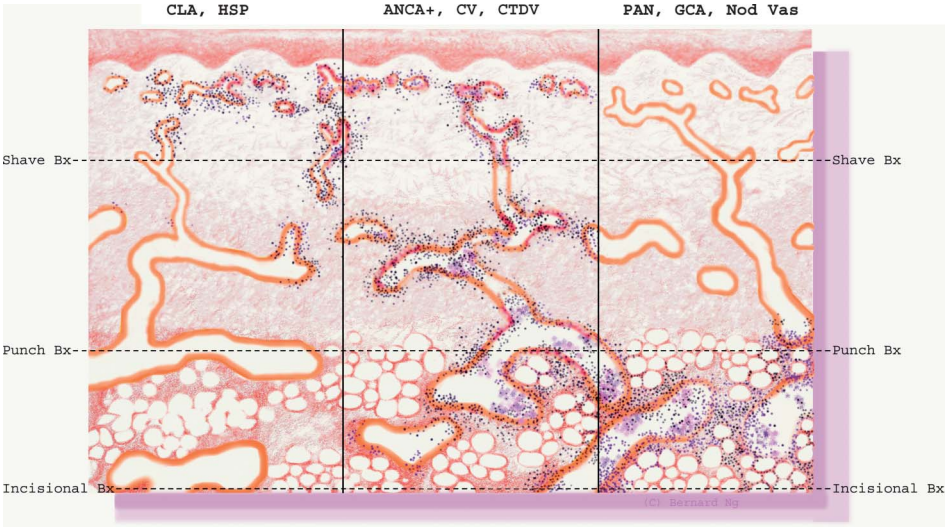

FIGURE 1. The size of vessel involvement is one histologic feature in conjunction with the dominant inflammatory cell that allow for classification of most common forms of cutaneous vasculitis. In general, Henoch-Schönlein purpura (HSP) and cutaneous leukocytoclastic angiitis (CLA) (aka, leukocytoclastic or hypersensitivity vasculitis) affect the superficial vessels of the skin whereas polyarteritis nodosa (PAN), nodular vasculitis (Nod Vas), and giant cell arteritis (GCA) affect deep muscular vessels found at the dermal-subcutis interface and within the subcutis. Most other forms of vasculitis such as cryoglobulinemic vasculitis (CV), connective tissue disease (CTDV) vasculitis, and anti-neutrophilic antibody associated vasculitides (ANCA+ vasculitis: Wegener vasculitis, Churg-Strauss syndrome, and microscopic polyangiitis) can affect both small and muscular vessels (although not necessarily in the same biopsy). The diagnostic yield of a skin biopsy is greatly influenced by the depth biopsy. In general, punch biopsy or excision biopsy extending into the subcutis is the preferred means to sample a vasculitic lesion to sample vessels of all sizes.

classification of vasculitis is essential. Moreover, to study the epidemiology of vasculitis and to compare treatment regimens from different studies/regions/medical centers, reproducible classification schemes are required.

Examples of vasculitis classification schemes include categorization by pathogenesis (mechanism) (eg, ANCA mediated (Arthus Type II) or immune complex mediated (Arthus Type III)), by anatomic involvement (eg, vessel size and organ distribution), by histopathologic pattern (eg, type of inflammation and vessel distribution), or by clinical manifestations (eg, by clinical syndrome for comparison of groups by outcome or response to therapy). Zeek was the first to develop a classification system for vasculitis differentiating patients mostly on organ system involvement.[17] This initial scheme served as the basis for the American College Rheumatology's (ACR) published classification system[18–25]; however, this system did not have input by dermatologists who have trouble placing patients in one category or another.[26] In fact, the referring rheumatologist's diagnosis served as the gold standard in developing the ACR classification criteria, which have sensitivities ranging from 71% to 94% and specificities ranging from 87% to 92%.[27,28] Applying ACR criteria for WG, PAN, giant cell arteritis (GCA), and hypersensitivity vasculitis to patients suspected of having vasculitis reveals a poor positive predictive value ranging from 17% to 29%.[29] In that study by Rao et al,[29] the clinical findings of palpable purpura, neuropathy, and microscopic hematuria were significantly more likely to be found in vasculitis patients, and tissue biopsy (skin, kidney, or temporal artery) significantly aided in diagnosis.

Today, the most widely adopted vasculitis classification system is that of Chapel Hill Consensus conference,[30] but even this system is not problem free.[26] Most of the classification criteria derived from groups such as the CHCC or the ACR were not originally developed as diagnostic criteria for individual patients (particularly those with early disease), but for comparisons of groups of patients.[30,31] Table 1 lists the diagnostic criteria for primary vasculitis promulgated by the CHCC and ACR. Examples of either system's shortcomings for the classification of individual patient's vasculitis follow below. The positive predictive value for the ACR criteria for hypersensitivity vasculitis (CLA in the CHCC) is 30%,[29] and significant overlap exists between ACR's criteria of HSP and hypersensitivity vasculitis.[22,23] Indeed, some authors consider HSP to be a subset of CLA mediated mainly by IgA immune complexes.[32] Contrarily, based on CHCC nomenclature, many HSP patients with systemic symptoms could also be classified as the systemic vasculitis-microscopic polyangiitis (MPA).[33] Supplementing CHCC criteria with surrogate parameters such as proteinuria and hematuria with red blood cell casts for the presence of glomerulonephritis or radiologic lung infiltrates or cavities greater than 1 month's duration for lung granulomas, the CHCC nomenclature still fails to identify many patients with WG and MPA.[8] In addition, the criteria of ACR and CHCC identify different groups of patients. Classic PAN as defined by the CHCC is rare but common by ACR criteria, because small vessel involvement is excluded from this definition by the CHCC.[9,34–36]

Clearly, distinctions based solely by vessel size are imprecise means of classification as overlap in vessel size involvement is common particularly for the ANCA+ vasculitides with CLA.[37] However, to date, no ideal system of classification exists for vasculitis, and the major advances in the classification have been in the recognition of dominant blood vessel size involved, the distinction between primary and secondary vasculitis, and the incorporation of pathophysiologic markers such as direct immunofluorescent (DIF) and anti-neutrophil cytoplasmic antibodies (ANCA).[14,15] In the clinical evaluation of patients with vasculitis, biopsy specimens are essential to confirm the presence of vasculitis, reveal the presence of extravascular granulomas or tissue eosinophilia, and assess for the presence of immune deposits in vessels walls. To confirm the presence of vasculitis and correctly classify the type of vasculitis, criteria must exist to allow for histologic recognition of vasculitis.

Histologic Diagnostic Criteria

The diagnosis of vasculitis of medium or small vessels is made primarily by biopsies and examination of H&E-stained sections. Table 2 lists criteria for diagnosis of cutaneous vasculitis. Most observers will agree that the term vasculitis should reflect conditions in which inflammatory cells significantly damage vessels and not merely transverse them to enter the surrounding tissue.[38,39] Fibrinoid necrosis (fibrin deposition within and around the vessel wall) is a common histologic feature of nearly all early vasculitic lesions and is due to the accumulation of plasma proteins, including coagulation factors that are converted to fibrin, at sites of vessel wall destruction (Fig. 2).[40]

Histologic Evidence of Vessel Wall Injury (Vasculitis)

The diagnosis of vasculitis can be unequivocally be made if there are inflammatory infiltrates within and around the walls of vessels accompanied by fibrin deposition (fibrinoid necrosis). Not only fibrin, but its precursors and metabolites (fibrinogen fibrinopeptides), necrotic endothelial and inflammatory cells, and immunoreactants are present in zones of fibrinoid necrosis.[40,41] These changes commonly coexist with signs of endothelial damage in the form of endothelial swelling, shrinkage (apoptosis), or sloughing. Secondary changes in which vascular damage can be inferred are the histologic findings of extravasation of red blood cells (purpura), necrosis (infarct), and ulceration secondary to the ischemia from vessel obstruction or destruction by the inflammatory insult (Fig. 3). Abnormal eccrine (sweat) glands secondary to tissue ischemia can also be found and is recognized by solitary cell or whole gland necrosis, regeneration, and basal cell hyperplasia within ducts (Fig. 4).[42] Neovascularization of the adventia, formation of small capillaries, is prominent feature of mature and older lesions of medium and large vasculitides such as polyarteritis nodosa and giant cell arteritis (Fig. 5).[43] New capillary formation is also a prominent feature of chronic localized small vessel vasculitis such as erythema elevatum dinutum; these new capillaries may be more susceptible to immune complex (IC) deposition.[44]

TABLE 1. Names and Definitions of Vasculitides Adopted by the Chapel Hill Consensus Conference and America College of Rheumatology on the Nomenclature of Systemic Vasculitis

	Chapel Hill Consensus Conference Criteria	American College of Rheumatology Criteria
Large vessel vasculitis		
Giant cell (temporal) arteritis (GCA)	Granulomatous arteritis of the aorta and its major branches, with a predilection for the extracranial braches of the carotid artery. Often involves the temporal artery. Usually occurs in patients older than 50 and often associated with polymyalgia rheumatica.	1. Age >50 years at onset 2. New type of headache 3. Abnormal temporal artery on examination 4. Elevated erythrocyte sedimentation rate 5. Temporal artery biopsy shows vasculitis Sensitivity 93.5%, specificity 91.2% for 3 criteria
Takayasu arteritis	Granulomatous inflammation of the aorta and its major branches. Usually occurs in patients younger than 50.	1. Age <40 years at onset 2. Limb claudication 3. Decreased brachial artery pulses 4. Blood pressure >10 mg Hg difference between arms 5. Bruits 6. Abnormal arteriogram Sensitivity 90.5%, specificity 97.8% for 3 criteria
Medium-sized vessel vasculitis		
Polyarteritis nodosa (PAN)	Necrotizing inflammation of medium-sized or small arteries without glomerulonephritis or vasculitis in arterioles, capillaries, or venules.	1. Weight loss >4 kg 2. Livedo reticularis 3. Testicular pain or tenderness 4. Myalgias, myopathy, or tenderness 5. Neuropathy 6. Hypertension (diastolic >90 mg Hg) 7. Renal impairment (elevated BUN or creatinine) 8. Hepatitis B virus 9. Abnormal arteriography 10. Biopsy of artery showing neutrophils Sensitivity of 82.2%, specificity 86.6% for 3 criteria
Kawasaki disease	Arteritis involving large, medium-sized, and small arteries, and associated with mucocutaneous lymph node syndrome. Coronary arteries are often involved. Aorta and veins may be involved. Usually occurs in children.	
Small vessel vasculitis		
Wegener granulomatosis (WG)	Granulomatous inflammation involving the respiratory tract, and necrotizing vasculitis affecting small to medium-sized vessels (eg, capillaries, venules, arterioles, and arteries). Necrotizing glomerulonephritis is common.	1. Nasal or oral inflammation 2. Chest X-ray showing nodules, infiltrates, or cavities 3. Microscopic hematuria or red cell casts in urine 4. Granulomatous inflammation on biopsy Sensitivity of 88.2%, specificity 92% for 2 criteria
Churg-Strauss syndrome (CSS)	Eosinophil-rich and granulomatous inflammation involving respiratory tract, and necrotizing vasculitis affecting small to medium-sized vessels, and associated with asthma and eosinophilia.	1.Asthma 2. Eosinophilia (>10%) 3. Neuropathy 4. Pulmonary infiltrates (non-fixed) 5. Extravascular eosinophils on biopsy Sensitivity 85%, specificity 99.7% for 4 criteria
Microscopic polyangiitis (MPA)	Necrotizing vasculitis, with few or no immune deposits, affecting small vessels (capillaries, venules, and arterioles). Necrotizing arteritis involving small and medium-sized vessels may be present. Necrotizing glomerulonephritis is very common. Pulmonary capillaritis often occurs.	
Henoch-Schönlein purpura (HSP)	Vasculitis, with IgA dominant immune deposits, affecting small vessels (capillaries, venules, and arterioles). Typically involves skin, gut, and glomeruli and is associated with arthralgias or arthritis.	1. Palpable purpura 2. Age at onset <20 years 3. Bowel angina 4. Vessel wall neutrophils on biopsy Sensitivity 87%, specificity 88% for 2 criteria

(*continued on next page*)

TABLE 1. (*continued*) Names and Definitions of Vasculitides Adopted by the Chapel Hill Consensus Conference and America College of Rheumatology on the Nomenclature of Systemic Vasculitis

	Chapel Hill Consensus Conference Criteria	American College of Rheumatology Criteria
(Essential) cryoglobulinemic vasculitis (CV)	Vasculitis, with cryoglobulin immune deposits, affecting small vessels (ie, capillaries, venules, or arterioles), and associated with cryoglobulins in the serum. Skin and glomeruli are often involved.	
Cutaneous leukocytoclastic vasculitis (CLA) (aka, hypersensitivity vasculitis)	Isolated cutaneous leukocytoclastic angiitis without systemic vasculitis or glomerulonephritis.	1. Age >16 years at onset 2. Medications that may have precipitated event 3. Palpable purpura 4. Cutaneous eruption 5. Positive biopsy results Sensitivity of 71%, specificity 83.9% for 3 criteria

From Jennette et al[30] and ACR.[18–25]

Reactive angioendotheliomatosis is another histologic pattern that can be seen as a consequence of medium vessel vasculitis such as PAN or other causes of vascular obstruction.[45] This reactive vascular pattern is characterized by a diffuse or lobular proliferation of capillaries in the dermis, often harboring fibrin microthrombi and reactive, fasciitis-like dermal alterations, and foci of epithelioid endothelium (Fig. 6). The livedoid pattern or atrophic blanche pattern overlying cutaneous PAN[46] may represent a variant of reactive angioendotheliomatosis.

