

Giant-Cell Arteritis and Polymyalgia Rheumatica

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Giant-cell arteritis is an immune-mediated disease characterized by granulomatous infiltrates in the wall of medium-size and large arteries. The immunopathology consists of 2 components. Excessive cytokine production (for example, of interleukin-1 and interleukin-6) induces systemic inflammation with an exuberant acute-phase response. In parallel, interferon- γ , which is released by T cells captured in the arterial wall, activates tissue-injurious macrophages. In response to the immune injury, the artery generates hyperplasia of the intima that leads to luminal occlusion and subsequent tissue ischemia. Despite the systemic character of the disease, distinct vascular territories are preferentially affected. On the basis of the predominant involvement, clinical subtypes can be distinguished: cranial giant-cell arteritis with ischemic complications in the eye, the face, and the central nervous system; large-vessel giant-cell arteritis with occlusions in the subclavian or axillary vessels; aortic giant-cell arteritis; giant-cell arteritis presenting as an intense systemic inflammatory syndrome with

nonstenosing vasculitis; and "isolated" polymyalgia rheumatica with myalgias, systemic inflammation, and subclinical vasculitis. Temporal artery biopsy remains the diagnostic procedure of choice to detect arteritis in cranial vessels. In other vascular territories, giant-cell arteritis is most commonly diagnosed by vascular imaging. Laboratory studies characteristically document the marked elevations of nonspecific acute-phase reactants, such as C-reactive protein and erythrocyte sedimentation rate. Cytokines, such as interleukin-6, that induce the acute-phase reaction are currently being explored as more sensitive biological markers of disease activity. Corticosteroids are highly effective in suppressing systemic inflammation, but they do not eliminate the immune responses in the vessel wall. In general, the clinical outcome of giant-cell arteritis is excellent, and efforts must now concentrate on tailoring therapies to the needs of the individual patient.

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Giant-cell arteritis, formerly called temporal arteritis or granulomatous arteritis, is an inflammatory vasculopathy that affects large and medium-size arteries. Arterial lesions are composed of T cells and macrophages, often arranged in granulomas. Vessel wall inflammation leads to luminal occlusion and tissue ischemia. The vascular bed of the cranial arteries is particularly susceptible, but the aorta and its primary and secondary branches can be affected as well. Tissue ischemia in the optic nerve, the masseter muscles, and the posterior circulation of the central nervous system is particularly important in causing the clinical manifestations of this vasculitis. Involvement of the subclavian and axillary arteries leads to upper-extremity ischemia, and giant-cell arteritis and aortitis cause aortic dilatation and aneurysm. Vessel wall inflammation almost always coexists with a syndrome of systemic inflammation. In polymyalgia rheumatica, a closely related entity, vessel wall inflammation is incomplete, and the systemic inflammation is combined with myalgias of the neck, shoulder, and pelvic girdle. Giant-cell arteritis and polymyalgia rheumatica frequently occur together in the same patient. Whereas the diagnosis of giant-cell arteritis can be proven by temporal artery biopsy, no pathognomonic test is currently available for polymyalgia rheumatica.

Giant-cell arteritis is the most frequent primary vasculitis (1); the incidence is 15 to 25 per 100 000 in at-risk populations. The disease is most prevalent in white persons, particularly those of Scandinavian descent, and is rare in Hispanic persons (2). Women are more susceptible than men. The single most important risk factor is age. Susceptible persons are usually older than 50 years of age, and incidence rates increase with advancing age (3). Given that the population in developed countries is increasingly getting older, the number of people at risk can be expected to

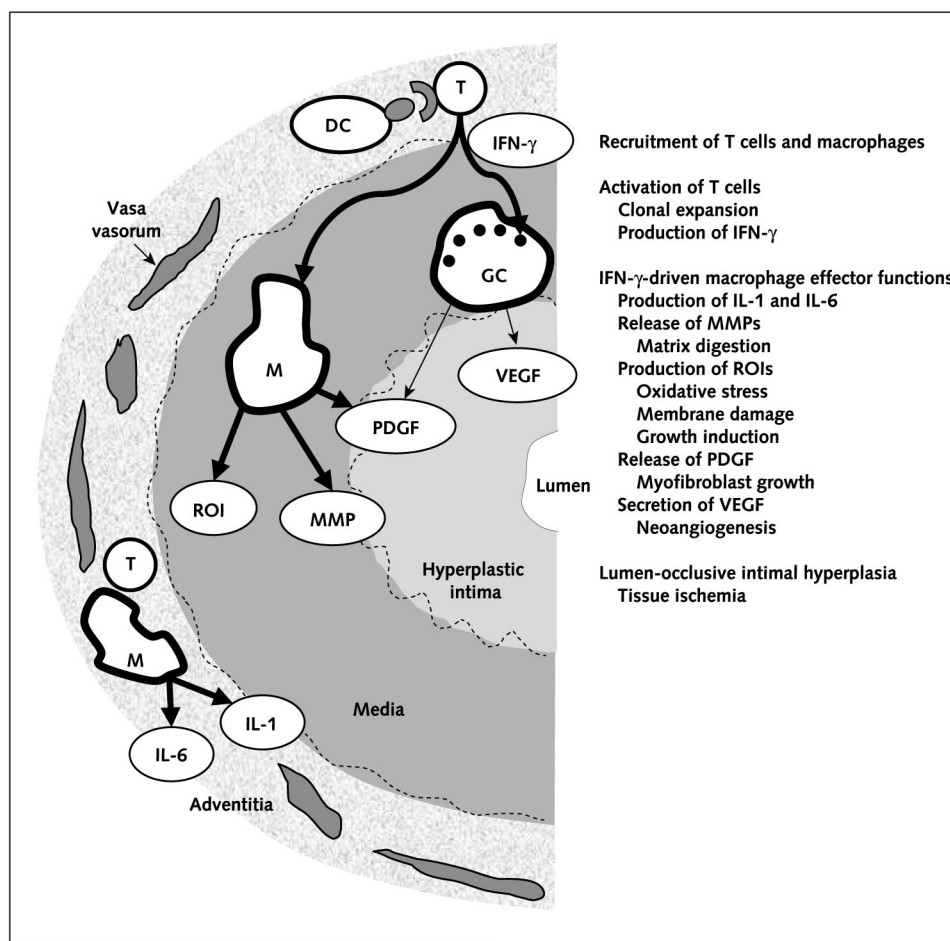
double in the next 25 years. Granulomatous arteritis can occur in individuals younger than 40 years of age; however, it then manifests as Takayasu arteritis. In contrast to giant-cell arteritis, Takayasu arteritis primarily targets the aorta and its proximal branches, compromising blood flow to major organs, such as the brain, the kidney, or entire extremities (4).

