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The role of pathology in the diagnosis of systemic vasculitis

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ABSTRACT

Pathologic processes are underlying defining features of systemic vasculitis. When these pathologic processes can not be observed directly, surrogate signs and symptoms of disease must be used to conclude that vasculitis is present in a patient and, if so, to determine what specific type of vasculitis is present. This review briefly describes the most defining pathologic features of giant cell arteritis, Takayasu arteritis, polyarteritis nodosa, Henoch-Schönlein purpura, cryoglobulinemic vasculitis, Kawasaki disease, microscopic polyangiitis, Wegener's granulomatosis and Churg-Strauss syndrome; and discusses how these pathologic features can be integrated with clinical and laboratory data to reach an actionable diagnosis.

Introduction

Pathologic demonstration of inflammation in vessel walls is the most definitive method for making a diagnosis of vasculitis. However, the lesions may not be specific for a specific form of vasculitis. Nevertheless, the pathologic identification of certain patterns of vasculitis can be extremely useful for reaching the most appropriate diagnosis. In this brief review, the pathologic lesions observed in a number of systemic vasculitides will be described and their value in differential diagnosis discussed.

Reaching a diagnosis is a complex process that involves the evaluation of signs and symptoms not only to identify the most likely diagnosis but also to rule out alternative diagnostic possibilities. Direct observation of pathologic lesions may not be possible. However, even when not directly observable, a pathologic lesion may be the critical defining feature of a disease whose presence is documented by surrogate clinical or laboratory findings. For example, the defining feature of a myocardial infarction is ischemic myocardial coagulative necrosis; however, histologic confirmation is not required to fulfill acceptable diagnostic criteria for myocardial infarction. Likewise, the defining lesion of vasculitis is inflammation of blood vessels; however, compelling symptoms and signs other than direct pathologic examination can provide adequate evidence for a particular form of vasculitis to allow an actionable diagnosis.

Requirements for making a diagnosis are 1) a name for the disease (the diagnosis), 2) a definition of the disease (which often refers to distinctive pathology), and 3) diagnostic criteria for concluding that the disease fulfills the accepted definition for that disease. The nomenclature and definitions of vasculitis proposed by the Chapel Hill Consensus Conference on the Nomenclature of Systemic Vasculitis (1) will be used in this review. There are no widely accepted diagnostic criteria designed to discriminate among the major forms of vasculitis. Criteria have been developed for the classification of vasculitis patients into groups for clinical trials (2, 3) and epidemiologic studies (4), but these classification criteria are not appropriate for diagnosis of specific patients.

Systemic vasculitis can be classified as: 1) large vessel vasculitis (LVV) causing chronic granulomatous inflammation predominantly of the aorta and its major branches, 2) medium-sized vessel vasculitis (MVV) causing necrotizing inflammation predominantly of mid-sized arteries, and 3) small vessel vasculitis (SVV) causing cause necrotizing inflammation of predominantly capillaries, venules, arterioles and small arteries (Table I; Fig. 1) (1).

Large vessel vasculitis

Giant cell arteritis (GCA) and Takayasu arteritis (TA) are the two major forms of large vessel vasculitis. These categories of vasculitis can not be confidently distinguished by pathology alone. The most distinguishing criterion is the age of the patient at onset, with GCA rarely occurring before age 50 and the TA rarely after 50 (1).

Giant cell arteritis

GCA also has been called temporal arteritis, but this is not the preferred term because all patients with GCA do not have temporal artery involvement and many other forms of vasculitis affect the temporal arteries (1, 5). The inflam-

Table I. Nomenclature and definitions of vasculitis proposed by the Chapel Hill Consensus Conference on the Nomenclature of Systemic Vasculitis (Modified from reference 1 with permission).