The diagnosis of vasculitis is much more problematic if fibrin deposits are not identified. To separate such cases from the much larger group of perivascular dermatitides, one can look for circumstantial evidence of vessel wall damage. This evidence may include lamination of the adventia, media, and/or intima of vessels (so-called onion skinning) (Fig. 7); perivascular nuclear dust (leukocytoclasia) without fibrin deposits (early, evolving LCV) (Fig. 8); sharply defined loss of the elastic lamina associated with acellular scar tissue (the healed stage of muscular vessel vasculitis) (Fig. 9); or in the case of muscular (large) vessels, subendothelial, intramuscular, and/or advential inflammatory cells (Fig. 10). Regarding the latter finding, the walls of these vessels are not the sites of diapedesis—a process that is restricted to post-capillary venules; thus, the presence of inflammatory cells in these vessel regions is indicative of inflammation directed at vessel wall constituents. In the case of large vessel vasculitis, the adventia is believed to be the site of antigenic stimulation.

The end-stage phenomenon of luminal obliteration (endarteritis obliterans) is an irreversible, ischemic consequence of vasculitis and typically affects small-to-medium-sized arteries. Healed lesions of muscular vessel vasculitis, the acellular scar stage, do not progress to endarteritis obliterans and can be associated with either luminal stenosis or aneurysm formation; however, persistence of vessel wall inflammation, either medial or intimal, can eventually lead to luminal obliteration or aneurysm rupture (Fig. 11). The life history of lesions of suspected inflammation-promoted endarteritis obliterans are found in Sneddon syndrome (cerebrovascular lesions and livedo racemosa), a putative example of lymphocytic vasculitis.[47] Initially, a lymphocytic endothelialitis (endarteritis) occurs that is followed by the formation of a sponge-like plug composed of mononuclear cells, fibrin, and red blood cells resulting in partial to complete obstruction (Fig. 12). A perivascular lymphohistiocytic (non-neutrophilic) inflammatory infiltrate develops around affected arteries, which is then followed by formation of dilated capillaries in obstructed vessels' adventia. Smooth muscle cells are suspected to immigrate and proliferate in the subendothelial zone, organizing the occluding plug during the intermediate stage. The final stage is characterized by fibrosis, shrinkage, and atrophy of the occluded artery.

Incidental Vasculitis

It is not uncommon to find changes of neutrophilic small vessel vasculitis underlying an ulcer formed by another process (trauma or surgery). This is incidental vascular injury and can usually be differentiated from primary vasculitis by correlation with history and the focal nature of the vessel damage that is restricted to the area of trauma or ulceration; the vessels in the surrounding skin will be unaffected. (The term secondary vasculitis is not used as it refers to vasculitis developing *secondarily* in systemic disease, for example rheumatoid or lupus vasculitis) (Fig. 13). Neutrophilic dermatoses (eg, Sweet syndrome), can also exhibit neutrophil-mediated vessel damage that can resemble small vessel neutrophilic vasculitis in approximately 29% of cases, typically affecting vessels within the diffuse dermal neutrophilic infiltrate compared with the angiocentric neutrophilic infiltrate of LCV. In the setting of a neutrophilic dermatosis, vasculitis is suspected to be an epiphenomenon due to neutrophil byproducts such as reactive oxygen species and degradative enzyme, and not a primary immune-mediated event (Fig. 14).[48,49]

Histologic Patterns Indicative of Vasculitis Subtype, Presence of Systemic Disease, or Infectious Trigger

In most cases of cutaneous vasculitis, the histologic changes will be centered on around vessels and involve the dermis (purpura) or epidermis (ulcer or infarction) when significant vessel damage or tissue ischemia has occurred.

TABLE 2. Histologic Diagnostic Criteria for Cutaneous Vasculitis

Histologic signs of acute (active) vasculitis
Dermal small vessels (venules and arterioles) (2 of 3* criteria needed)
*Angiocentric† and/or angioinvasive inflammatory infiltrates
*Disruption and/or destruction of vessel wall by inflammatory infiltrate
*Intramural and/or intraluminal fibrin deposition ("fibrinoid necrosis")
Dermal-Subcutaneous muscular vessels (small arteries and veins) (both* criteria needed)
*Infiltration of muscular vessel wall by inflammatory cells
*Intramural and/or intraluminal fibrin deposition ("fibrinoid necrosis")‡
†Secondary changes of active vasculitis (suggestive of, but not diagnostic of vasculitis)
RBC extravasation (petechiae, purpura, hematoma)
Nuclear dust, perivascular (leukocytoclasia)
Endothelial swelling, sloughing or necrosis
Eccrine gland necrosis (or regeneration with basal cell hyperplasia)
Ulceration
Necrosis/infarction
Histologic sequelae of vasculitis (chronic signs and healed lesions of vasculitis)
†Lamination (onion-skinning) of vessel wall constituents (concentric proliferation of pericytes and smooth muscle cells)
†Luminal obliteration (endarteritis obliterans)
Intimal or medial proliferation of cellular elements leading to luminal occlusion with preservation of the internal elastic lamina
*Segmental or complete loss of elastic lamina in medium and large vessels associated with acellular scar tissue
Reactive angioendotheliomatosis
Neo-vascularization of the adventitia
Changes adjacent to vasculitis indicative of subtype or etiology
Lamellar or storiform fibrosis
Erythema elevatum diutinum, granuloma faciale, or inflammatory pseudotumor
Palisading (necrotizing) granulomatous dermatitis ("Winkelmann granuloma")
"Red" extravascular granuloma (eosinophils, flame figures)
Churg-Strauss syndrome
"Blue" extravascular granuloma (neutrophils, nuclear dust)
Wegener granulomatosus, rheumatoid vasculitis, Churg-Strauss syndrome (rarely)
Vacuolar interface dermatitis (sometimes dermal mucin deposition)
Connective tissue disease, for example, lupus erythematosus, dermatomyositis
"Pustular" dermatosis with intraepidermal or subepidermal neutrophilic abscesses
Infectious trigger

*Required for diagnosis of vasculitis; †Other types of vessel injury can cause same pattern; ‡Intraluminal fibrin deposition can be found in non-vasculitic arterial lesions such as malignant hypertension and anti-phospholipid syndrome.

However, other reaction patterns can be found in the surrounding tissues that indicate the presence of systemic disease, most frequently connective tissue disease (CTD) or the presence of a primary systemic vasculitis (PSV). Palisading granulomatous (necrobiotic) dermatitis associated with small vessel neutrophilic vasculitis can be seen in both PSV such as WG and Churg-Strauss Syndrome (CSS) as well as CTD such as rheumatoid arthritis and lupus erythematosus

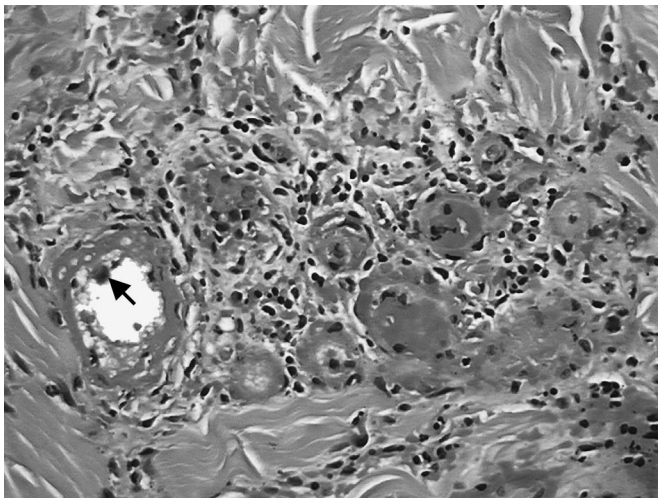

FIGURE 2. Fibrinoid necrosis. The salient features of vasculitis are endothelial swelling, inflammatory infiltrates, and ''fibrinoid necrosis'' of the vessel wall. Fibrinoid necrosis, fibrin-like, is thought to be the most characteristic histopathological manifestation of vasculitis. Illustrated herein is multiple small vessel walls replaced by fibrinous material associated with scant lymphocytic infiltrates and extravasated red blood cells; the arrow highlights a necrotic endothelial cell.

(Fig. 15).[50–54] Extravascular granulomas exhibiting eosinophilic debris around degenerated collagen bundles due to tissue eosinophilia and flame figures (so-called red granuloma) are found in CSS,[55] whereas extravascular granulomas with basophilic debris ("blue" granuloma due to mucin, neutrophilic nuclear dust) are found in WG and rheumatoid vasculitis.[56] Interface dermatitis associated with either a neutrophilic or lymphocytic small vessel vasculitis can be found in entities such as perniosis (chilblains) or CTD such as

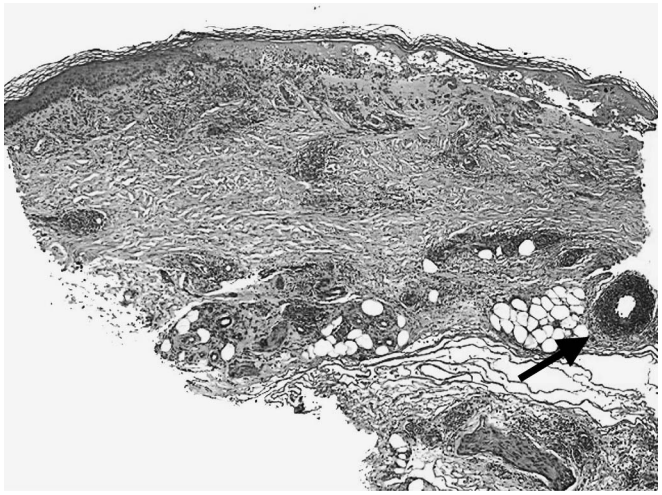

FIGURE 3. Necrosis secondary to vasculitis. Epidermal infraction associated with a pan-dermal and subcutaneous vasculitis. Note the involvement of the muscular artery (arrow). Infracts and ulcers are commonly associated with arterial vasculitis.

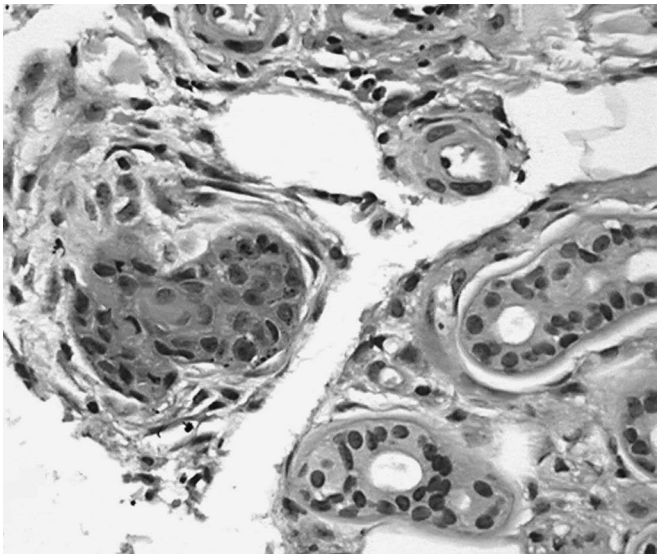

FIGURE 4. Eccrine gland necrosis found at the base a cutaneous infarct due to Churg-Strauss syndrome. This finding is typically associated with coma- or pressure-induced blisters, but can be also be found in cutaneous vasculitis.

dermatomyositis and lupus erythematosus (Fig. 16).[57–61] Focal small vessel neutrophilic vasculitis found in the midst of a fibrotic dermis or subcutis showing lamellar or storiform pattern of fibrosis indicates chronic localized fibrosing form of vasculitis found in either granuloma faciale, erythema elevatum diutinum, or an inflammatory pseudotumor (Fig. 17).[62] Lastly, the presence of intraepidermal or dermal papillae pustules in

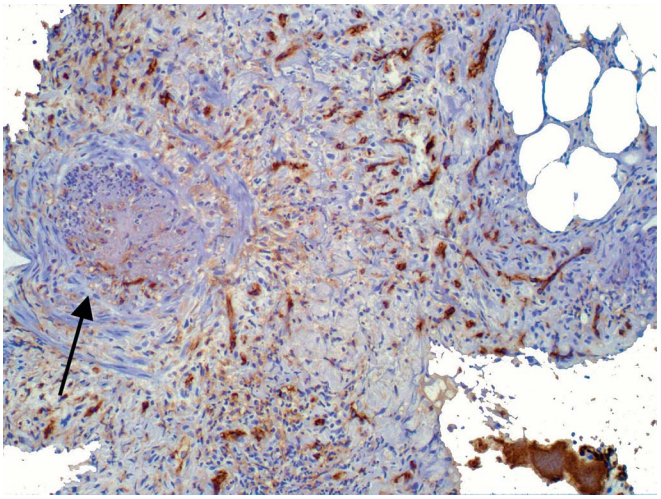

FIGURE 5. Neoangiogenesis: inflammation-promoted angiogenesis or neo-vascularization found in some lesions of both cutaneous and systemic vasculitides may represent a double-edged sword compensating for ischemia on one hand and promoting inflammation, thus maintaining vasculitis on the other.[43,44] Antibodies to CD31 highlight the numerous small vessels emanating from the adventia of this subcutaneous muscular artery involved by polyarteritis nodosa. Note that the lumen is obliterated by a fibrinous plug (arrow).