Advances in the understanding of the immunologic events causing giant-cell arteritis have provided new opportunities for diagnostic testing and therapeutic interventions. Studies of the nature and diversity of the pathogenic immune response have established a conceptual framework within which different clinical phenotypes may be identified. The goal is to develop reliable diagnostic procedures that detect vasculitis in distinct vascular beds. Adaptation of therapeutic management to the specific needs of individual patients is on the horizon.

PATHOGENESIS

The molecular and cellular pathogenesis of medium- and large-vessel vasculitis has recently been reviewed (5). The clinical manifestations of giant-cell arteritis are a result of 2 different immunopathogenetic processes (Figures 1 and 2). Inflammatory cells infiltrate the arterial wall and cause structural damage that eventually leads to the vascular complications (Figure 1). In most patients, a syndrome of systemic inflammation is also present (Figure 2), but the systemic inflammatory response does not seem to be simply a spillover from the vascular lesions. The systemic and the vascular components of giant-cell arteritis seem to have different underlying pathomechanisms—the vascular inflammation results from abnormal adaptive immune responses, whereas the systemic inflammation bears the signature of an excessively activated innate immune system.

Figure 1. Pathogenic mechanisms in the vascular lesions of giant-cell arteritis.



Activated T cells and macrophages form granulomatous reactions in the arterial wall. T-cell triggering occurs in the adventitia, where the vasa vasorum provide a port of entrance for inflammatory cells. Upon stimulation, T cells secrete interferon- γ (*IFN- γ*), a cytokine regulating effector functions of macrophages recruited to the lesions. Recruited macrophages differentiate into distinct subsets of tissue-injurious effector cells and produce matrix metalloproteinases and reactive oxygen intermediates. Macrophages and multinucleated giant cells also provide growth factor and angiogenic factors that support the response-to-injury program of the artery. The artery's reaction is maladaptive and leads to the formation of lumen-occlusive intimal hyperplasia. DC = dendritic cell; GC = multinucleated giant cell; IL = interleukin; M = macrophage; MMP = matrix metalloproteinases; PDGF = platelet-derived growth factor; ROI = reactive oxygen intermediates; T = T cell; VEGF = vascular endothelial growth factor.

The Innate and Adaptive Immune Systems

The immune system is composed of innate and adaptive branches, both involved in pathologic immune responses (6). Innate immunity is an ancient form of host defense. It relies on mechanisms that are not specific for a particular antigen or pathogen. Innate immune cells (neutrophils, monocytes or macrophages, and dendritic cells) rely on the principle of pattern recognition. Through a set of inherited receptors (such as Toll-like receptors), they sense infection and tissue invasion by recognizing molecular patterns that are shared by many microorganisms and dying cells (7). Upon stimulation, the innate immune system induces the production of cytokines and generates inflammation. By contrast, adaptive immunity is highly specific for an immunogen and has the remarkable property of memory. Adaptive immune responses are mediated by T cells and B cells that possess antigen-specific receptors. The enormous spectrum of the necessary antigen-specific recep-

tors is generated by random recombination of gene segments. To avoid self-reactivity and autoimmunity, self-reactive T cells and B cells must be eliminated or suppressed. The value of highly diverse and specific receptors is obvious; however, adaptive immune responses are delayed because rare lymphocytes expressing the fitting receptor are infrequent and must be expanded to eliminate offending antigens (8, 9).

Innate and acquired immunity are highly interconnected. Whereas the adaptive arm is superior in selectively identifying and memorizing antigen, it depends on the innate arm to find antigens in the tissue (to transport them to lymphoid organs) and to prime T cells. Primed T cells leave the secondary lymphoid organs, travel to peripheral tissue, re-identify the antigen, and initiate effector functions that eventually destroy the antigen and repair tissue damage. These effector functions are often delegated to

cells of the innate immune system, such as monocytes or macrophages, and resident cells at the tissue site (10).