	LARGE VESSEL VASCULITIS*
Giant cell arteritis	Granulomatous arteritis of the aorta and its major branches, with a predilection for the extracranial branches of the carotid artery. *Often involves the temporal artery. Usually occurs in patients older than 50 and often is associated with polymyalgia rheumatica.*
Takayasu arteritis	Granulomatous inflammation of the aorta and its major branches. *Usually occurs in patients younger than 50.*
	MEDIUM-SIZED VESSEL VASCULITIS*
Polyarteritis nodosa	Necrotizing inflammation of medium-sized or small arteries without glomerulonephritis or vasculitis in arterioles, capillaries or venules.
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's granulomatosis	Granulomatous inflammation involving the respiratory tract, and necrotizing vasculitis affecting small to medium-sized vessels, e.g. capillaries, venules, arterioles, and arteries. *Necrotizing glomerulonephritis is common.*
Churg-Strauss syndrome	Eosinophil-rich and granulomatous inflammation involving the respiratory tract and necrotizing vasculitis affecting small to medium-sized vessels, and associated with asthma and blood eosinophilia
Microscopic polyangiitis	Necrotizing vasculitis with few or no immune deposits affecting small vessels, i.e. capillaries, venules, or arterioles. *Necrotizing arteritis involving small and medium-sized arteries may be present. Necrotizing glomerulonephritis is very common. Pulmonary capillaritis often occurs.*
Henoch-Schönlein purpura	Vasculitis with IgA-dominant immune deposits affecting small vessels, i.e. capillaries, venules, or arterioles. *Typically involves skin, gut and glomeruli, and is associated with arthralgias or arthritis.*
Cryoglobulinemic vasculitis	Vasculitis with cryoglobulin immune deposits affecting small vessels, i.e. capillaries, venules, or arterioles, and associated with cryoglobulins in serum. *Skin and glomeruli are often involved.*
Cutaneous leukocytoclastic angiitis	Isolated cutaneous leukocytoclastic angiitis without systemic vasculitis or glomerulonephritis.

*Large artery refers to the aorta and major branches directed toward body regions (e.g., to the extremities and the head); medium-sized artery refers to main visceral arteries (e.g. renal, hepatic, coronary and mesenteric arteries), and small artery refers to distal arterial radicals that connect with arterioles. Small vessels include small arteries, arterioles, venules and capillaries.

mation has a predilection for the aorta and its major branches, especially the extracranial branches of the carotid artery. Fully developed lesions affect the adventitia, media and intima (Fig. 2A) (6). The lesions are segmental, which complicates pathologic diagnosis by biopsy. The inflammatory infiltrate consists primarily of monocytes, macrophages and lymphocytes, often with a granulomatous appearance. Multinucleated giant cells are often but not always present. The internal elastic lamina frequently is fragmented (Fig. 2A), and multinucleated giant cells often accumulate around this disrupted elastica. Fibrinoid necrosis is absent or inconspicuous. Extensive fibrinoid necrosis should raise the possibility of another form of vasculitis, including polyarteritis nodosa, microscopic polyangiitis, or Wegener's granulomatosis. Clinical evidence for LVV includes signs and symptoms of ischemia affecting the head or extremities and imaging of the aorta or its major arterial branches showing focal narrowing or occlusion.

Temporal artery biopsy is a common source of specimens for confirming or supporting a diagnosis of GCA. The length of biopsy specimens affects the likelihood that useful information will be obtained. Although 3 cm has been advocated by many, specimen at least 0.5 cm long may be as likely to provide useful information (7). A definitive pathologic diagnosis is possible in only 10-20% of temporal artery biopsies (7-9). This is influenced by the anti-inflammatory treatment the patient has received, the clinical activity of disease at the time of biopsy, and the diligence of pathologic evaluation (9).