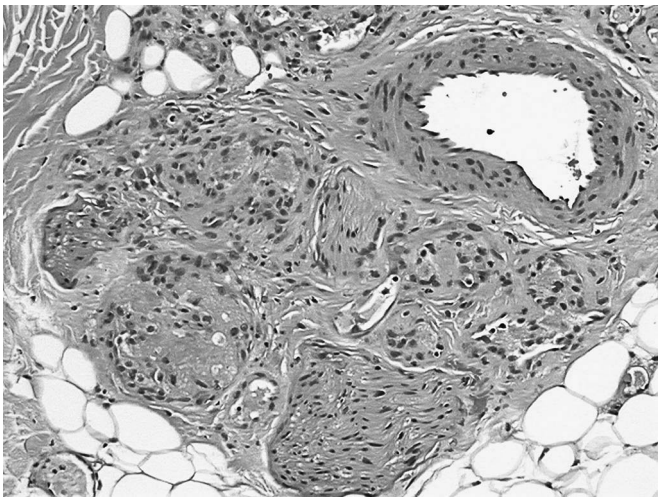

FIGURE 6. Reactive angioendotheliomatosis can be the consequence of either vasculitis or a thrombo-occlusive disorder. In this case, a lobular proliferation of capillaries in the dermis with fibrin thrombi is evident. Diffuse or mixed lobular and diffuse capillaries, reactive dermal fasciitis-like stromal changes, and hobnail or epithelioid endothelial formation can be seen in lesions of reactive angioendotheliomatosis.

concert with a neutrophilic-rich small vessel vasculitis implicates an infectious trigger.[63]

ETIOLOGY AND EPIDEMIOLOGY

Once a patient has been determined to have cutaneous vasculitis by biopsy, an attempt must be made to determine the etiology as its withdrawal (eg, drug) or treatment (eg, infection) leads to resolution. Cutaneous vasculitis can represent

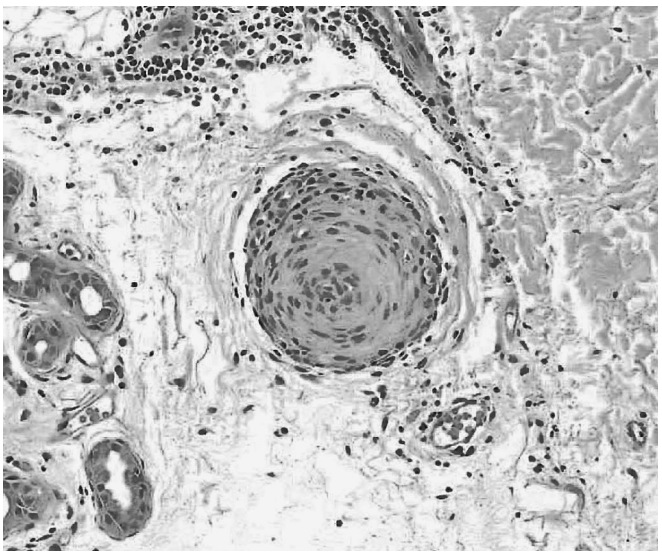

FIGURE 7. ''Onion-skinning'' of this small vessel, likely an arteriole found in the subcutaneous tissue in a patient with perniosis (chilblains) is a sign of primary vessel disease and a clue to the possible presence of vasculitis.

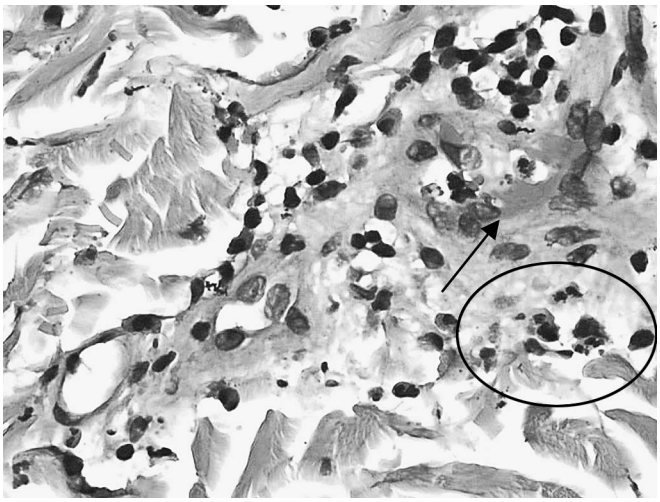

FIGURE 8. Perivascular nuclear debris. In the absence of marked fibrin deposits, the presence of perivascular nuclear debris or leukocytoclasis (circle) is clue to presence of vasculitis, in this case, urticarial vasculitis. The arrow highlights focal fibrin deposits coating the lumen wall.

a primary or idiopathic process (eg, PSV, WG, CSS, GCA, CLA), a secondary process associated with another systemic, often chronic inflammatory disease, or an eruption triggered by infection or recent drug ingestion. Table 3 lists those disorders and agents that have been associated with vasculitis. Case-control studies of patients, mostly adults, presenting with biopsy-confirmed cutaneous vasculitis reveals a broad range in the frequency and incidence of associated conditions that is dependent on the population studied and clinical setting (primary versus tertiary care).[13,33,63–90] Table 4 lists the frequency of finding specific diseases in patients presenting with cutaneous vasculitis. In general, the presence of severe systemic vasculitis is low in the community practice settings compared with tertiary care centers. The differences in infection-related vasculitis mirrors the prevalence of disease in the community with a high rate of hepatitis C-related vasculitis in Barcelona, Spain where the incidence of hepatitis C

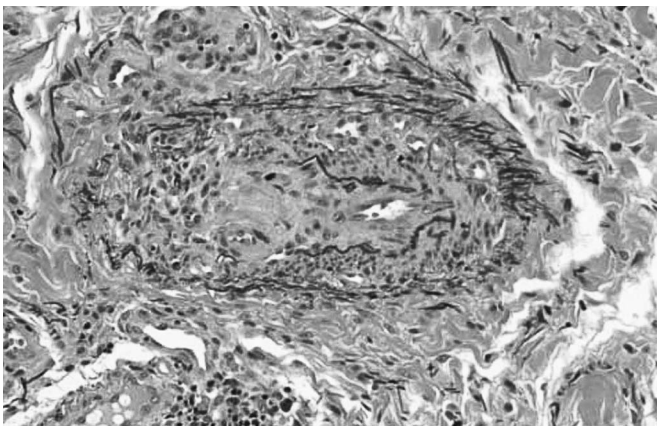

FIGURE 9. The healed scar of past arteritis in a patient with rheumatoid vasculitis. Note the loss of the elastic lamina and loss of vessel lumen by the fibrous scar.

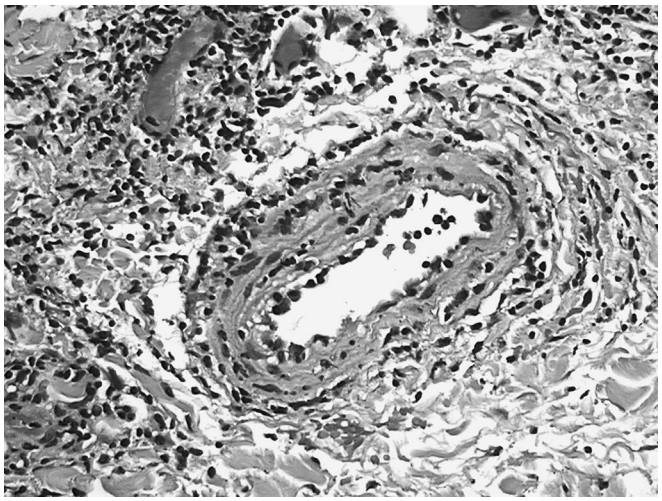

FIGURE 10. Muscular vessel walls are not the site of diapedesis, so the finding of inflammatory cells within the adventia, media, and/or intima is a sign of vasculitis. Illustrated here from a biopsy of a patient with an unclassified collagen vascular disease presenting with nodules and livedo reticularis is a muscular vessel (artery) whose endothelium is disrupted by lymphocytes (endothelialitis) and both the media and adventia harbor lymphocytes.

seropositivity is 0.8%.[13] In comparison, beta-hemolytic streptococcal related vasculitis in Cape Town, South Africa[65] was the most frequent infection and hepatitis-related vasculitis was not reported. The absence of MPA in most of these series is likely due to criteria for diagnosis, as many of the patients diagnosed with PAN would be called MPA by the CHCC definitions and MPA does not exist in the ACR criteria.[34] Children, who are often not biopsied, can represent up to 44% of patients with signs of cutaneous vasculitis, most frequently

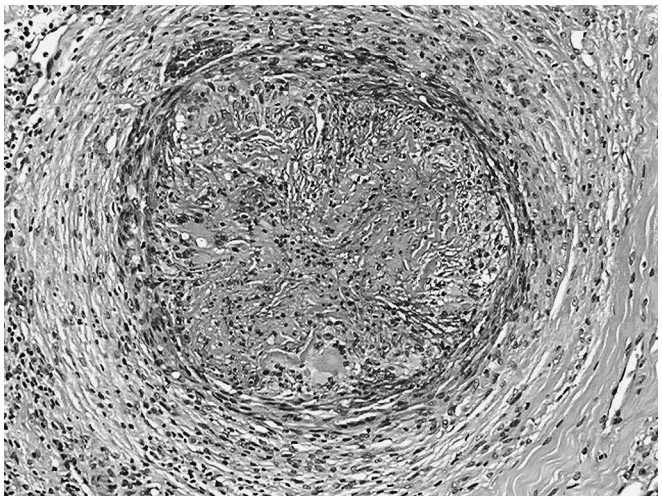

FIGURE 11. Endarteritis obliterans—a chronic rather than acute consequence of vasculitis leading to tissue ischemia and infarction due to loss of the vessel lumen. This biopsy was taken from a patient with giant cell arteritis who developed scalp necrosis: occluded muscular vessels were identified in the deep dermis underlying his ulcer.

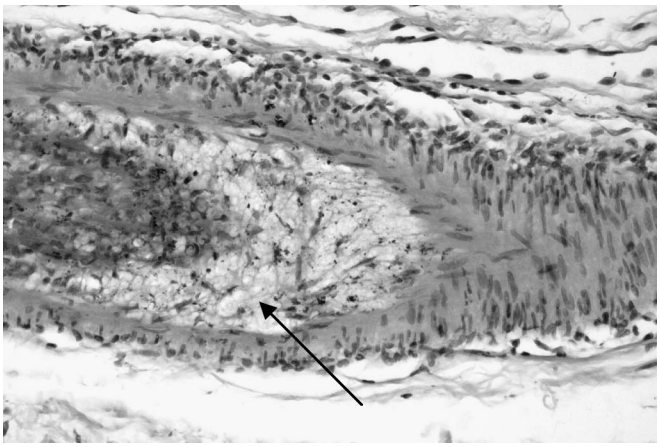

FIGURE 12. In the early phase of endarteritis obliterans as found in Sneddon syndrome is a sponge-like plug of mononuclear cells, containing fibrin and erythrocytes in its interstices; this stage follows the initial insult produced by lymphocytic endothelialitis as illustrated in Figure 10. Also note the expansion of the intimal region (arrow) by fibromyxoid tissue admixed with nuclear debris that diminishes the vascular lumen. (Courtesy of Dr. Bernhard Zelger, Innsbruck, Austria).

