

# Large-Vessel Vasculitis

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## Introduction

The vasculitides and their treatments pose great risks for patients and difficult challenges for physicians. Clinicians are confronted with the task of treating diseases for which the understanding of pathophysiology is incomplete and the etiologies, in most cases, remain unknown. Nevertheless, the past several years have witnessed studies of systemic vasculitis on an unprecedented scale, including multicenter clinical trials. In this 2-part series, we review the recent vasculitis literature with the intention of addressing questions that confront physicians regarding the diagnosis and treatment of these conditions. This first article focuses on the large-vessel vasculitides—giant cell arteritis (GCA) and Takayasu's arteritis (TA). The second article will focus on questions relevant to the diagnosis and treatment of small- and medium-vessel vasculitides.

## Which clinical features predict positive temporal artery biopsies?

Smetana and Shmerling (1) performed a metaanalysis to determine the utility of historical features, physical examination findings, and the erythrocyte sedimentation rate (ESR) in diagnosing GCA. The authors identified 21 core studies reported between 1966 and 2000 that included patients with both positive and negative temporal artery biopsy results and provided detailed descriptions of the patients' clinical characteristics. The studies represented a total of 2,680 patients who underwent temporal artery biopsy, of whom 1,050 (39.2%) had biopsy-proven diagnoses of GCA. The GCA patients' mean age (73 years) and ethnicity (86% were white) were consistent with the known epidemiologic characteristics of this disease (2–4).

*What is the role of the history?* This study makes 2 major points regarding the value of information obtained from the history. First, jaw claudication and diplopia are powerful predictors of a positive temporal artery biopsy result. The presence of jaw claudication was associated

with a likelihood ratio (LR) of 4.2 (95% confidence interval [95% CI] 2.8–6.2), the highest LR of any historical feature (Table 1). More surprising perhaps was the LR of 3.4 (95% CI 1.3–8.6) for diplopia. In GCA, diplopia is caused by ischemia of the extraocular muscles, cranial nerves, or brainstem (5). The value of diplopia in predicting a positive temporal artery biopsy result has probably not been appreciated sufficiently.

*What symptoms are not discriminatory?* Headache, polymyalgia rheumatica (PMR), and visual symptoms (excluding diplopia)—all classic symptoms of GCA—were not associated with increased likelihoods of a positive biopsy result. Other systemic and constitutional symptoms commonly associated with GCA (e.g., fever, anorexia, fatigue, and arthralgias) also failed to discern which patients were likely to have positive biopsy samples.

The failure of classic disease features to discriminate between patients with GCA and those without that diagnosis is disheartening, but instructive. In general, only patients who manifest some features, usually several, suggestive of GCA are ever subjected to temporal artery biopsy. Clinicians already do a very good job of screening patients for biopsy: nearly 40% of all temporal artery biopsies performed yield positive samples. The ability of jaw claudication and diplopia to heighten the pretest probability of a positive biopsy result is therefore even more impressive.

Despite their high LRs, neither jaw claudication nor diplopia is very sensitive for the presence of GCA. Jaw claudication was present in only 34% of patients with biopsy-confirmed diagnoses, and diplopia in only 9%. Thus, the absence of these features does not exclude GCA (Table 2).

*What is the role of the physical examination?* Positive findings on the physical examination are more powerful predictors of an abnormal temporal artery biopsy sample than are most elements of the history (Table 1). The presence of a prominent or enlarged temporal artery, for example, was associated with an LR of 4.3 (95% CI 2.1–8.9), and temporal artery tenderness was associated with an LR of 2.6 (95% CI 1.9–3.7). Conversely, synovitis was associated with an LR of 0.41 (95% CI 0.23–0.72); i.e., its detection actually lowered the likelihood of a positive biopsy. Synovitis is reported in GCA and more commonly in PMR (6), but this sign is more compatible with rheumatoid arthritis and other conditions than with GCA.