Takayasu arteritis

TA is granulomatous inflammation of the aorta and its major branches that almost always occurs in patients younger than 50 years old. TA has a predilection for elastic arteries, including the aorta and the pulmonary arteries. The earliest pathologic changes are focal inflammation and necrosis in the media, with later extension into the adventitia and intima (6, 10). The inflammatory cell infiltrates are composed predominantly of lymphocytes, monocyte and macrophages. As in GCA, multinucleated giant cells are often but not always present. In elastic arteries, the inflammation causes focal disruption of the elastic fibers in the media (Fig. 2B). In advanced stages of the disease, the injury transforms into fibrosis with little or no inflammation.

A classification system for childhood vasculitis proposes classification criteria for TA that include angiographic abnormalities of the aorta or its main branches plus at least one of the following features: decreased peripheral artery pulses or extremity claudication, blood pressure difference >10 mm Hg between extremities, bruits over the aorta or major branches, or hypertension (2). Pathologic confirmation is not required, in part because the involved arteries usually are not amenable to biopsy. Pathologic confirmation usually occurs only when surgical intervention is required to improve vascular perfusion and a diseased segment of artery or aorta is removed. However, the clinical criteria are in essence surrogate

markers for the vascular inflammatory injury, which is the defining feature of TA.

Medium-sized vessel vasculitis

Polyarteritis nodosa (PAN) and Kawasaki disease (KD) are the two major forms of MVV, which is necrotizing vasculitis affecting arteries (1). Zeek (11), Goodman and Churg (12) and other pathologists recognized that patients with necrotizing arteritis fall into two broad categories: those with necrotizing vasculitis confined to arteries versus those with vasculitis affecting not only arteries but also vessels smaller than arteries, including venules and capillaries. The former includes PAN and KD, and the latter includes a multiple forms of SVV.

Polyarteritis nodosa

The pathologic hallmarks of PAN are transmural fibrinoid necrosis and inflammation (Fig. 2C), which initially is composed predominantly of neutrophils, but later has predominantly monocytes, macrophages and lymphocytes. This necrotizing inflammation may result in aneurysms (actually pseudoaneurysms), which causes the arterial nodules that prompted the term "nodosa". In biopsy specimens, for example from skin, peripheral nerves, skeletal muscle or kidney, arteritis in the arteries that are sampled does not allow differentiation between a MVV (e.g. PAN) versus a SVV (e.g. microscopic polyangiitis) because these are small arteries that can be affected by MVV or SVV. A diagnosis of PAN should be made only after a reasonable search for clinical and pathologic evidence for SVV is negative, including no evidence for glomerulonephritis or pulmonary capillaritis (Table II) (13, 14). Serologic evidence for hepatitis B or angiographic evidence for aneurysms supports a diagnosis of PAN; however, PAN definitely occurs in the absence of hepatitis (15).

Kawasaki disease arteritis

The other major necrotizing MVV occurs in KD, which is a febrile illness of childhood that usually occurs before 5 year of age. The most definitive feature is the mucocutaneous lymph node syndrome, which includes fever, erythematous rash, oropharyngeal erythema, redness or fissuring of the lips, indurative edema of the extremities, desquamation, conjunctivitis, and nonsuppurative lymphadenopathy. A classification system for childhood vasculitis proposes the following criteria: fever persisting for at least five days (mandatory criterion) plus four of the following five features (unless coronary artery involvement is documented which requires fewer criteria): desquamation in peripheral extremities or perianal region, polymorphous exanthema, conjunctival injection, changes in the oral or pharyngeal muc-osa, and cervical lymphadenopathy (2). However, many patients with KD who have clear evidence for coronary artery arteritis do not manifest all of the features of the mucocutaneous lymph node syndrome (16).

Necrotizing arteritis is a frequent component of KD (17). Pathologically, compared to PAN, the arteritis of KD has less fibrinoid necrosis and more medial edema (Fig. 2D). In addition, even in the acute phase, KD arteritis has a predominance of monocyte and macrophages rather than neutrophils in the inflammatory infiltrates.