Surveillance of tissues for pathogens, emerging tumors, and cellular breakdown products relies mostly on dendritic cells (11–13). Dendritic cells are placed in strategic positions in the tissue and are phagocytic. Upon activation, they become migratory and ferry antigens to the central lymphoid organs where T cells have an opportunity to test their antigen receptors for an exact fit. Recent data suggest that dendritic cell activation and differentiation hold seminal positions in the pathogenesis of giant-cell arteritis. Indeed, dendritic cells positioned in the wall of medium-size arteries emerge as the cellular link between a highly activated innate immune system, which causes the exuberant systemic inflammatory disease of giant-cell arteritis, and the formation of granulomas in the vessel wall (14). This novel disease model of granulomatous vasculitis proposes a stepwise process, beginning with the activation of innate immunity and progressing to the loss of self-tolerance in the artery. Persistent innate immune activation emerges as the major cause of the systemic inflammatory syndrome, whereas misguided adaptive responses mediate arteritis.

The Vascular Lesion

Vascular lesions of giant-cell arteritis are a consequence of inappropriate activation of the adaptive immune system, particularly T cells (15–17). As for many autoimmune diseases, infectious microorganisms have been suspected as possible instigators. The spectrum ranges from viral agents to bacterial organisms (for example, human parainfluenza type I virus, parvovirus B19, herpesvirus, chlamydia, and mycoplasma) (18–25). However, episodic reports of microbial antigens in affected temporal arteries have not been corroborated (26–28), and direct evidence for an immune response directed against pathogens in the vessel wall is lacking. It seems that the recruitment of mac-

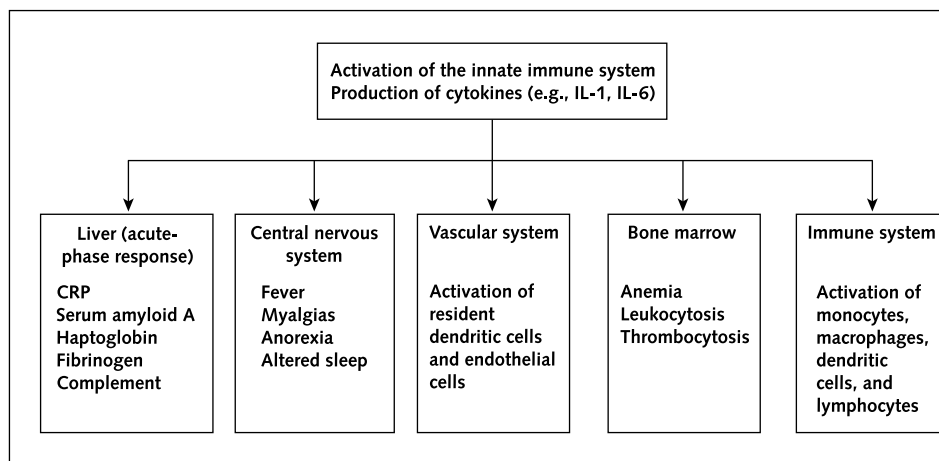
rophages carrying antigens from former infections is a regular event in inflammatory lesions, but this may have no role in initiating the disease process.

CD4⁺ T cells and activated macrophages are the major components of vessel wall infiltrates. Lymphocytes and macrophages penetrate through all layers of the arterial wall, but the primary immunologic injury occurs in the adventitia (29). T cells seem to enter the artery through the vasa vasorum and not from the main lumen. In the adventitial layer, T cells encounter stimulatory signals, expand clonally (30, 31), and release cytokines, particularly interferon- γ (29). The major target cells for interferon- γ are macrophages, which are recruited into the vessel wall to form the prominent granulomatous reaction. Stimulated macrophages use a spectrum of effector pathways to mediate structural damage in the artery (16, 17).

Two factors determine the course of the intra-wall inflammation: the type of T-cell differentiation (32) and the cellular and matrix composition of the affected blood vessel (16, 33). Intense stimulation of T cells with the production of high concentrations of interferon- γ in the tissue correlates with marked intimal hyperplasia and tissue ischemia (32). If T-cell differentiation in the vascular lesions is biased toward production of high levels of interleukin-2 and low levels of IFN- γ , the vasculitis evolves without luminal occlusion. At the end of this spectrum of vascular inflammation are patients with “isolated” polymyalgia rheumatica who lack vasculitis by histomorphologic criteria but have sufficient arterial infiltration of T cells and macrophages to allow for the in situ detection of interleukin-2, interleukin-1, and interleukin-6 transcripts (34).

Macrophages residing in different regions of the arterial wall are committed to distinct effector mechanisms (Figure 2) (35). In the adventitia, they specialize in the production of proinflammatory cytokines that optimize T-

Figure 2. The systemic inflammatory response in giant-cell arteritis and polymyalgia rheumatica.



Vessel wall inflammation is preceded and accompanied by an intense acute-phase response. Circulating macrophages are activated and release interleukin (IL)-1 and interleukin-6, critical inducers of a multiorgan reaction involving the liver, the central nervous system, the vascular system, the bone marrow, and the immune system. Hepatic acute-phase reactants are useful in the laboratory diagnosis of giant-cell arteritis and polymyalgia rheumatica. The systemic inflammatory response can exist in the absence of fully developed vasculitis, as in the case of polymyalgia rheumatica. CRP = C-reactive protein.