HSP (88%),[71] but children can be affected by PSV such as WG and PAN.[91] Secondary cutaneous vasculitis is uncommon in children, affects approximately 4%, and is associated with CTD such as SLE and dermatomyositis.[71,91]

In addition to infectious, drug, and systemic and chronic disease associations, epidemiologic studies on vasculitis have implicated geographic, genetic, and environmental factors in the risk for vasculitis.[92,93] Environmental factors such as silica, solvents, allergies, and farm work account for some of the differences in the incidence of the vasculitides among individuals.[94,95] Non-whites appear to be protected against GCA.[96] Differences in the major histocompatibility complex (MHC) and cytokine polymorphisms are also implicated in both susceptibility and severity of some forms of vasculitis. HSP is associated with HLA DRB*01 in northwest Spain,[97] and the presence of polymorphisms in the *ICAM-1* and *IL-Ra* genes appear to be protective against gastrointestinal complications[98] and control inflammatory responses,[99] respectively, in HSP. Similarly, *ICAM-1* gene and endothelial nitric oxide synthetase (eNOS) polymorphisms were found to be risk factors for susceptibility and severity in GCA.[100]

All ages (range 1–90 years), slightly less males than females (94:100, M:F, range 1:2 to 3:1) and adults more often than children (1:5, child: adult, range 1:100 to 3:4) can develop cutaneous vasculitis.[66,68,70,72,75,77,81,82,84–86,88,90,101] The mean age of onset of vasculitis is 47 years (mean of means, range 36–60 years).[65–68,70,76,77,80–82,84–86,88,90,101] Among children, the mean age of onset is 7 ± 4.7 years.[33,91] The onset of vasculitis after exposure to a trigger such as a drug or infection is 7 to 10 days. For patients with cutaneous vasculitis secondary to systemic disease, the interval between the onset of symptoms and signs of the systemic disease can vary from days to years, mean of 6 months, before the onset of cutaneous vasculitis.[73]

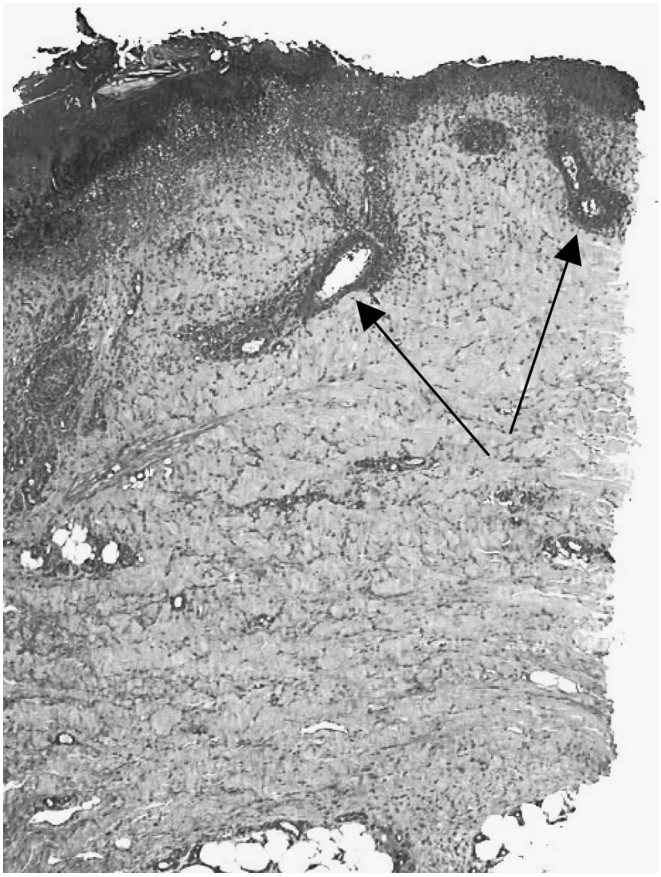

FIGURE 13. Incidental vasculitis. Punch biopsy of an excoriation reveals marked fibrin deposits affecting superficial vessels underlying the ulcerated surface, but no changes affecting mid and deep dermal vessels.

Three patterns of disease evolution occur in cutaneous vasculitis: (1) single acute, self-limited episode (resolved in ≤6 months) of vasculitis typically associated with a drug or infectious trigger (~60% of all cases, range 24%–100%); (2) relapsing disease with symptom-free periods usually found in patients with HSP- and CTD-associated vasculitis (~20%; 0%–53%); and (3) a chronic, unremitting disease often associated with cryoglobulinemia and malignancy (~20%; 0%–44%).[13,33,66,68–72,76,77,101] The duration of vasculitis can range from 1 week to 318 months, with mean and median duration of 28 months and 3.7 months, respectively.[13] Fatal disease occurs in a minority of patients (4%; range 0%–25%).[13,33,66,68,69,71,72,76,77,101]

Vasculitis is an uncommon disorder as long as the inflammation found in atherosclerosis and ruptured plaques are not classified as vasculitis.[102] The annual incidence of biopsy-proven cutaneous vasculitis in Norwich, England was 39.6 per million.[79] In the Capital District of New York, biopsy-proven cutaneous vasculitis composed 0.38% (95/~25,000) of all dermatopathology accessions during 2 years (2003–2004) at Albany Medical Center, a tertiary care hospital. Based on a population of 794,293 in the year 2000, the estimated incidence of biopsy-proven cutaneous vasculitis is 59.8 per

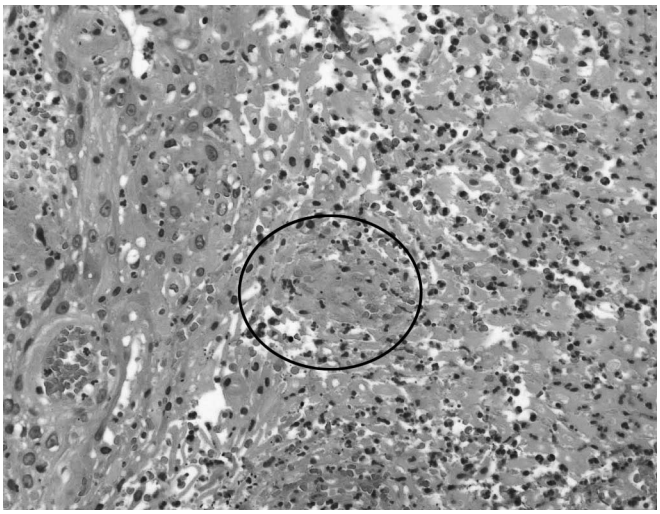

FIGURE 14. Incidental vasculitis occurring in pustular dermatosis of the dorsum of the hands (aka, pustular vasculitis). Note that the focus of fibrinoid necrosis (circle) in a sea of neutrophils and nuclear debris. Vasculitis in this histologic setting is suspected to represent an effect to reactive neutrophilic byproducts such as reactive oxygen species that damages the endothelium.

million. These incidence figures are likely an underestimate as patients with clinically obvious and/or mild disease may not have been biopsied, or their specimens were interpreted by another, private laboratory. These 2 calculated rates for cutaneous vasculitis are higher than that reported for isolated, primary cutaneous vasculitis, HSP and CLA at 13.0 to 14.3 per million and 15.4 per million,[66,79] but lower than that for PSV

FIGURE 15. The finding of extravascular collagenolytic granulomas can be a clue to the presence of systemic vasculitis such as Wegener granulomatosis, rheumatoid vasculitis, and Churg-Strauss syndrome. These findings can be seen in the absence or presence of necrotizing vasculitis. The ''blue'' extravascular granuloma illustrated herein is due to basophilic degeneration of collagen bundles that are coated with nuclear debris and can occur in the setting of Wegener granulomatosis (this biopsy) or rheumatoid vasculitis.

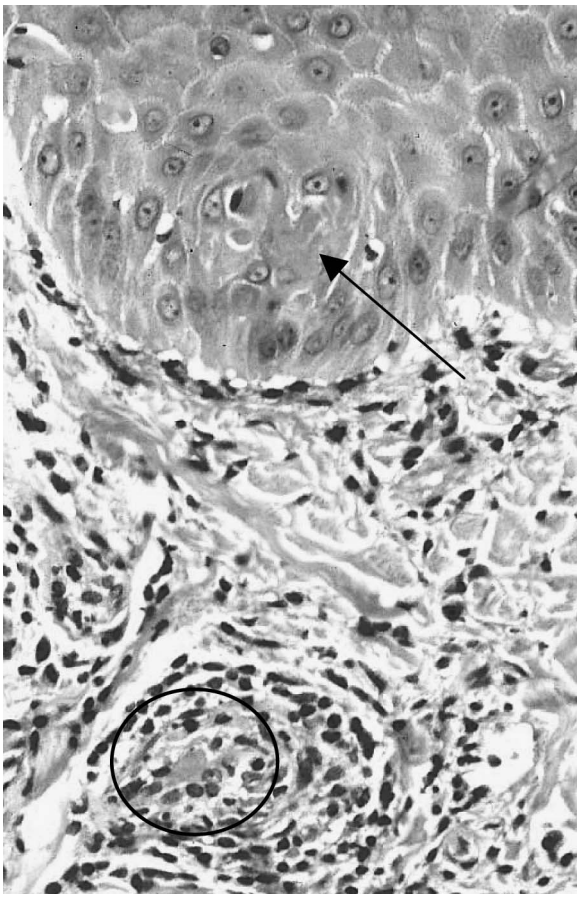

FIGURE 16. Interface dermatitis and vasculitis. Perniosis and connective tissue diseases such as lupus erythematosus and dermatomyositis can simultaneously exhibit interface dermatitis and lymphocytic vasculitis. In this example of perniosis, both fibrin occluding a small vessel (circle) obscured by a lymphocytic infiltrate and necrotic keratinocytes (arrow) near the dermal-epidermal junction are present.

with an incidence and prevalence at 115.04 per million[103] and 439 per million,[104] respectively. The variation in the incidences of vasculitis between different regions of the world studied likely reflects both population and environmental differences.[92,93,105] In Europe, the incidence of PSV appears to be increasing with age where WG appears to be more common at high latitudes and MPA more common at lower latitudes.[92] In contrast, perhaps due to better control of inflammation with therapeutics such as methotrexate, the incidence of rheumatoid vasculitis has decreased in Norwich, England.[106]

PATHOGENESIS

Cutaneous vasculitis is an infrequent event compared with its associated triggers (eg, infection, drug exposure, and chronic inflammatory disease), which are relatively common (Table 5). Moreover, most patients with cutaneous vasculitis present with a self-limited eruption of palpable purpura affecting the lower extremities of older individuals where venous hypertension and stasis have developed. These observations

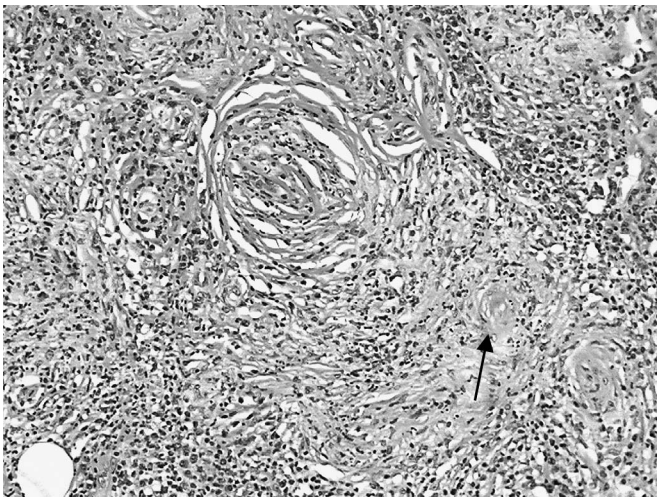

FIGURE 17. Patterned fibrosis. Lamellar, storiform, and concentric vascular fibrosis can be found in chronic lesions of neutrophilic small vessel vasculitis. In this case of inflammatory pseudotumor, concentric and lamellar fibrosis is evident and associated with a mixed inflammatory infiltrate. Focally, fibrin deposits can be identified in small vessels associated with nuclear debris (arrow).

underscore how the development of vasculitis and its perpetuation and progression to systemic disease is a unique combination of variables that include individual predisposition, host responses, local (endothelial) conditions, and exposure to triggering agents. Highlighting how an individual defect is a critical element in the development of vasculitis is a mouse model of murine gammaherpesvirus (γHV68) infection where minimal symptomatic infection or different disease phenotypes are dependent on genotype; fatal vasculitis develops in mice that lack interferon-γ or its receptor.[107]

Host Factors Localizing and Enhancing Vasculitis

Abnormal coagulation, blood flow (stasis), chronic inflammation, and endothelial cell activation all contribute to the development of individual lesions of vasculitis.[43,108] Hypercoaguable states (eg, factor V Leiden, protein C or S deficiency) are significantly more frequent in patients with ulcerative CLA.[109,110] Due to the long-term effects of gravitational stasis, the legs are the most frequent site of vasculitis as blood flow is slowest in these capillaries even when patients are supine.[108] Stasis at points of pressure from belts and braces, at sites of dependency (eg, back, buttocks) in bed-ridden patients, and from trauma (eg, suction cups) can also be the sites of cutaneous vasculitis and represent examples of the Koebner phenomenon.[108,111] How endothelial cells respond to trauma may also be a key factor. The skin prick test, used to initiate skin pathergy, induced endothelial expression of E-selectin, which recruits neutrophils, in Behçet patients, but not in controls.[112] Persistent inflammation may play an important role in the development of ANCA, which can themselves amplify and maintain inflammation by activating neutrophils and endothelial cells, and disrupt apoptosis and clearance of neutrophils.[113] Indeed, sub-clinical localized granulomatous inflammation is believed responsible for disease re-activation or relapse, the primary clinical problem in WG.[114] Cytokine-mediated, pro-inflammatory changes in the expression and function of adhesion molecules together with inappropriate activation of leukocytes and endothelial cells are suspected to be key factors influencing vessel inflammation and damage.[3,115] Langerhan cells and other dendritic cells may perpetuate the inflammatory vasculitic response by promoting adhesion and cell-cell contact.[116,117]

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. On the contrary, the preferential small vessel involvement by small vessel ANCA+ and DIF+ vasculitides appears secondary to the requirement for close apposition between neutrophils and endothelial cells.[115] An example of these distinct mechanisms is the arteritis of Kawasaki disease and that of polyarteritis nodosa (PAN). The pathology of the necrotizing vasculitis of Kawasaki disease is most consistent with a primary role for T lymphocytes in the acute injury (lymphocytic vasculitis). In contradistinction, the necrotizing vasculitis of PAN is consistent with a primary role for neutrophils in the acute injury (neutrophilic vasculitis).