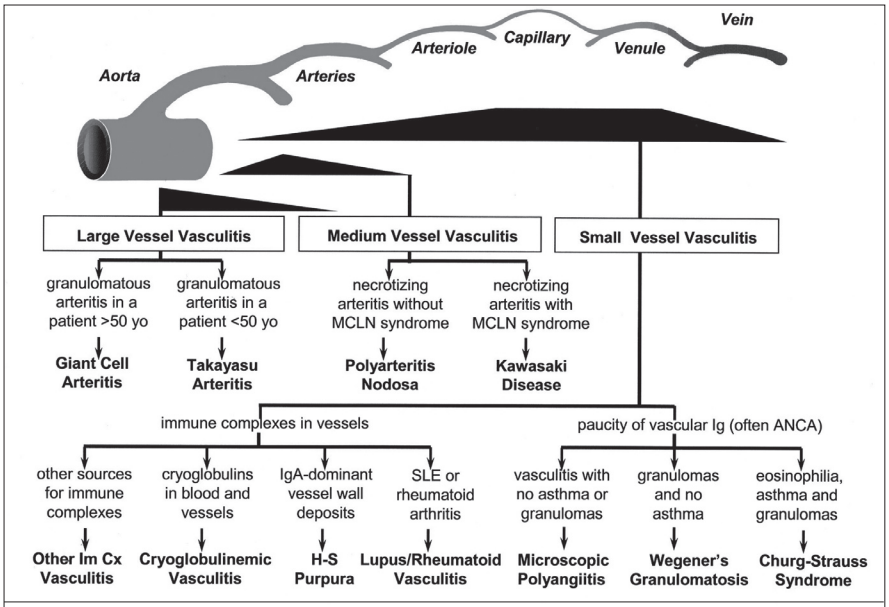

Fig. 1. Diagram depicting the predominant vascular distributions of different forms of systemic vasculitis and an algorithm showing pathologic and clinical features that allow diagnostic differentiation among these different forms of vasculitis (From J.C. Jennette with permission).

Small vessel vasculitis

SVV has a predilection for capillaries and venules, but arterioles and arteries, especially small arteries, may be involved (18). The two major immunopathologic categories of SVV are: 1) those with substantial vessel wall immunoglobulin (immune complexes), and 2) those with little or no immunoglobulin deposited in vessel walls (i.e. pauci-immune SVV). There are many forms of immune complex mediated SVV, for example Henoch-Schönlein purpura (HSP) and cryoglobulinemic vasculitis. Pauci-immune SVV often is accompanied by circulating anti-neutrophil cytoplasmic autoantibodies (ANCA) and thus also is called ANCA-associated SVV (18, 19). The major forms of systemic pauci-immune SVV are microscopic polyangiitis (MPA), Wegener's granulomatosis (WG) and Churg-Strauss syndrome (CSS).

Henoch-Schönlein purpura

HSP is characterized by IgA-dominant immune deposits in capillaries, venules or arterioles. HSP often affects the skin, gut and glomeruli, and usually is accompanied by arthralgias or arthritis. The lungs are rarely affected. Glomerular involvement is pathologically indistinguishable from IgA nephropathy. The typical histologic lesion in skin