Table 1. The Spectrum of Clinical Features in Giant-Cell Arteritis

Feature	Manifestation
Manifestations related to vascular injury	
Common features (30%–80% of patients)	
Headaches	No particular pattern; severe, sometimes throbbing; often localized
Scalp tenderness	Often temporal; elicited by touching, grooming, or wearing glasses; temporal artery can be thickened, tender, or nodular
Jaw claudication	Elicited by prolonged talking or chewing
Less common features (<20% of patients)	
Ocular symptoms	Partial or complete visual loss, amaurosis fugax, or ocular motor deficit
Blindness	Unilateral or bilateral; usually permanent
Painful dysphagia	Sore throat
Respiratory symptoms	Dry, nonproductive cough
Limb claudication	Elicited by use of arms; combined with paresthesias
Absent or asymmetrical pulses	
Asymmetrical blood pressure readings	
Infrequent features (<5% of patients)	
Ischemia of the central nervous system	Typically vertebrobasilar insufficiency; imbalance; cortical blindness; confusion
Tongue claudication	
Aortic regurgitation	Dilatation of the proximal aorta
Myocardial infarction	
Peripheral neuropathy	
Deafness	
Tissue gangrene	Scalp, tongue, or extremities
Manifestations related to systemic inflammation	
Common features (40%–100% of patients)	
Intense acute-phase response	Elevated erythrocyte sedimentation rate, C-reactive protein level, interleukin-6 level, levels of other acute-phase proteins; elevated liver function test results; thrombocytosis
Anemia	Normocytic, normochromic
Polymyalgia rheumatica	Pain and stiffness in neck, shoulders, and pelvic girdle
Wasting syndrome	Fever, anorexia or weight loss, malaise, night sweats, depression
Infrequent features (<20% of patients)	
Peripheral synovitis	Typically wrist

cell stimulation. Macrophages in the smooth-muscle cell layer of the tunica media focus on oxidative stress and the production of matrix metalloproteinases (which are probably instrumental in the fragmentation of the internal elastic lamina). Reactive oxygen intermediates induce lipid peroxidation and injury of smooth-muscle cells (36, 37). Finally, macrophages at the media-intima junction release growth and angiogenic factors, including platelet-derived growth factor (38) and vascular endothelial growth factor (39), which regulate the process of intimal hyperplasia.

The immune assault elicits a response-to-injury program in the artery (17). In one of the response patterns, myofibroblasts are mobilized and migrate toward the lumen. They settle under the endothelial layer of the intima, proliferate, and deposit extracellular matrix. As a result, the arterial lumen is stenosed or occluded. There is no good evidence that thrombotic occlusion plays a role in tissue ischemia. Because some patients do not develop vascular obstructions, it is likely that host risk factors determine the pattern of arterial reaction to injury. It is important to note that aneurysmal destruction of the vessel and hemorrhage do not occur in the medium-size arteries targeted by giant-cell arteritis (temporal artery, subclavian artery, and axillary artery) but are restricted to the aorta (40, 41).

Recognizing that structural determinants of the arterial wall modulate the course of inflammation has importance for the clinical approach toward patients with sus-

pected giant-cell arteritis. Disease in distinct vascular territories, for example, the aortic arch and the temporal artery, produces different pathologic conditions, necessitates different diagnostic procedures, and may require specifically adapted therapeutic regimens (33).

The Systemic Inflammatory Responses

The systemic inflammatory component of giant-cell arteritis is best described as an exuberant acute-phase response. Acute-phase responses are systemic reactions to severe stress and injury, including infection and tissue necrosis. Acute-phase responses are mediated by the innate immune system and represent the most primitive of the host immune defense mechanisms (42). Acute-phase responses are generated via a cascade of signals, with interleukin-6 playing a critical role by stimulating the production of acute-phase proteins in the liver (43, 44). Many such hepatic acute-phase proteins are elevated in giant-cell arteritis (45, 46). Circulating monocytes are a major source of interleukin-6 (47). Their presence and state of activation are not a consequence of vascular inflammation because circulating monocytes in patients with polymyalgia rheumatica without identifiable vascular lesions are activated to a similar extent (47). The mechanisms and sites of monocyte or macrophage activation in giant-cell arteritis and polymyalgia rheumatica are unknown.

Table 2. Specificity and Sensitivity of Signs and Symptoms in Patients with Suspected Giant-Cell Arteritis*

Sign or Symptom	Sensitivity (95% CI)†	Positive Likelihood Ratio (95% CI)‡
Jaw claudication	0.34 (0.29–0.41)	4.2 (2.8–6.2)
Diplopia	0.09 (0.07–0.13)	3.4 (1.3–8.6)
Prominent or enlarged temporal artery	0.47 (0.40–0.54)	4.3 (2.1–8.9)
Synovitis		0.4 (0.2–0.7)
Headaches	0.76 (0.72–0.79)	1.2 (1.1–1.4)
Erythrocyte sedimentation rate	0.96 (0.93–0.97)	1.1 (1.0–1.2)

* Modified with permission from Smetana and Shmerling (52).