The site specificity and persistence of vasculitis may, in part, be also related to localized endothelial dysfunction mediated by interactions between stromal cells and endothelium.[118] For instance, smooth muscle cells and pericytes might activate endothelium, amplifying its response to pro-inflammatory agents such as tissue necrosis factor (TNF)-alpha resulting in leukocyte recruitment and fibrin deposition resulting in and enhancing vasculitis. In turn, this localized vessel wall inflammation can have systemic effects by eliciting diffuse endothelial dysfunction in distant vascular beds via release of secondary mediators such as TNF and CRP directly into the blood stream.[119,120] In fact, systemic vasculitis has been found to be associated with arterial stiffness, a marker of diffuse endothelial dysfunction, which directly correlates with the degree of inflammation and disease activity.[121] Anti-TNF-alpha therapy can reverse this endothelial dysfunction highlighting its role in the pathogenesis of vasculitis and its accompanying diffuse endothelial dysfunction.[122,123] Lastly, inflammation-promoted angiogenesis or neovascularization found in some lesions of both cutaneous and systemic vasculitides may represent a double-edged sword compensating for ischemia on the one hand and promoting inflammation, thus maintaining vasculitis on the other.[43,44] Of note, the persistence of inflammation and endothelial dysfunction in systemic vasculitis appears to have long-term consequences, leading to the acceleration of atherosclerosis and premature ischemic heart disease.[120,124,125]

Pathogenic Mechanisms (Table 5)

Many different types of injury, mostly immune mediated or due to direct infection, can cause identical responses in the vessel wall resulting in the morphologic pattern of fibrinoid necrosis, diagnostic of vasculitis. One reason for this common morphologic endpoint is that many different pathogenic mechanisms (eg, immune complex-Arthus reaction, endotoxin-Schwartzman reaction, and venom from

TABLE 3. Factors Associated with Vasculitis

Disease State or Associated Factor	Specific Entity or Agent
Gene polymorphisms	MHC, ICAM-1, IL-Ra, eNOS
Chronic infection	Bacteria (Neisseria sp, Staphylococcus aureus, Streptococcus sp, Mycobacteria sp), rickettsia (Rocky Mountain Spotted fever), virus (Hepatitis viruses A, B, & C, Hantavirus, Herpesviridae, parvovirus B19, and human immunodeficiency virus), fungus, protozoa (malaria), helminthic infections (gnathostomiasis, schistosomiasis)
Drugs	Insulin, antibiotics (penicillin, sulfonamides, chloramphenicol, streptomycin), anticonvulsants (hydantoin), diuretics (thiazides, furosemide), analgesics (aminosalicylic acid, phenylbutazone), phenothiazine, vitamins, quinine, streptokinase, tamoxifen, oral contraceptives, serum (sickness), propylthiouracil, potassium iodide, granulocyte colony stimulating factor (GCSF), leukotriene inhibitors (montelukast), interferons (IFN-γ/α), nicotine patches, TNF inhibitors
Vaccines	Anti-influenza, anthrax, hepatitis B
Chemicals, environmental agents, external factors	Insecticides, petroleum products, particulate silica (quartz, granite, sandstone, and grain dust), solvents, farm work, drug abuse (cocaine), radiocontrast media, protein A column pheresis, arthropod assaults, prolonged exercise, coronary artery bypass surgery, coral ulcers
Allergy	Food allergens (milk proteins, gluten), drug allergy, atopy, hyposensitization antigen
Connective tissue diseases	Systemic lupus erythematosus, rheumatoid arthritis, Sjögren syndrome, mixed connective tissue disease, scleroderma, dermatomyositis/myositis, relapsing polychondritis, ankylosing spondylitis, primary biliary cirrhosis, adult Still disease
Other systemic inflammatory diseases	Behçet disease, sarcoidosis, inflammatory bowel disease
Chronic disease	Cryoglobulinemia, hyperglobulinemic states, cystic fibrosis, bowel-bypass syndrome, alpha-1 anti-trypsin deficiency, St. Jude aortic valve replacement, diabetes mellitus, chronic hepatitis (viral, alcoholic), endocarditis, Wiskott-Aldrich syndrome, Hemolytic anemia
Immunodeficiency states	Primary combined immunodeficiency, acquired immunodeficiency syndrome (AIDS)
Cancer, lymphoproliferative disorders	Hodgkin disease, mycosis fungoides, chronic lymphocytic leukemia, B- and T-cell lymphomas, myeloma, adult T-cell lymphoma/leukemia, Waldenström macroglobulinemia, angioimmunoblastic lymphadenopathy, Hairy cell leukemia
Cancer, solid tumors/carcinomas	Lung, colon, renal, breast, prostate, head and neck squamous cell carcinoma, nasopharyngeal carcinoma, Barrett esophagus

From (7, 13, 32, 33, 63–81, 94, 95).
eNOS, endothelial nitric oxide synthetase; MHC, major histocompatibility complex.

Loxoscelism) lead to activation of neutrophils and abnormal neutrophil diapedesis, 2 factors that may be common denominators in pathogenesis of neutrophil-associated small vessel vasculitis.[126] Other morphologic patterns of inflammatory vessel injury (vasculitis) exist, which include lymphocytic endarteritis and endarteritis obliterans of transplant vascular rejection (so-called transplant endarteritis and sclerosing transplant vasculopathy). This form of inflammatory vascular injury is not typically associated with abundant fibrin deposits and destruction of the vessel wall with loss of the elastic lamina,[127,128] and therefore would not be considered by some to represent vasculitis as the inflammation is not transmural and the histology can overlap with vaso-occlusive disorders such as the antiphospolipid antibody syndrome. Nonetheless, this morphology is similar to the life history described for arterial lesions of Sneddon syndrome, which appear to be initially lymphocyte mediated (lymphocytic endothelialitis)[47] or due to the effects of toxic oil syndrome, a secondary form of vascular injury that has an immune component.[129] Confounding the pathogenic evaluation of vasculitis is the fact that an interval of minutes to days between the vascular insult and a clinically recognizable skin lesion can exist. During this time, varied responses may reduce, enhance, or modify the vascular response.[108] The characteristics of the initial insult can be lost in these subsequent events, which likely represent a final common morphologic pathway where transformation from active, acute inflammatory lesions evolves into older, often sclerotic, lesions where T cells and macrophages predominate.[115] Therefore, early vasculitic lesions, 12 to 48 hours old, must be sampled to identify the primary pathogenic event(s). Although non-immunologic factors such as direct infection of endothelial cells can cause vasculitis, most vasculitic lesions are mediated by immunopathogenic mechanisms. These mechanisms can be classified into 4 basic types of hypersensitivity reactions per Coombs and Gell.[130] Specifically, vasculitis can be pathogenically termed (1) allergic vasculitis, (2) antibody-mediated vasculitis, (3) immune complex (IC)-mediated vasculitis, and (4) T-cell mediated hypersensitivity vasculitis. Other immunopathologic mechanisms such as antibody neutralization (eg, activation/deactivation of endothelial cell function by antibody binding), granulomatous inflammation resulting from non-immune mechanisms, and T-cell mediated cytotoxic reactions may also cause some forms of vasculitis.[131] However, the majority of cutaneous lesions of vasculitis are likely due to IC deposition/type III hypersensitivity reactions as approximately 81% (range 54%–100%) of direct immunofluorescence exams (DIF) are positive for vessel wall immunoglobulin and/or complement deposition (Fig. 18).[13,67,74,75,77,81,84–88,132–134] For some cases of IC-mediated vasculitis, a remote pathogenic event such as viral infection (eg, hepatitis C) may have triggered a

TABLE 4. Frequency of Etiologic Factors and Associated Diseases in Patients Presenting With Cutaneous Vasculitis Along With Incidence

	Frequency* Mean%, Range	Incidence† Median Rate, Range (regions studied)
Idiopathic vasculitis (CLA)‡	39.0%, 3–72%	$15.4/10^6$–$29.7/10^6$ (Norwich, England/Lugo, Spain)§
Henoch-Schönlein purpura (HSP)	10.1%, 0–88%	$13.0/10^6$–$14.3/10^6$ (Norwich, England/Lugo, Spain)
Primary systemic vasculitis	4.4%, 0–13%	$19.8/10^6$ (Norwich, England)
Wegener Granulomatosis (WG)	1.1%, 0–6%	$4.9/10^6$ (Lugo, Spain), $0.5/10^6$–$15.0/10^6$ (Bath/Bristol, England/Northern Norway)
Polyarteritis nodosa (PAN)	2.5%, 0–10%	$7.0/10^6$ (Olmsted County, Minnesota), $2.0/10^6$–$77/10^6$ (Michigan/Alaska)
Churg-Strauss syndrome (CSS)	0.6%, 0–8%	$2.4/10^6$ (Norwich, England), $1.1/10^6$–4.010^6 (Lugo, Spain/Olmsted county, Minnesota)
Giant cell arteritis (GCA)	0.1%, 0–2%	$10.2/10^5$ (Lugo, Spain), 0.1–$27/10^5$ (Japan/northern India/Iceland)
Microscopic polyangiitis (MPA)	≤1%¶	$8.0/10^6$ (Norwich, England), $0.5/10^6$–$24/10^6$ (Leicester, England/Kuwait)
Connective tissue disease (CTD)	11.7%, 0–44%	
Systemic lupus erythematosus (SLE)	3.5%, 0–19%	$5.3/10^6$ (Lugo, Spain)
Rheumatoid arthritis (RA)	5.2%, 0–20%	$7.9/10^6$ (Norwich, England 2004), $6.0/10^6$–$12.5/10^6$ (Norwich, England 1994/Lugo, Spain)
Sjögren syndrome (SS)	1.3%, 0–25%	
Other systemic disorders	2%, 0–15%	
Behçet disease (BD)	0.6%, 0–3%	
Sarcoidosis	0.2%, 0–2%	
Inflammatory Bowel disease	0.7%, 0–8%	
Cryoglobulinemic vasculitis (CV)	2.9%, 0–28%	$4.8/10^6$ (Lugo, Spain)
Infections (mostly upper respiratory tract)	22.5%, 0–62%	
Viral hepatitis	3.1%, 0–22%	
Strepococcus sp	2.1%, 0–28%	
Septicemia/severe bacterial infections	1.2%, 0–11%	
Drugs	20.1%, 0–69%	
Malignancy	4.3%, 0–16%	

*Pooled data (n = 2161) from studies (13, 33, 63–90) examining for triggering factors and/or associated conditions in patients, mostly adults, presenting with cutaneous vasculitis.
†Rates and ranges derived from Gonzalez-Gay & Garcia-Porrua,[93] Watts & Scott[92] and Watts et al.[106] Rates are dependent on period and population studied.
‡Many of these case would be termed hypersensitivity vasculitis per ACR or cutaneous leukocytoclastic angiitis (CLA) per CHCC criteria.
§Per criteria of ACR for hypersensitivity vasculitis.
¶From Watts et al[79]; cases of MPA would have fallen under the diagnosis of PAN per ACR criteria.

persistent B-lymphocyte proliferation that culminates in the production of auto-antibodies, cryoglobulins, and IC.[135,136]

Direct Infection of Vessels

Some intracellular infectious agents directly infect endothelial cells triggering vasculitic lesions. Rickettsial organisms and herpesviridae are 2 of the best-documented examples.[137–142] In these cases, endothelial cells may be directly lysed through active replication or be the target of immune-mediated cytotoxicity.[43] One theory of the sequence of events for the formation of tache noire (eschar) consists of the following: (1) inoculation of *R. conorii* into the dermis of a non-immune individual by tick bite; (2) entry, proliferation, and spread of rickettsiae to contiguous endothelial cells in the dermis; (3) rickettsial injury to vascular endothelium; (4) consequent increased vascular permeability and dermal edema; and (5) variable occurrence of ischemic necrosis of the epidermis and dermis, possibly due to reduced blood flow caused by intradermal edema compressing the microcirculation.[138] Endothelial swelling with secondary luminal occlusion could also account for ischemic necrosis.