*Can GCA occur in patients younger than 50 years of age?* The study by Smetana and Shmerling (1) answers this question convincingly. In this portion of their article, the authors

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**Table 1. Likelihood ratios for symptoms and signs among patients with suspected GCA\***

Symptom/sign	Number of patients with data	Positive LR (95% CI)	Negative LR (95% CI)
<b>Symptoms</b>			
Anorexia	674	1.2 (0.96–1.4)	0.87 (0.75–1.0)
Weight loss	1,417	1.3 (1.1–1.5)	0.89 (0.79–1.0)
Arthralgia	582	1.1 (0.86–1.4)	1.0 (0.92–1.1)
Diplopia	703	3.4 (1.3–8.6)	0.95 (0.91–0.99)
Fatigue	1,095	1.2 (0.98–1.4)	0.94 (0.86–1.0)
Fever	1,708	1.2 (0.98–1.4)	0.92 (0.85–0.99)
Temporal headache	386	1.5 (0.78–3.0)	0.82 (0.64–1.0)
Any headache	2,475	1.2 (1.1–1.4)	0.7 (0.57–0.85)
Jaw claudication	2,314	4.2 (2.8–6.2)	0.72 (0.65–0.81)
Myalgia	681	0.93 (0.81–1.1)	1.1 (0.87–1.3)
Polymyalgia rheumatica	1,383	0.97 (0.76–1.2)	0.99 (0.83–1.2)
Unilateral vision loss	341	0.85 (0.58–1.2)	1.2 (1.0–1.3)
Any vision symptoms	2,083	1.1 (0.93–1.3)	0.97 (0.9–1.0)
Vertigo	212	0.71 (0.38–1.3)	1.1 (0.93–1.2)
<b>Signs</b>			
Optic atrophy or ischemic optic neuropathy	142	1.6 (1.0–2.5)	0.8 (0.58–1.1)
Scalp tenderness	923	1.6 (1.2–2.1)	0.93 (0.86–1.0)
Synovitis	734	0.41 (0.23–0.72)	1.1 (1.0–1.2)
Beaded temporal artery	323	4.6 (1.1–18.4)	0.93 (0.88–0.99)
Prominent/enlarged temporal artery	508	4.3 (2.1–8.9)	0.67 (0.5–0.89)
Tender temporal artery	755	2.6 (1.9–3.7)	0.82 (0.74–0.92)
Absent temporal artery pulse	68	2.7 (0.55–13.4)	0.71 (0.38–0.75)

\* GCA = giant cell arteritis; LR = likelihood ratio; 95% CI = 95% confidence interval. Adapted, with permission from ref. 1.

identified 26 studies that provided the age of the patients with biopsy-proven GCA. Of the 1,435 patients with biopsy-proven GCA, only 2 were younger than 50 years.

**Does GCA ever occur with a low ESR?**

Salvarani and Hunder (7) performed a population-based study of patients with biopsy-proven GCA in Olmsted County, Minnesota. Between 1950 and 1998, 167 patients were diagnosed with GCA. In that cohort, 18 patients (11%) had ESRs <50 mm/hour—the lower limit used in

the American College of Rheumatology classification criteria study (8)—and 9 (5%) had ESRs <40 mm/hour. Thus, GCA can occur with a low ESR, and its occurrence is not rare. GCA patients whose ESRs were <40 mm/hour were less likely to experience systemic symptoms such as malaise, fever, or weight loss, but their clinical manifestations (including risk of visual loss) were otherwise indistinguishable from those of patients with higher ESRs.

Data from the metaanalysis by Smetana and Shmerling (1) are also useful here. According to their analysis, a normal ESR is more useful in excluding the disease than a high ESR is in diagnosing it. Of the 941 biopsy-proven GCA patients with sufficient information about ESR to permit analysis, only 4% had “normal” ESRs (although in many of the studies included in the metaanalysis, “normal” was not defined). In this analysis, a normal ESR diminished the probability of a positive temporal artery biopsy by a factor of 5.