† Defined as the frequency in patients with biopsy-proven giant-cell arteritis.

‡ Defined as the frequency of the sign or symptom in patients with giant-cell arteritis compared with the frequency in patients who had a negative result on temporal artery biopsy.

Clinical Presentation and Classification

Giant-cell arteritis presents abruptly or insidiously in persons older than 50 years. The spectrum of clinical manifestations is broad (48–52), with features attributable to systemic inflammation and to local complications of vascular injury (Table 1). A recent meta-analysis (52) has examined the sensitivity and specificity of signs and symptoms in predicting a positive temporal artery biopsy result (Table 2). This analysis confirmed that common clinical features, such as headaches or elevated erythrocyte sedimentation rate, are nonspecific. Jaw claudication and diplopia, both related to vascular insufficiency, had some specificity, but they are encountered in only 10% to 30% of

patients. Of interest, synovitis on clinical examination was associated with reduced likelihood of a positive biopsy result, emphasizing that joint inflammation and vasculitis may be inversely related (53).

Physicians need to be familiar with the typical manifestations of giant-cell arteritis, such as headaches, blindness, polymyalgia rheumatica, and elevated erythrocyte sedimentation rate. The challenge lies in recognizing atypical cases that lack the more specific manifestations of vascular insufficiency of cranial arteries or reflect vasculitis in less frequently involved vascular territories. Clinical subtypes can be distinguished on the basis of the type and topography of vascular involvement. Such subtypes are those in which cranial manifestations dominate, those characterized by involvement of the aorta and its large branches, those in which the clinical consequences are mainly caused by systemic inflammation and not tissue ischemia, and those characterized by “isolated” polymyalgia rheumatica (Table 3). It is important to recognize that disease subtypes share pathogenic principles and are not mutually exclusive but are overlapping.

Cranial Arteritis

Most patients with giant-cell arteritis have arteritic lesions in the branches of the carotid arteries, such as the superficial temporal, occipital, ophthalmic, and posterior ciliary arteries, and in the vertebral arteries. The internal and external carotid arteries can be affected. Characteristically, patients seek evaluation for headaches that are severe

Table 3. Characteristic Features and Diagnostic Approaches to the Different Subtypes of the Giant-Cell Arteritis Syndrome*

Feature or Diagnostic Approach	Clinical Subtypes of Giant-Cell Arteritis			
	Cranial Arteritis	Systemic Inflammatory Syndrome with Arteritis	Large-Vessel Arteritis or Aortitis	Isolated Polymyalgia Rheumatica
Temporal artery biopsy				
Morphology	Granulomatous vasculitis	Infiltrates of T cells and macrophages	Often negative (~50%)	Negative
Giant cells	Often	Infrequent	Variable, if positive	Negative
Intimal hyperplasia	Often pronounced	Infrequent	Variable, if positive	Negative
Cytokine concentration in tissue				
IFN- γ	High	Low	High, if positive	Absent
IL-2	Low	High	High, if positive	Present
IL-6	High	Variable	Variable	Present
IL-1 β	High	Variable	Variable	Present
PDGF	High	Low	Not known	Not known
VEGF	High	Low	Not known	Not known
X-ray angiography	—	—	Stenosis or occlusion of primary and secondary aortic branches Aortic root dilatation or aneurysm	—
Digital subtraction angiography	—	—	Stenosis or occlusion of subclavian or axillary arteries	—
MR angiography	—	—	Stenosis or occlusion of primary and secondary aortic branches Aortic root dilatation Wall inflammation and edema (sensitivity unknown)	—
Computed tomography	—	—	Aortic aneurysm Aortic wall irregularities and thickening	—

* IFN = interferon; IL = interleukin; MR = magnetic resonance; PDGF = platelet-derived growth factor; VEGF = vascular endothelial growth factor.

and often refractory to analgesic therapy (48). Scalp tenderness should heighten the suspicion for giant-cell arteritis. On examination, scalp arteries are often abnormal. Reduced blood flow can produce intermittent claudication of the masseter and temporalis muscles, leading to the syndrome of jaw claudication, which is relatively disease-specific (52) (Table 2). Infrequently, patients have ischemia of the tongue, face, or neck; facial swelling; or painful dysphagia.

The array of possible ophthalmic complications is wide; ischemia anywhere along the visual pathway can cause visual loss (54, 55). Most commonly, visual failure is related to stenosis in the ophthalmic artery. Occlusion of the posterior ciliary arteries leads to anterior ischemic optic neuropathy (56). Visual loss is sudden and painless. One or both eyes can be affected; in untreated patients, the risk for loss of sight in the second eye approaches 50% (57). Warning symptoms of visual loss include amaurosis fugax, posture-related visual blurring, and diplopia (58). Funduscopic examination may reveal a pale edematous disc. Sometimes, splinter hemorrhages at the disc margin or cotton wool spots in the peripapillary region may be observed.

In patients with ischemic complications, morphologic and molecular findings of the vascular lesions of temporal arteries are those of intense intimal hyperplasia, luminal obstruction, elevated tissue levels of interferon- γ and interleukin-1, and an abundance of platelet-derived growth factor-producing macrophages (32, 38).