Type I Allergic or Anaphylactic Reactions

Elevated IgE levels and both tissue and blood eosinophilia are found in patients with CSS.[143–145] In the vasculitic phase of CSS, many cases do not show a classic necrotizing, neutrophilic vasculitis, but rather an angiocentric infiltration of vessel walls by eosinophils (Fig. 19).[145] This is similar to the histology of eosinophilic vasculitis, a recently described entity that is associated with CTD, hypocomplementemia, and decreased tissue mast cells. In eosinophilic vasculitis, wall destruction appears related to deposition of cytotoxic eosinophil granule major basic protein (MBP), implicating eosinophils as the mediators of vascular damage. The decrease in mast cells suggests also that mast cell degranulation occurs.[146] Vascular adhesion molecule 1 (VCAM-1) expression by activated endothelial cells and very late antigen-4 expression by adhering eosinophils distinguishes this form of vasculitis from type III/IC-mediated vasculitis where E-selectin expression, IC, nuclear debris, and neutrophils are evident.[147] Like most forms of type I allergic or anaphylactic reactions, an antigenic trigger such as inhalation of foreign particles has been reported in cases of CSS.[148]

Type II Antibody-Mediated Cytolytic/Cytotoxic Reactions

The correlation of c-ANCA and p-ANCA with WG and MPA, respectively, and disease activity implicate ANCA in the pathogenesis of these vasculitides,[149] and a direct causal link

TABLE 5. Pathogenic Mechanisms Implicated in Cutaneous Vasculitis

Pathogenic Mechanism*	Vasculitic Syndrome	Vasculitis Pattern	In Situ Blood Vessel	Serologic Studies	References
Direct infection	Rickettsial infections	Lymphocytic small vessel	Intra-endothelial *Rickettsia* species, T cells	IgG to Rickettsia species	(138, 255–257)
Type I Anaphylactic	Eosinophilic vasculitis	Eosinophilic small vessel	MBP, ICAM, ↓ mast cells/tryptase	↑ Eos, ↑ MBP, ↓ Neut, ↑ ESR, ↓ C	(146, 147)
	Churg-Strauss Syndrome (CSS)	Eosin-/neutrophilic mostly small and medium	ECP, ↑ Eos, ExGr with eosinophilic necrosis	↑ Eos, ↑ IgE, p-ANCA, ↑ ESR, ↑ IFN-α, ↑ IL-2	(145, 258–260)
Type II Cytotoxic-cytolytic antibody	Wegener granulomatosis (WG)	Neutrophilic mostly small and medium	ExGr with basophilic necrosis, CD4+CD25-	cANCA, ↑ ESR, ↑ WBC, ↑ CRP, ↑IFN-α, ↑ IL-2, lymphopenia, ↑ CD4+CD25+	(151, 258, 261–263)
	Microscopic polyangiitis (MPA)	Neutrophilic mostly small and medium	No ExGr, CD4+CD25-	pANCA, lymphopenia, ↑ CD4+CD25+	(144, 151, 264)
Type III Immune complex	Henoch-Schönlein Purpura (HSP)	Neutrophilic small vessel	IgA IC, MAC	↑ IgA	(189)
	Cutaneous leukocytoclastic angiitis (CLA/LCV/ hypersensitivity vasculitis)	Neutrophilic small vessel	IC, MAC, NE, ICAM-1, E-selectin, VLA	↓ C, ↑ , IΛ−1β, ↑ IL-2, ↑ Il-2r, ↑ IL-8, ↑ TNΦ-α, ↑ VEGF	(86, 88, 170–172, 179, 265)
	Cryoglobulinemic vasculitis (CV)	Neutrophilic mostly small and medium	IgG-mRF immune deposits	↓ C, Hepatitis C virus, ↑ Cryocrit	(266)
	Polyarteritis nodosa (PAN)	Neutrophilic medium	IC, MAC, E-selectin, ICAM	↓ C, Hepatitis B virus, ↑ IFN-α, ↑ IL-2	(174, 188, 258, 267)
Type IV Delayed hypersensitivity	Giant cell arteritis (GCA)	Granulomatous medium vessel	↑ CD3+/CD4+, ↑ activated CD68+, IL-1b, VEGF, PDGF, IL-2, IFN-γ	↓ CD3+/CD8+, ↑ activated CD68+, Il-1β, TNFα, IL-6	(193)
	Chronic graft-vs.-host disease	Lymphocytic small vessel†	↓ microvessel density, CD8+, GMP-17, Granzyme B	↑ vWF	(204, 205, 211)
	Sneddon Syndrome	Lymphocytic medium vessel†/endarteritis obliterans	T-cells, ↑ SMC, ↑ collagen	AECA	(47, 268, 269)

Adapted from Schmitt and Gross[270] and Jennette.[271]
*Coombs and Gell classification[130].
†Endothelialitis.
ANCA, antineutrophil cytoplasmic antibodies; pANCA, perinuclear and cANCA-cytoplasmic; AECA, antiendothelial antibodies; CRP, C-reactive protein; EBV, Epstein-Barr virus; ECP, eosinophilic cationic protein; Eos, eosinophils; ESR, erythrocyte sedimentation rate; ExGr, extravascular granulomas; GMP-17, granule membrane protein 17, marker of activated effector cytotoxic T cells; IC, immune complexes; MAC, membrane attack complex, C5b-9; MBP, major basic protein; MRF, monoclonal rheumatoid factor; Neut, neutrophils; NE, neutrophil elastase; SMC, smooth muscle cells; VEGF, vascular endothelial growth factor; VLA, very late activation antigen; vWF, von Willebrand factor.

between ANCA and the development of glomerulonephritis and vasculitis has been demonstrated in an experimental model: passive transfer of ANCA was sufficient to induce disease in mice.[150] Lymphopenia and persistent activation of CD4 T cells (CD25+) may play a role in the development of ANCA and ANCA-associated vasculitis.[151] ANCA are believed to activate neutrophils and endothelial cells as well as induce accelerated neutrophil apoptosis leading to release of proinflammatory cytokines that maintain and amplify and inflammation. In addition, release of degradative enzymes and reactive oxygen species leads to tissue destruction.[43]

Anti-endothelial cell antibodies (AECA) are also suspected to cause vasculitis and are capable of direct, complement- and antibody directed cell-mediated cytotoxicity.[43,152] AECA levels also correlate with disease activity.[152] AECA have specificity for distinct vascular regions: AECA found in Behçet preferentially react with small vessel endothelial cells whereas AECA from Takaysu's react with large vessel endothelial cells.[152] However, AECA are not suspected to be a primary factor in vasculitis as they are heterogeneous, mostly uncharacterized, and suspected to develop secondarily to inflammation and antigen modification.[43,153]

Type III Immune-Complex Reactions

The classical experimental model for IC-mediated injury is the Arthus reaction.[154] In the rabbit model of serum sickness, repeated injections of heterologous proteins results in antigen-antibody complexes (IC) and vasculitis when the

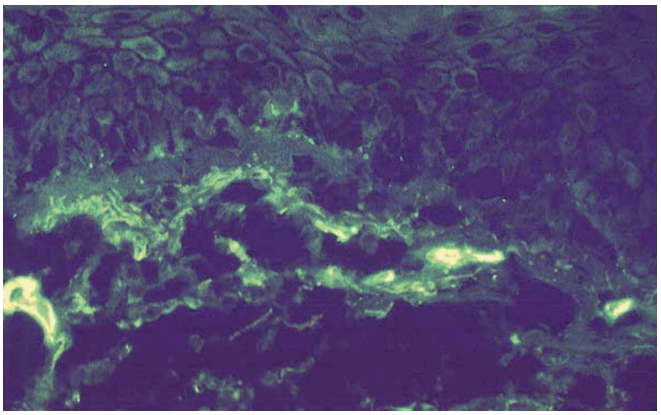

FIGURE 18. Complement deposition, C3, is one of the most frequent immunoreactants identified in small vessel cutaneous vasculitis, and it persists the longest, found in lesions more than 72 hours old.

antigen is in excess.[155] Optimal factors for vasculitis exist and consist of the size of IC (intermediate or small),[156] net charge (cationic/positive),[157] and rate of clearance (decreased), the latter of which is dependent on the immunoglobulin Fc receptor status.[158,159] Deposition of IC results in complement activation and release of anaphylotoxins C3a and C5a that recruit inflammatory cells.[160] Accumulation of neutrophils and mast cells is necessary for the progression of IC-mediated vascular damage.[161–167] The infiltration of vessel walls and the consequent vessel injury associated with IC-mediated vasculitis is highly regulated by adhesion molecules[166,168,169]; the absence of intracellular adhesion molecule 1 (ICAM-1), P-selectin, E-selectin, and/or P-selectin glycoprotein ligand leads to significant decreases in neutrophil infiltration, edema, and hemorrhage. In humans, expression of these adhesion molecules has been demonstrated in sites of vasculitis.[112,170–176]

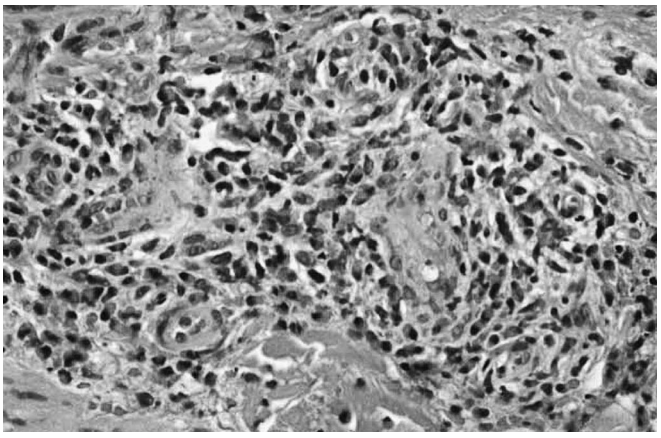

FIGURE 19. Eosinophilic vasculitis, as identified in Churg-Strauss syndrome or associated with connective tissue disease exhibits marked angiocentric infiltrates of eosinophils associated with eosinophilic degranulation. Fibrin deposits are typically not abundant; none are identified in this case, but the endothelial cells are swollen, occluding the lumen allowing a diagnosis of vasculitis.

Induction and upregulation of these adhesion molecules can occur due to complement activation products (C1q)[177] and cytokines (IL-1β, Il-2, IL-6, IL-8, tumor necrosis factor–alpha (TNF-α), and interferon-γ (INF-γ) produced by activated lymphocytes and macrophages.[177–179]

In most cases of cutaneous vasculitis, vascular immunoglobulin (IgM> IgA> IgG) and/or complement deposition (C3) are found by DIF examination (mean 81%, range 58%–100%) implicating IC deposition in its pathogenesis.[13,63,70,74,75,77,81,85,180,181] In addition, vascular immunoglobulin and complement deposition can also be found in the vessels of non-lesional skin (mean 78%, range 54%–86%)[81,88,182–184] indicating that immunoreactant deposition is not an event secondary to vessel damage, but of primary significance. This finding is supported by studies of histamine-induced vasculitis where immunoreactants preceded vessel wall inflammation.[181,185] IC are formed during periods of antigen excess when there is overwhelming infection or tissue destruction or there is insufficient antibody to solubilize the antigens, which circulate until some event (decreased blood flow at vessel bifurcations or release of vaso-active compounds) occurs causing deposition their in blood vessel walls.[186] When deposited in vessels, IC are typically located in post capillary venules, which are more susceptible to injury because of low oxygen content, slow blood flow, and stasis.[176,187] Deposition of IC leads to adhesion molecule expression (ie, E-selectin) and complement pathway activation with formation C3a and C5a chemotactic factors that attract neutrophils and basophils and deposition of terminal complement components.[108,186] Adhesion molecules interact in a sequential fashion where neutrophils first roll, are arrested, and then firmly adhere to the vessel wall enabling migration outside the vessel wall. Release of proteolytic enzymes, especially collagenases and elastases, along with free oxygen radicals, damage the vessel walls and the surrounding tissues. The membrane attack complex, C5b-9, the final product of the complement activation cascade has been found in the majority of lesions of CLA (mean 84%), HSP (73%), and PAN (82%) indicating that it plays a significant role in endothelial cell damage found in IC vasculitis[86,88,180,188,189]; by direct insertion into the endothelial cell membrane, the membrane attack complex releases an array of growth factors and cytokines that lead to thrombosis, inflammation, and neoangiogenesis.[190,191]

Type IV Cell-Mediated Hypersensitivity Reactions

The severe clinical consequences of granulomatous arteritis are suspected to be directly related to luminal vessel occlusion that results from a maladaptive response-to-injury of the blood vessel wall due to immunologic attack. Granulomatous arteritis is characterized by the presence of vessel wall infiltrates induced by Th1 lymphocytes that initiate the migration of clonally expanded INF-γ producing T cells into the adventitia where an unknown antigen is suspected to reside.[192,193] In neovessels of the adventia and within the granulomatous inflammation at the intima-media junction, adhesion molecule expression occurs pointing to inflammation starting in the adventia's vaso vasorum rather than arriving via the vessel lumen.[173] INF-γ expression leads recruitment and

activation of macrophages, which destroy arterial elastic tissue. The production of other factors promoting neoangiogenesis and proliferation of medial and intimal cells are responsible for luminal obliteration (endarteritis obliterans) and the ischemic manifestations of the disease. The balance of cytokine production based on the state of differentiation of T cells and macrophages is believed to underlie the varied clinical and pathologic manifestations of GCA.[193] For instance, GCA with ischemic manifestations is associated with presence of multinucleated giant cells producing high levels of interleukin 1beta (IL-1β), vascular endothelial growth factor (VEGF), and platelet-derived growth (PDGF), T cells producing high levels of interferon-gamma (IFN-γ) and low levels of interleukin-2 (IL-2), and lumen occlusive intimal hyperplasia. In contrast, GCA with fever, malaise, wasting, and no ischemic complications exhibits a non-stenosing panarteritis without multinucleated giant cells in lesional tissue and low levels of IL-1β, VEGF, PDGF, and IFN-γ.