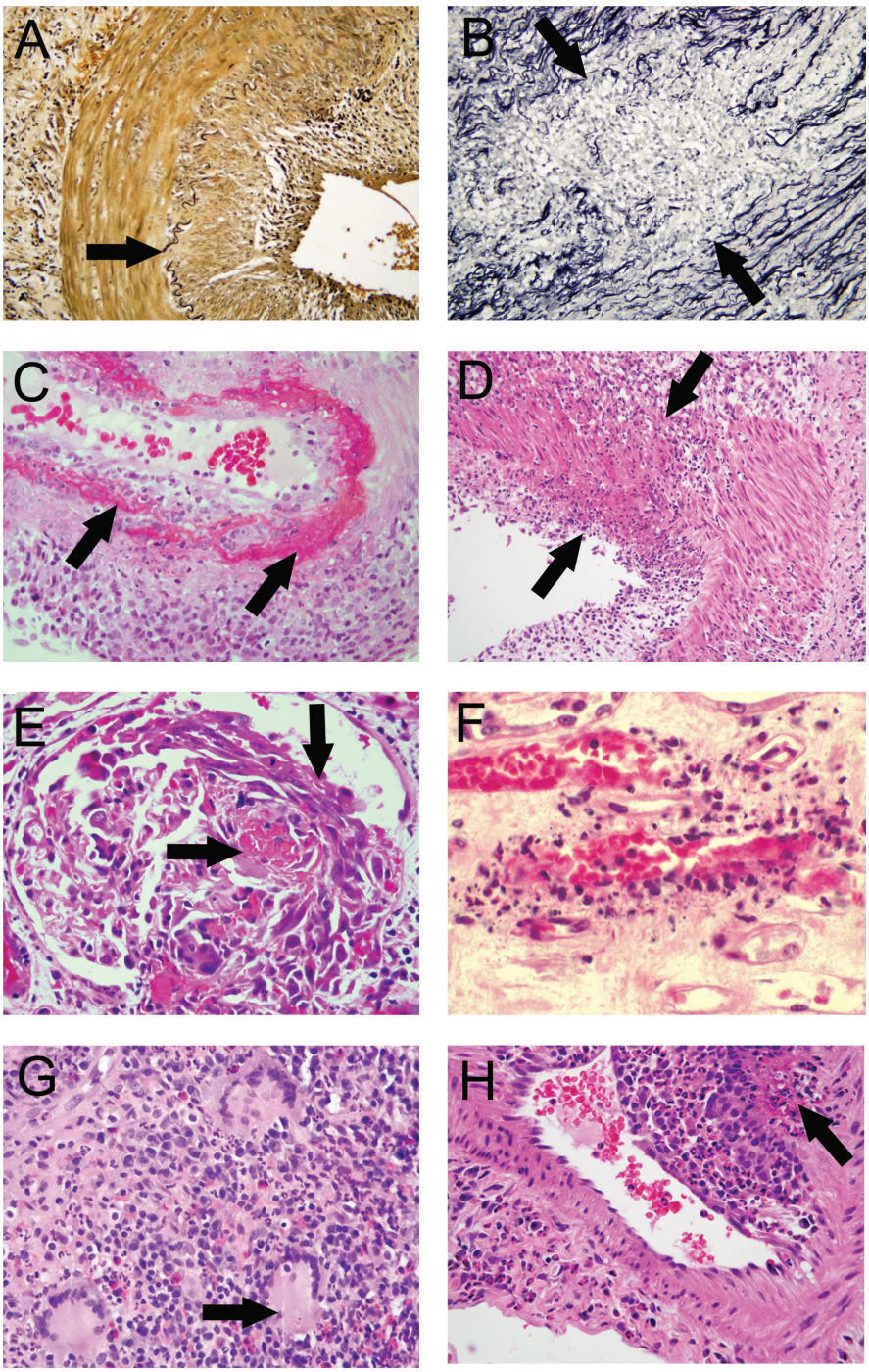

Fig. 2. Photomicrographs of A) GCA with fragmentation of the internal elastica (arrow) and transmural inflammation (temporal artery, elastic tissue stain); B) TA of the aorta causing focal dissolution of the elastic media (elastic tissue stain); C) arteritis in a skeletal muscle biopsy with marked fibrinoid necrosis (H&E stain); D) KD arteritis with transmural inflammation and necrosis (arrows) (renal lobar artery, H&E stain); E) ANCA-associated glomerulonephritis with fibrinoid necrosis (horizontal arrow) and crescent (vertical arrow) (H&E stain); F) ANCA-associated leukocytoclastic angiitis in the renal medulla (H&E stain); G) WG acute inflammation with multinucleated giant cells (arrow) (nasal mucosa, H&E stain); H) CSS arteritis with necrosis (arrow) and transmural inflammation with eosinophils (lung, H&E stain).

biopsy specimens is leukocytoclastic angiitis affecting postcapillary venules, capillaries and arterioles. By light microscopy alone, HSP can not be distinguished from other causes for cutaneous leukocytoclastic angiitis, such as cryoglobulinemic vasculitis, MPA, WG, CSS and many others. The most specific pathologic criterion for HSP is the demonstration of IgA-dominant immune complexes vessel walls (20).