Large-Vessel Arteritis or Aortitis

Formerly considered an infrequent pattern of giant-cell arteritis, large-vessel arteritis affecting the subclavian and axillary arteries is increasingly recognized (33). Approximately 50% of patients with giant-cell arteritis of the subclavian or axillary arteries have negative temporal artery biopsy results (33), emphasizing the compartmentalization of the vasculitis. The diagnosis of large-vessel arteritis is made by vascular imaging and not by biopsy (59, 60). Symptoms associated with large-vessel vasculitis include aortic arch syndrome with claudication in the arms, absent or asymmetrical pulses and blood pressure readings, peripheral paresthesias, and, occasionally, tissue gangrene (41). Lack of cranial symptoms (headaches, jaw claudication, or visual symptoms) may complicate the diagnostic process. Temporal arteries, if positive for inflammation, show a molecular fingerprint of high interleukin-2 transcription (33).

Aortic involvement has been estimated to occur in 10% to 15% of patients, but, because of clinical silence, this involvement may be more frequent (40, 61, 62). Manifestations in the cranial vascular bed usually precede aortitis. The entire aorta can be affected, but complications are often focused on the thoracic aorta. In contrast to cranial giant-cell arteritis, which targets medium-size arteries, aortitis does not lead to arterial obstruction; instead, it leads to arterial dilatation and aneurysm formation. Clini-

cal consequences include aortic dissection, sudden rupture of the aorta, and aortic valve insufficiency (40, 61). It is not unusual for a diagnosis to be made from a vessel biopsy in patients who undergo aneurysm repair but are not known to have giant-cell arteritis. Histomorphologic features of aortic giant-cell arteritis and Takayasu arteritis are often indistinguishable (63). Risk factors that predispose affected patients to aortic involvement have not been determined. Because the outcome of aortic rupture is often fatal, it is important to monitor patients for aortic wall disease even several years after the initial diagnosis. Dilatation of the aorta can be seen with chest radiography. Earlier stages of aortitis are detected by computed tomography (CT) or magnetic resonance imaging (MRI).

Systemic Inflammatory Syndrome with Arteritis

Arteritis can present without hyperplasia of the arterial intima and without luminal stenosis. Accordingly, not all patients develop manifestations of tissue ischemia. In patients who do, the systemic inflammatory syndrome often dominates clinical manifestations. Fever of unknown origin and a wasting syndrome with progressive weight loss, night sweats, and anorexia are the presenting symptoms (49). The risk for visual loss may be less than that observed in cranial arteritis. Temporal artery biopsy is the diagnostic procedure of choice and should be performed even in the absence of arterial tenderness or nodularity.

Polymyalgia Rheumatica

Polymyalgia rheumatica and giant-cell arteritis are closely related entities. Polymyalgia rheumatica occurs in the same population as giant-cell arteritis, is restricted to the elderly, exhibits identical disease-risk genes (53, 64), and has immune abnormalities and elevated acute-phase responses similar to those of giant-cell arteritis (46). Typically, patients present with severe stiffness and pain in the muscles of the shoulders and pelvic girdle. Passive range of motion of large joints is maintained. Approximately 40% of patients with arteritis have polymyalgia rheumatica; about 10% of patients originally presenting with isolated polymyalgia rheumatica have vasculitis on histologic examination (48), requiring a change in diagnosis to giant-cell arteritis. In patients with giant-cell arteritis who are undergoing steroid withdrawal, muscle pain and stiffness are the most frequent signs of flaring disease (65). The precise localization of disease-initiating triggering of the immune system in polymyalgia rheumatica is not known. It has been suggested that patients with polymyalgia rheumatica have bursitis of the shoulder and hip joints (66, 67). However, care must be taken to distinguish polymyalgia rheumatica from seronegative rheumatoid arthritis. Both diseases occur in the elderly, cause shoulder pain and stiffness, and promptly respond to corticosteroids. A recent study on the diagnostic value of clinical findings in suspected giant-cell arteritis found that synovitis was a negative predictor for positive temporal artery biopsy (52). Genetic associations studies in polymyalgia rheumatica have been contro-

versial (68–70), supporting the notion that the patients with polymyalgia-like symptoms are heterogeneous with respect to the underlying disease and may not always have classic polymyalgia rheumatica. In the absence of robust clinical measures and objective findings to establish the diagnosis of polymyalgia rheumatica, the medical field could benefit from genetic and molecular markers to be sure that patients with a clinical presentation of muscle pain and stiffness are properly assigned to either an underlying vasculitic syndrome or a rheumatoid arthritis–like disease.

DIAGNOSTIC APPROACHES TO GIANT-CELL ARTERITIS

Laboratory Findings

Acute-phase proteins are easily detected in the serum and are useful markers in giant-cell arteritis and polymyalgia rheumatica. Information is not available on whether any particular acute-phase response test has higher diagnostic value than others. Highly elevated erythrocyte sedimentation rate generally triggers suspicion for giant-cell arteritis, particularly in at-risk populations. C-reactive protein is a dynamic acute-phase protein that, expectedly, is elevated in most untreated patients (65). There is some evidence that interleukin-6, being “upstream” of C-reactive protein level and erythrocyte sedimentation rate, may be particularly sensitive for detecting the disease-associated acute-phase response (65).

As a result of the acute-phase response, hematopoiesis decreases and patients may develop normocytic, normochromic anemia. Thrombocytosis is a well-recognized feature, and abnormal results on liver function tests, particularly elevation of alkaline phosphatase levels, are not uncommon.