Superantigen-Induced T-Cell Responses

Superantigens are microbial products that activate polyclonal T lymphocytes bearing a specific V-beta segment of the T-cell receptor, and are also suspected to play a role in the arteritis and vascular injury of Kawasaki disease, WG, and GCA.[194–199] Indeed, chronic nasal carriage of *Staphylococcus aureus* has been associated with higher rates of relapses in WG, favoring the hypothesis that bacterial antigens play a role in WG, at least with disease flares.[104] Experimental proof of this pathogenic mechanism was demonstrated in a rabbit ear model where repeated injections of streptococcal erythrogenic toxins produced chronic-type arteritis characteristic of lymphocytic infiltration found in Kawasaki disease.[200] In contrast, injections of human serum albumin in immunized rabbits produced neutrophilic-leukocytoclastic vasculitis of both medium and small vessels similar to PAN and CLA, respectively.

Cell-Mediated Cytotoxicity

Most of the evidence supporting the existence of skin lymphocyte-mediated vasculitis is based on transplantation studies.[201–206] In the experimental skin allograft rejection model, microvascular damage preceded significant epidermal necrosis and affected initially and primarily those venules and arterioles enveloped by T lymphocytes indicating that the vasculature is the critical target of the immune response leading to ischemic damage.[202,203] Notably, lymphocyte inflammation was also directed at the epidermis; in most examples of clinical histologic small vessel lymphocytic vasculitis, such as perniosis, an interface dermatitis is also part of the inflammatory reaction.[61,207] In clinical studies of lymphocytic small vasculitis, endothelial and keratinocytic expression of ICAM-1 and CD11a (lymphocyte function associated antigen-1) was detected,[170] and suggests that in entities where lymphocytic vasculitis occurs a common antigen exists in both the keratinocytes and endothelium (Fig. 16). For allograft transplantation rejection of solid organs, endothelial cells are one of the principal targets of alloreactive cytotoxic T cells,[208] and these cytotoxic cells can produce an endothelialitis/intimal arteritis resulting in severe acute rejection.[209] Chronic rejection is denoted by progressive vascular occlusion followed by replacement fibrosis of the parenchyma.[210] Granzyme B is suspected to play a role in endothelial cell death with resultant luminal narrowing.[211] In allogenic stem cell transplants, arterial lesions similar to that of solid organ rejection[206] and vascular injury mediated by cytotoxic T cells[205] and associated with nuclear dust and fibrin[204] has been described; histologic evidence of lymphocytic vasculitis. Diminishment of the vascular bed leads to replacement fibrosis that ultimately results in sclerodermoid graft versus host disease.[205] Scleroderma patients have circulating lymphocytes that are cytotoxic to endothelial cells *in vitro* implicating similar pathway to dermal sclerosis.[212]

Vascular Intimal Hyperplasia (Endarteritis Obliterans)

Arterial luminal obliteration or endarteritis obliterans is along with aneurysm rupture one of the most drastic consequences of vascular injury, either due to vasculitis or due to vaso-occlusive disorders such as the antiphospholipid syndrome. Endarteritis obliterans is infrequently identified in skin biopsies where its presence signifies primary vascular disease.[213] In cases of suspected vasculitis, entities such as Sneddon syndrome, CTD such as Sjögren syndrome or scleroderma, and Dego disease (malignant atrophic papulosis) are found.[47,213–215] Intimal hyperplasia is the underlying process of endarteritis obliterans where smooth muscle cells of the innermost layer of the arterial wall proliferate and promote turnover of the extracellular matrix, triggered by stimuli such as vessel wall injury, inflammation, and vessel wall stress/stretching.[193,216] Physiologically, intimal hyperplasia results in the closure of the ductus arteriosus and involution of the uterus after pregnancy. Pathologically, it occurs in pulmonary hypertension, atherosclerosis, after angioplasty, in vein grafts, in transplant rejection, in thrombotic disorders, PAN, and GCA. Injury, inflammation, or stretch can initiate extracellular proteases (matrix metalloproteinases, urokinase palsminogen activator) that lead to disruption of smooth muscle-extracellular interactions. Degradation of smooth basement membrane and contact with interstitial matrix components (fibronectin, monomeric types I/II collagen) activates smooth cells. Activated smooth muscle cells migrate, proliferate, and promote turnover of the extracellular matrix. In vasculitis-induced causes of intimal hyperplasia leading to vessel occlusion, macrophage-derived growth factors are key.[193] In inflammatory thrombotic disorders such as Beurger disease (thromboangiitis obliterans) lymphocyte-mediated inflammation is suspected to play an instrumental role in luminal hyperplasia.[217]

Pathogenic Implications for Management of Vasculitis

Increased understanding of the pathogenesis of vasculitis is creating the potential to specifically target and/or monitor the immune responses responsible for vessel damage (targeted therapy).[190,218,219] Knowledge that P-/E-/L-selectins and P-selectin glycoprotein ligand regulate IC-mediated LCV diseases provides a target to block the inflammatory cascade and consequent tissue damage. Byproducts of complement activation and complement regulatory proteins are

potential targets for mechanism-specific drugs to block the inflammatory cascade that initiates vasculitis.[190] In addition, critical mediators of inflammation, such as release of TNF-alpha by macrophages leads to activation of endothelium with expression of adhesion molecules and further release of other pro-inflammatory cytokines (ie, IL-1, Il-6, IL-8) as TNF-alpha is one of the major cytokines of Th1 inflammatory responses. Blockade of TNF-alpha pro-vasculitic effects has shown great promise in the management of systemic vasculitis.[123] In giant cell arteritis, cytokines are encountered in 2 locations, the inflammatory infiltrates accumulating in the arterial wall and in the circulation. Interleukin-6, a cytokine involved in stimulating acute-phase responses, is located upstream of many of the laboratory abnormalities considered helpful in diagnosing and managing giant cell arteritis, including elevated ESR (erythrocyte sedimentation rate) and CRP (C-reactive protein).[220] Interleukin-6 has the potential to be helpful in predicting disease severity as well as detecting disease activity; thus, monitoring its levels may allow for a tailoring of immunosuppressive therapy.[221,222] In addition, interferon-γ has emerged as a key regulator in determining the nature and direction of the inflammatory response and may be critically involved in modulating the process of intimal hyperplasia and subsequent endarteritis obliterans. Therefore, interferon-γ could be the chief target for new therapies.[221] Other therapeutic targets include interferon-α, matrix metalloproteinases, reactive oxygen species, platelet-derived growth factors and vascular endothelial growth factors, the interleukin-10/interleukin-12 balance, interleukin-1/interleukin-1 receptor antagonist, and CTLA-4 and other co-stimulatory molecules.

EVALUATION AND MANAGEMENT OF CUTANEOUS VASCULITIS

Clinical Examination and Review of Systems

Palpable purpura may be the first clinical sign of vasculitis in a patient at risk for life-threatening alveolar hemorrhage, rapidly progressive glomerulonephritis, or a debilitating mononeuritis multiplex. Indeed, up to half of patients presenting with cutaneous LCV can be found to have renal involvement.[37] In assessing the extent of disease, it is important to review for signs and symptoms of visceral or generalized involvement; the Birmingham Vasculitis Activity Score is one tool that can identify patients with concurrent systemic disease.[223,224] Recognition of a localized cutaneous versus systemic vasculitis is important in terms of making the correct diagnosis, prescribing treatment, and arranging appropriate clinical follow-up. (See Table 6).

Biopsy: Histologic and Direct Immunofluorescence Evaluation

Choice of clinical lesions and type of pathologic assessment has great impact on the diagnostic yield of cutaneous biopsies. Firstly, the optimal time for skin biopsy is 24 to 48 hours after the appearance of a vasculitic lesion. If the biopsy is poorly timed, the pathologic features of vasculitis may be absent—a fact that clinicians must bear in mind when interpreting a negative biopsy from a patient whose clinical findings suggest vasculitis. A punch biopsy of a lesion at the appropriate stage ("lesions have life-spans" and therapy affects the histopathologic findings) will enable histologic confirmation of most small vessel vasculitides. Purpuric lesions obtained in the first 24 hours are characterized by fibrin deposits within the vessel wall accompanied by neutrophilic infiltration of the wall and surrounding hemorrhage and nuclear debris. After 24 hours, neutrophils are replaced by lymphocytes and macrophages.[175,225] Biopsy of lesions greater than 48 hours old, regardless of the underlying form of vasculitis, may show lymphocyte-rich infiltrates. Secondly, choice of a shave biopsy, punch biopsy, or excisional biopsy will affect which vessels are examined as the type of vessel is dependent on location within the skin and subcutis (ie, the deeper the location, the larger the vessel). Thus, if a medium vessel vasculitis such as polyarteritis nodosa (PAN) is suspected, the biopsy must include the subcutaneous fat where medium-sized vessels are situated. Incisional biopsy is required for cases affecting larger vessels (nodular vasculitis and giant cell arteritis) (Fig. 1). In the case of livedo reticularis/racemosa, a deep biopsy extending to the subcutis should be taken from the center of the circular livedo segment (the 'white' center, not the 'red' periphery) because this is where the stenosed vessel responsible for the cyanotic periphery is located.[226,227] Thirdly, biopsies should be obtained from non-ulcerated sites, or if not possible, from the edge of an ulcer. Lastly, omission of a biopsy for direct immunofluorescence (DIF) studies wastes an opportunity to collect potentially valuable information and often leads to misdiagnosis.[1] For example, DIF provides the only way of diagnosing HSP (IgA vasculitis). It is best to take 2 biopsies, 1 for light microscopy and 1 for DIF examination, rather than split 1 specimen. In fact, multiple biopsies and extending the biopsy depth to the subcutis and fascia can significantly increase the diagnostic yield for vasculitis.[1,226,228]

Incidental histologic finding of granulomatous arteritis of GCA has been documented in a skin cancer excision.[229] Typically, biopsy of the temporal artery is utilized for diagnosis of GCA; however, temporal arteritis is not restricted to GCA and can been found in patients with WG, MPA, PAN, CV, and rheumatoid vasculitis[230,231]; many of these later vasculitis also show concurrent small vessel involvement (mixed small and medium vessel vasculitis). In patients with suspected systemic vasculitis without obvious cutaneous involvement, but with cephalic symptoms such as headache, scalp tenderness, or jaw claudication, temporal artery biopsy is a simple tool for diagnosis of vasculitis as it is a low-risk and simple procedure. However, histologic findings do not always discriminate between GCA and systemic vasculitis syndromes such as PAN, which can harbor giant cells in the media, so correlation with additional clinical and laboratory data is indicated.[231]

Direct Immunofluorescent Studies

The absence of immune complexes, so-called pauci-immune vasculitis, is the expected finding in WG, CSS, and MPA with or without medium-sized vessel involvement. Deposition of IgG, IgM, IgA, and/or C3 in or around the vessels

TABLE 6. Clinical Assessment and Laboratory Work Up for Extracutaneous (systemic) Vasculitis and Associated Disorders

Signs and Symptoms of Vasculitis		Ancillary Studies
Systemic (generalized) disease	Malaise, myalgia, arthralgia/arthritis, headache, fever, weight loss	Skin biopsy (3 specimens) 1) 4–6-mm punch or excisional biopsy extending to the subcutis for routine histologic examination 2) 4-mm punch biopsy for direct immunofluorescence 3) 4-mm punch biopsy for tissue culture and sensitivity
Mucous membranes and eyes	Oral or genital ulcers, proptosis, conjunctivitis, episcleritis, visual disturbances, uveitis, retinal exudates/hemorrhages	
Ear, nose, and throat disease	Nasal obstruction, bloody nasal discharge, crusting, sinus involvement, new deafness, hoarseness/stridor, subglottic stenosis	Laboratory studies 1) Routine blood tests for full blood count, erythrocyte sedimentation rate, aminotransferases, alkaline phosphatase, albumin, bilirubin, creatinine, blood urea nitrogen, serum electrolytes, and urine analysis 2) Tests for ANCA, antinuclear antibodies (ANA), rheumatoid factor, antidouble-stranded DNA, cryoglobulins, precipitins (Ro, La, RNP, Sm), and complement studies (CH50, C3, C4) 3) Thrombophilia tests for anticardiolipin antibody, lupus anticoagulant (activated partial thromboplastin time, Russell viper venom test), thrombin time, prothrombin time, antigenic and functional antithrombin III, protein C, protein S, factor V Leiden mutation, and serum homocysteine levels 4) Paraproteinemia screens including serum protein electrophoresis, serum protein immunofixation, serum immunoglobulins, and random urine protein immunofixation 5) Viral serologic screens for human immunodeficiency virus and hepatitis B and C 6) ECG, Chest X-ray
Respiratory disease	Persistent cough, dyspnea, wheeze, hemoptysis, pulmonary hemorrhage, nodules, cavities, infiltrates, pleurisy, pleural effusion, respiratory failure	
Genitourinary disease	Hypertension >95 mg Hg diastolic, proteinuria >0.2 g/24 hr, hematuria >10 red blood cells/ml, renal impairment/failure, rise in creatinine >30% or fall in creatinine clearance >25%	
Neurologic disease	Organic confusion/dementia, seizures (not hypertensive), stroke, cord lesion, sensory peripheral neuropathy, cranial nerve palsy, motor mononeuritis multiplex	
Gastrointestinal disease	Severe abdominal pain, bloody diarrhea, intestinal perforation/infarction, acute pancreatitis	