Cryoglobulinemic vasculitis

Patients with cryoglobulinemic vasculitis have cryoglobulinemia and deposits of cryoglobulins in small vessels, i.e. capillaries, venules or arterioles. Skin and glomeruli are often involved. Lungs are rarely involved. Hepatitis C virus infection and hypocomplementemia are frequent. The typical histologic lesion is a leukocytoclastic angiitis. The most specific histologic findings are hyaline aggregates of cryoglobulins within vessel lumens; however, the most definitive diagnostic criterion is serologic confirmation of cryoglobulinemia in a patient with immune complex vasculitis.

Microscopic polyangiitis

According to the Chapel Hill nomenclature system (1), MPA is necrotizing vasculitis with few or no immune deposits affecting small vessels, i.e. capillaries, venules, or arterioles. Pulmonary and renal involvement is common. Necrotizing arteritis occurs in some but not all patients. Necrotizing glomerulonephritis (Fig. 2E) and necrotizing pulmonary capillaritis are common. Approximately 80% of MPA patients have ANCA, either with specificity for myeloperoxidase (MPO-ANCA) or proteinase 3 (PR3-ANCA) (19, 21).

The acute vascular lesions have segmental fibrinoid necrosis with neutrophilic infiltration and leukocytoclasia (Fig. 2F) (19, 21). Within several days, the predominant infiltrating leukocyte shifts from neutrophils to monocyte, macrophages and lymphocytes. Necrotizing glomerulonephritis and necrotizing alveolar capillaritis are common. Immunohistology reveals an absence or paucity of immunoglobulin staining in typical MPA. However, some patients with ANCA-positive SVV consistent with MPA have substantial vascular immunoglobulin deposition (22). Whether this represents MPA with unusually prominent immunoglobulin deposition, or concurrent MPA and immune complex SVV is debatable.

Wegener's granulomatosis

WG is defined by the presence of necrotizing granulomatous inflammation (Fig. 2G), often involving the upper or lower respiratory tract, and frequently accompanied by necrotizing vasculitis affecting small to medium-sized vessels, such as capillaries, venules, arterioles, and arteries (1, 12). Necrotizing glomerulonephritis is common. Approximately 90% of patients with active, untreated systemic disease have ANCA, more often PR3-ANCA than MPO-ANVA; although this predominance of PR3-ANCA may not occur in all ethnic groups and geographic locations (23).

The vasculitis and the glomerulonephritis of WG are pathologically indistinguishable from that of MPA and CSS (19). The differential diagnosis depends on the clinical or pathologic identification of granulomatous inflammation to make a diagnosis of WG and the identification of asthma and blood eosinophilia for a diagnosis of CSS (Tables I and II) (1).

Churg-Strauss syndrome

CSS is characterized by asthma and blood eosinophilia in a patient with eosinophil-rich and granulomatous inflammation involving the respiratory tract and necrotizing vasculitis affecting small to medium-sized vessels (Fig. 2H) (1, 24). Patients with CSS can have involvement of the same organ systems as MPA and WG, however, on average, they have more involvement of the peripheral nerves and less involvement of kidneys; and are less often ANCA-positive. Although glomerulonephritis occur less often and usually is less severe in CSS, the histologic appearance of the glomerular lesions is identical to those in patients with WG or MPA. The necrotizing granulomatous inflammation of CSS has histologic features that are similar to the granulomatous inflammation of WG; however, eosinophils are typically much more numerous.

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