Erythrocyte sedimentation rates are not elevated in all patients (71, 72). In a recent study, 24% of patients with biopsy-proven giant-cell arteritis had normal erythrocyte sedimentation rates before starting corticosteroid therapy (65). In these cases, the C-reactive protein level may be helpful. Nonetheless, a normal erythrocyte sedimentation rate or C-reactive protein level does not exclude the diagnosis of giant-cell arteritis, and a temporal artery biopsy should be performed in cases of suspected vasculitis.

Tissue Examination

A definite diagnosis of giant-cell arteritis requires histomorphologic examination of arterial tissue. Considering the lack of specificity of the clinical and laboratory markers and the not trivial therapeutic implications of prolonged corticosteroid therapy, histologic confirmation of the diagnosis should be sought whenever possible. Temporal artery biopsy has a high diagnostic yield and associated risks are low. Because vascular inflammation is discontinuous, arterial specimens of sufficient size (2 to 3 cm) are needed (73–76). Optimally, frozen sections from the first temporal artery are inspected, and, if they do not reveal inflammatory infiltrates, the contralateral side is biopsied.

A critical clinical issue is the question of treating patients with corticosteroids before biopsy. Retrospective studies and animal experiments suggest that vascular lesions are rather resistant to therapy (77, 78). In patients at risk for visual loss, therapy should not be postponed while waiting for the biopsy. However, it is possible that vascular inflammation is reduced in response to high doses of steroids, causing false-negative findings in cases of mild arteritis. The preferred strategy, therefore, is to perform a biopsy without delay and before therapy.

Histomorphology of inflamed temporal arteries demonstrates panarteritis, with lymphocytes and macrophages often concentrated in the media and at the media–intima junction (79). Multinucleated giant cells are present in approximately 50% of cases but are not required to make the diagnosis of giant-cell arteritis. When present, they have a tendency to be grouped along the fragmented internal elastic lamina. It is now clear that inflammatory infiltrates limited to the adventitia can be the only histologic finding and that not all patients have full-blown panarteritis (80).

Infrequently, other types of arteritides are found in the temporal artery (81–83). Fibrinoid necrosis, rarely encountered in giant-cell arteritis, is a helpful clue to consider panarteritis nodosa or one of the antineutrophil cytoplasmic autoantibody–related vasculitides. Correlation with clinical symptoms and the pattern of organ involvement are critical in making the distinction between giant-cell arteritis and other vasculopathies.

Imaging

Imaging procedures are playing an increasingly important role in the evaluation of patients with giant-cell arteritis (Table 3). In patients with large-vessel giant-cell arteritis and negative temporal artery biopsy results, imaging is central in making the correct diagnosis. Typical lesions are smoothly tapered, both at the leading and trailing ends (59). The distal subclavian, any portion of the axillary, and the proximal part of the brachial artery are sites of predilection (33, 41). Evaluation of the carotid and vertebral arteries is important in patients with clinical evidence for cerebral ischemia (59). Vasculitic involvement of the intracranial arteries is not a feature of giant-cell arteritis.

In addition to conventional x-ray angiography and digital subtraction angiography, CT and MRI have emerged as fast and reliable methods to assess vessel anatomy and luminal status. Each method provides different information on stenosis, occlusion, dilatation, aneurysm, and wall irregularity, and each has its unique advantages (59, 60). Both CT with contrast enhancement and certain MRI sequences have the potential to also provide data about the vessel wall (thickness and perivascular inflammatory changes) and may have utility in estimating disease burden and activity. This question, however, has not been examined in appropriately designed studies.

Giant-cell arteritis aortitis leads to dilatation and aneurysm formation, which can be detected by CT and MRI.

Table 4. Key Considerations in the Therapeutic Management of Giant-Cell Arteritis

Prognosis is excellent. Life expectancy is normal (giant-cell arteritis) or prolonged (polymyalgia rheumatica) in treated patients. Many patients no longer receive therapy after 2 years.
Corticosteroids are the mainstay of treatment; no conclusive evidence for steroid-sparing effect of other immunosuppressants.
Adjunctive therapy should include bone-saving measures.
Systemic inflammatory responses and symptoms of polymyalgia rheumatica are highly sensitive to corticosteroids; vascular lesions, driven by adaptive immune responses, seem relatively resistant to immunosuppression.
In the chronic phase of the disease, most patients are clinically stable, although there is laboratory evidence of smoldering disease.
Vascular complications are infrequent after the initiation of corticosteroid therapy; some patients may develop aortic aneurysm, but the number of patients at risk for this complication and the responsiveness of aortitis to therapy are unclear.

High-resolution CT may be optimal to detect irregularities and thickening of the aortic wall (84). Disadvantages of this technique include nephrotoxicity of the contrast media and limitations of axial, coronal, and sagittal imaging. Three-dimensional MR angiography is the noninvasive method of choice to assess neck and aortic arch branch vessel pathology due to its capability for oblique plane imaging. It has been suggested that T2-weighted MR images are particularly helpful in determining wall thickness. Magnetic resonance imaging may be capable of detecting wall edema, a parameter potentially important in monitoring response to therapy. The major caveat of this technique is that no studies have been performed to prospectively correlate histomorphology, laboratory parameters of active vasculitis, and clinical signs of ongoing vascular disease with imaging findings. The sensitivity of MRI is unknown; patients with unequivocal signs of disease activity can lack wall thickening or edema on MRI. A recent study by Tso and colleagues (85) in patients with Takayasu arteritis has cast doubt on the reliability of T2-weighted MRI as a measure of disease activity.