Adapted from Luqmani et al[223] and Mimoune et al.[46]

characterizes IC-mediated vasculitis such as CV and most cases of CLA. In patients presenting with cutaneous vasculitis, up to 100% of patients can be found to have vascular immunoglobulin, complement, and/or fibrinogen immunofluorescence.[13,67,74,75,77,81,84–88,90,132–134,182–184] The most common immunoreactant found in vessels by DIF is C3 (mean 62%, range 8%–93%), followed by IgM (40%, range 0%–100%), IgA (32%, range 0%–82%), and IgG (18%, range 6%–42%).[13,67,74,77,81,84–90,134,182] Notably, some recent studies have demonstrated that IgA rather than IgM is the most frequently identified immunoglobulin in patients with cutaneous vasculitis, up to 82% of LCV cases[13,81,134]; this difference compared with older studies could be attributed to different methodologies, choice of sun-exposed or non-exposed skin,[81,232] or differing populations of cutaneous vasculitis patients. Fibrinogen vascular deposits are also commonly found in 72% (range 41%–100%). Similar to HE evaluation, the presence of diagnostic immunofluorescence patterns is inversely related to the age of the lesion biopsied.[13,90] One hundred percent of biopsies will harbor immunoglobulins within the first 48 hours, 30% will be negative at 48 to 72 hours, and after 72 hours only C3 is detected in positive DIF samples.[13,90] In addition, the type of immunoglobulin and pattern of deposits in DIF exams can add diagnostic value: predominate IgA vascular deposits are found in HSP and point towards renal involvement[81,134]; and basement membrane zone or keratinocyte nuclear (in vivo ANAs) immunoreactants, mostly IgG, can be found in CTDV such as systemic lupus erythematosus. In the evaluation of urticarial vasculitis (UV), the finding of basement membrane zone fluorescence may be seen in patients with hypocomplementemic states and who have CTD (Fig. 20).[1,64,233] In addition, IgM deposition in blood vessels may be readily seen in cases of vasculitis with a circulating rheumatoid factor or with monoclonal production of IgM as found in CV. In CV, IgA deposits are absent and HCV infection can be inferred if IgA is absent in both lesional and perilesional skin.[81]

Laboratory Studies

Active vasculitis is typically associated with an acute phase response with an increase in C-reactive protein, erythrocyte sedimentation rate, and plasma viscosity (Table 6). If no obvious cause or diagnosis is apparent, the

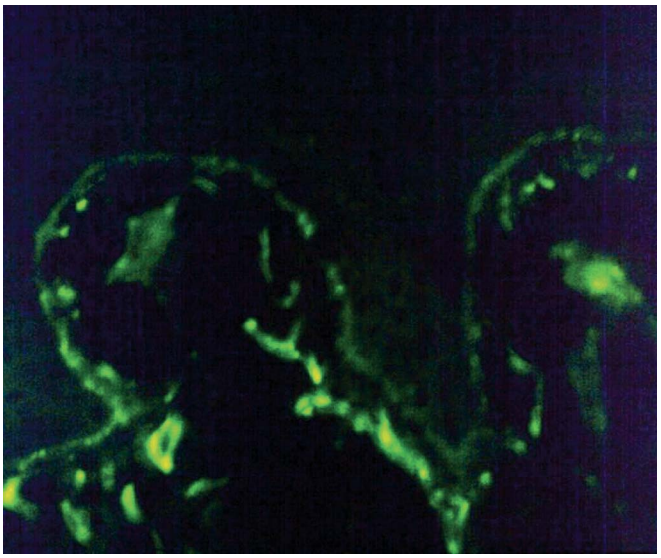

FIGURE 20. Urticarial vasculitis. Direct immunofluorescence examination can add valuable information in the assessment of cutaneous vasculitis patients be showing IGA predominate vascular deposits in Henoch-Schonlein purpura, anti-nuclear antibodies in connective tissue disease patients, or as in this case of urticarial vasculitis exhibiting IgM immunofluorescence of small vessels and the basement membrane zone (dermal-epidermal junction) in a patient determined to have systemic lupus erythematosus.

evaluation of the vasculitis patient should be completed with tests for rheumatoid factor, antinuclear antibodies, anti-dsDNA antibodies, antiprecipitin antibodies (Ro, La, RNP, and Sm), CH50, C3 and C4 levels, cryoglobulins, and ANCAs, as well as performing a chest X-ray and serum and urine electrophoresis. In addition, monitoring of levels of certain cytokines (IL-6, TNF-α), c-ANCA, acute phase reactants (eg, CRP), activated coagulation markers (thrombin-anti-thrombin III complexes), or markers of endothelial function (endothelial microparticles, thrombomodulin) can potentially measure disease activity and response to therapy.[178,220,234–236]

Antineutrophil Cytoplasmic Antibodies

Antineutrophil cytoplasmic antibodies (ANCA) testing has been established as a useful tool for the diagnosis of small vessel vasculitides. ANCAs[237–240] were first described as neutrophilic specific autoantibodies found in rheumatoid arthritis patients, many of whom had rheumatoid vasculitis.[241] ANCA-associated vasculitides include WG, MPA, CSS, and some drug-related vasculitis, but ANCA can be also found in patients with inflammatory bowel disease, CTD, and other chronic inflammatory diseases, some of whom may have vasculitis. Positive ANCA patterns should be separated into p-ANCA and c-ANCA. Perinuclear pattern of ANCA, pANCA, may be seen with myeloperoxidase (MPO) antibodies as well as others (eg, LF- lactoferrin, CG- cathepsin) and is found in MPA and CSS. Cytoplasmic, cANCA, are mostly anti-PR3 (proteinase-3), which is strongly associated with WG. However, the presence of ANCA is not diagnostic of systemic vasculitis as up to 60% of patients with cutaneous LCV can have a positive ANCA and disease limited to their skin,[13] and ANCA are found at low levels in many systemic inflammatory and pulmonary disorders that mimic vasculitis.[242] In this later group, atypical indirect immunofluorescent patterns are present and antibodies to PR-3 and MPO are rare by antigen-specific enzyme-linked immunosorbent assays (ELISAs) testing. In addition, serial testing is recommended because ANCAs can occur transiently in patients with acute parovirus infections.[243] The positive predictive value of ANCA testing by indirect immunofluorescence and ELISA testing for ANCA associated PSV is 79%.[244] Recently, IgA class of ANCA has been frequently detected in cases of erythema elevatum diutinum (EED), a chronic fibrosing variant of CLA[245] as well as in other variants of cutaneous LCV.[246]

Prognosis

The distinction between localized (cutaneous) versus systemic vasculitis is thought to be the most crucial point in determining patient outcome. Depending on the criteria employed such as exclusion of an associated disease or whether systemic involvement exists (ie, CLA versus MPA), or inclusion of all cases demonstrating LCV and/or muscular vessel vasculitis on skin biopsy,[26] patients diagnosed with cutaneous vasculitis can be said to have a benign cutaneous disease with excellent prognosis[33]; or, a systemic disease with prominent cutaneous involvement irrespective of whether clinical evidence exists of visceral involvement.[13] In fact, systemic involvement may be more common than currently appreciated as 43% of patients presenting with cutaneous LCV were found to have renal involvement.[37] The likelihood of progression to systemic disease is thought to be high if serologic evidence of CTD (eg, rheumatoid factor, antinuclear antibody) is present.[247] In addition, even patients with longstanding localized vasculitis such as cutaneous PAN can progress to systemic vasculitis.[247,248]

Based on the review of literature of case-control studies of patients with cutaneous vasculitis (mean mortality of 4%) and clinical experience, cutaneous vasculitis, in our opinion, should be considered a cutaneous disease with potential to progress to life-threatening systemic disorder as a minority of these patients will have internal organ involvement and a few of these patients will die of vasculitis.

On average, the duration of cutaneous lesions of vasculitis histologically diagnosed with LCV is about 28 months, and up to one third of these patients can have disease for 3 years or more.[13] The identification of cryoglobulins, and the presence of arthralgia and/or a normal temperature have been found to be risk factors for chronic cutaneous disease.[13] The presence of ulcers compared with palpable purpura also predicts for persistent and recurrent disease.[101] The risk factors for systemic disease include paresthesia, fever, and absence of painful lesions.[13] In patients with HSP, a history of recent infection, fever, and the spread of purpura to the trunk predict for renal involvement.[249] Similarly, the presence of cutaneous necrosis is stated to be an indicator of systemic disease either due to the manifestations of CTD or to PSU.[79] Histologically, the severity of vessel injury in cutaneous LCV correlates with clinical severity,[69,101] and deep dermal and subcutaneous vasculitis is associated with malignancy and CTD[67]; however,

one study did not find a significant correlation of systemic disease with pattern or severity of cutaneous vasculitis.[80] By DIF, the finding of lesional IgA deposits predicts for the presence of proteinuria/renal involvement.[81,134] Moreover, for these patients with HSP and kidney involvement, the percentage of crescents, the presence of interstitial fibrosis, and the presence of dense sub-epithelial deposits correlated with the risk for chronic renal failure.[250] Other poor prognostic factors in HSP include the presence of nephrotic syndrome, hypertension, decreased factor XIII activity, and renal failure at the outset.[251]

Therapy

As the pathogenic mechanisms for most vasculitides are still being defined, targeted therapy interrupting the vasculitis sequence has not been implemented to date with the exception of TNF blockade in systemic vasculitis.[123] Therefore, management of cutaneous vasculitis is by and large empiric in nature and defined by the principal of do no harm. The foremost reason to treat cutaneous vasculitis is to comfort the patient. For more severe vasculitis, the goal of treatment is to prevent extensive ulceration and infarction, thus, permanent damage of skin and other tissues. Treatment of small vessel neutrophilic vasculitis should follow a therapeutic ladder from safe and cheap (eg, support hose and antihistamines) for non-ulcerative, purpuric lesions to expensive and dangerous (eg, daily pulses of cyclophosamide) for severe systemic disease with ulcers and infarcts.[13,32,252] In cases not associated with systemic involvement or neuropathy, conservative treatment usually leads to good results. If an associated disorder can be identified, management of this disorder may result in abatement or clearing of the vasculitis. For example, hepatitis C-induced mixed cryoglobulinemia treated with IFN-α and antiviral medication (ribavirin) leads to decreased liver inflammation and resolution of the hepatitis C- associated vasculitis. Indeed, suppression of inflammation due to systemic inflammatory disorders such as CTD may reduce both acute and long-term vascular damage.[253] Patients should also be given basic instructions on self care, including diminishing factors known to exacerbate vasculitis such as excessive stress, or heat or cold exposure (in vasculitis caused by cryoglobulins). The bottom line in caring for patients with cutaneous vasculitis is to tailor treatment to disease severity.[254]

CONCLUSION

Vasculitis, inflammation of blood vessels walls, can arise from multiple pathogenic pathways that ultimately result in most cases with the histologic pattern of fibrinoid necrosis. The clinical and pathologic findings of vasculitis are due to the type of vessel affected and site of involvement. The degree of wall destruction leads to variable degrees of hemorrhage, ischemia, or infarction. Cutaneous vasculitis comprises a wide spectrum of overlapping primary and secondary disease entities that are characterized by predominant skin involvement and varying degrees of systemic manifestations. Biopsy confirmation of cutaneous vasculitis is crucial in confirming the diagnosis and separating true vasculitis from its mimics. The majority of cutaneous vasculitis cases will show neutrophilic small vessel vasculitis (leukocytoclastic vasculitis); however, some cases of cutaneous vasculitis will be identified by a predominate lymphocytic infiltrate (lymphocytic vasculitis), the finding of the healed scar of arteritis, or signs of chronic vessel damage in the form of endarteritis obliterans. In addition, extravascular histologic clues exist that point to the presence of a specific entity (patterned fibrosis in erythema elevatum dinutum) or the existence of systemic disease (deep small vessel and/or muscular vessel involvement). This information coupled with direct immunofluorescence data and a thorough history and physical examination and laboratory work-up that includes ANCA testing can lead to specific diagnosis, and ultimately more effective treatment.

RESOURCES AND GENERAL INFLAMMATION ON SYSTEMIC VASCULITIS

http://vasculitis.med.jhu.edu John Hopkins Vasculitis Center

www.vasculitis.org European Vasculitis Study Group

www.clevelandclinic.org/arthritis/vasculitis/default.htm Cleveland Clinic Center for Vasculitis

www.vascularite.com Groupe Français d'Etude des Vascularites

www2.ccf.org/inssys/default.htm International Network for the Study of Vasculitis

www.rheumatology.org American College of Rheumatology

www.wgassociation.org Wegener's Granulomatosis Association

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