TREATMENT OF GIANT-CELL ARTERITIS

Giant-cell arteritis can be effectively treated with corticosteroids. Almost all patients respond to initial doses of 1 mg/kg body weight of prednisone. Whether higher doses can prevent visual loss in patients with impending ischemia is not known. An equally important question that awaits examination in properly designed clinical trials relates to the impression that not all patients require initial doses of 60 mg of prednisone but that some patients could be appropriately managed with doses as low as 20 to 30 mg/d (86, 87). Promptness of the response of giant-cell arteritis to corticosteroids within 24 to 48 hours is often quoted as characteristic, but protracted clinical responses are possible. After response to initial therapy, corticosteroid doses are titrated to lower levels. The tapering schedule depends on the residual clinical activity, but reduction of daily doses by 10% to 20% every 2 weeks has been a useful guideline.

However, careful monitoring of clinical and laboratory signs of disease activity is necessary. Evidence suggests that the likelihood of vascular complications is low once corticosteroid therapy has been initiated (88). Accordingly, in prospective studies, most episodes of disease exacerbation were those of polymyalgia rheumatica and constitutional symptoms (65, 89).

Traditionally, corticosteroid tapering has relied on laboratory markers of acute-phase responses (erythrocyte sedimentation rate and C-reactive protein level). Erythrocyte sedimentation rate seems to be relatively insensitive for detecting reactivation of disease during steroid withdrawal. Interleukin-6 remains elevated in many patients during treatment, and it may be the most sensitive biological marker for the acute-phase response (65, 90). Its use in clinical practice as a guide for corticosteroid tapering needs to be formally tested.

To date, the evidence is not convincing that other immunosuppressive agents have an immunosuppressive effect that is similar or superior to that of corticosteroids. Controversial data have been reported on the steroid-sparing effect of methotrexate (89, 91, 92). A large double-blinded study showed similar relapse rates in patients treated with prednisone alone or with prednisone plus methotrexate (91). In a small study, 16 of 19 patients treated with prednisone and 9 of 20 patients treated with prednisone plus methotrexate had relapses (89). The lack of efficacy of immunosuppressant agents other than corticosteroids is remarkable and distinguishes giant-cell arteritis from other autoimmune syndromes. A possible explanation lies in the multidimensional nature of the giant-cell arteritis syndrome. Symptoms of systemic inflammation are exquisitely responsive to corticosteroids; their anti-inflammatory action in the vascular lesions is less impressive. Doses equivalent to 4 mg/kg/d of prednisone were required to achieve partial suppression of the vessel wall inflammation in an experimental model of giant-cell arteritis (78). Combination of distinct therapeutic principles will be necessary to adequately suppress systemic inflammation and eradicate vessel wall lesions.

A recent study in an experimental model of giant-cell arteritis suggests that acetylsalicylic acid has anti-inflammatory effects, particularly in the suppression of interferon- γ production in the artery (93). Recommendations for doses of acetylsalicylic acid necessary to capture the anti-inflammatory effect in patients have not been developed. Because patients with giant-cell arteritis were found to have increased risk for ischemic cardiovascular disease (94), which would possibly be aggravated by a procoagulant state related to systemic inflammation, the antiplatelet action of acetylsalicylic acid could also be beneficial.

As we move forward in the attempt to identify specific and sensitive markers of disease activity and to search for steroid-sparing therapies, it is important to reappraise our therapeutic goals (Table 4). Although the paradigm that the disease burns out after 2 to 4 years may not always hold

up, steroid treatment frequently can be discontinued. Patients with giant-cell arteritis have the same life expectancy as the general population, and patients with polymyalgia rheumatica may survive even longer, suggesting that current therapeutic regimens are quite successful (95, 96). The risk for vascular complications in treated patients seems to be low (65, 88). Evaluation with highly sensitive methods indicates that both the vascular lesion and the systemic inflammation persist at a low grade (65, 78). It could be argued that eradication of both components of the disease requires highly aggressive and risky interventions in patients that do well with traditional management. Indeed, the most frequent relapse manifestations of giant-cell arteritis in the chronically treated patient are symptoms of polymyalgia rheumatica, which are highly responsive to low doses of corticosteroids (increase of the prednisone dose by 2 to 5 mg/d). Another, and certainly less frequent, consequence of chronic giant-cell arteritis is the formation of aortic aneurysms (40). The proportion of patients at risk, the temporal delay required for significant aortic damage to occur, and the responsiveness of aortic wall destruction to therapeutic intervention are not known.

Steroid-induced osteopenia has been considered a major issue (97). Recent studies reported a nonsignificant reduction in bone mineral density of 0.2% over a 2-year study period while patients received cumulative corticosteroid doses of 4 to 5 g (98). The use of appropriate bone-saving therapeutic measures (99, 100) should be common practice in the management of giant-cell arteritis (Table 4).

From the Mayo Clinic, Rochester, Minnesota.

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