In contrast, an abnormal ESR is much less helpful diagnostically. An ESR >100 mm/hour was a less powerful predictor of a positive biopsy than many elements of the history and physical examination (Table 1). The LR of an ESR >100 mm/hour was only 1.9 (95% CI 1.1–3.3), considerably lower than the LRs associated with jaw claudication (LR 4.2, 95% CI 2.9–006.2), diplopia (LR 3.4, 95% CI 1.3–8.6), a beaded temporal artery (LR 4.6, 95% CI 1.1–18.4), or a prominent or enlarged temporal artery (LR 4.3, 95% CI 2.1–8.9).

**What is the yield of temporal artery biopsy in patients with GCA?**

Temporal artery biopsy remains our best test for GCA but, like all diagnostic tests, it is imperfect. Even under the

**Table 2. Sensitivities of symptoms among all patients with positive temporal artery biopsy results\***

Symptom	Sensitivity (95% CI)
Anorexia	0.35 (0.23–0.48)
Weight loss	0.43 (0.35–0.53)
Arthralgia	0.30 (0.21–0.40)
Diplopia	0.09 (0.07–0.13)
Facial pain	0.17 (0.12–0.23)
Fatigue	0.39 (0.28–0.52)
Fever	0.42 (0.33–0.52)
Temporal headache	0.52 (0.36–0.67)
Any headache	0.76 (0.72–0.79)
Jaw claudication	0.34 (0.29–0.41)
Myalgia	0.39 (0.23–0.56)
Polymyalgia rheumatica	0.34 (0.28–0.41)
Unilateral vision loss	0.24 (0.14–0.36)
Any vision symptoms	0.37 (0.30–0.44)
Vertigo	0.11 (0.05–0.19)

\* 95% CI = 95% confidence interval. Adapted, with permission, from ref. 1.

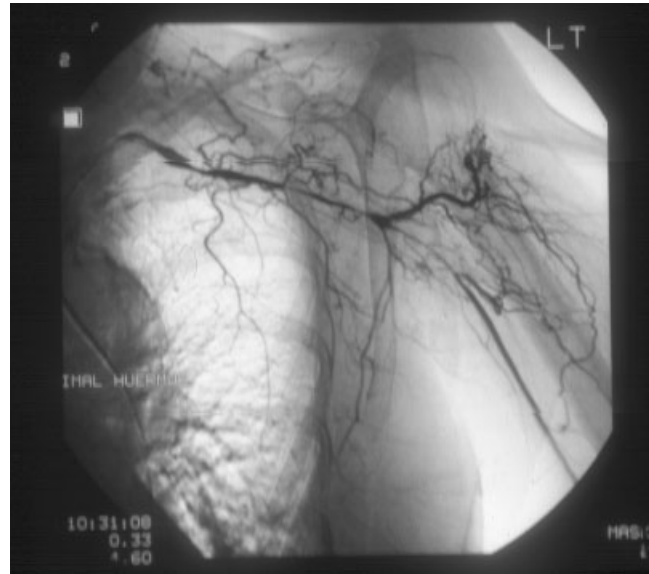
most careful conditions, the negative predictive value of a temporal artery biopsy is, at best, only in the range of 90%. This was shown 20 years ago by Hall et al (9), who identified all 134 residents of Olmsted County, Minnesota who underwent temporal artery biopsies between 1965 and 1980. The procedure for temporal artery biopsy procurement in this study included biopsy of the symptomatic side first, examination of a frozen section of the specimen while the patient remained in the operating room, and biopsy of the contralateral side if the first biopsy was negative. Eighty-eight of the 134 temporal artery biopsy samples (66%) did not demonstrate evidence of temporal arteritis, but GCA was diagnosed eventually (upon repeat biopsy, autopsy, or clinical grounds) in 8 of those 88 patients with negative biopsy results (9%). Thus, the negative predictive value of bilateral biopsies performed at the Mayo Clinic is 91%. The sensitivity of unilateral biopsies and of biopsies performed at centers not expert in this procedure is undoubtedly lower.

One possible explanation for the fallibility of temporal artery biopsy is variability of the disease pattern that may occur in GCA (10). The most common form of GCA involves the cranial arteries, but there are other phenotypes. One such variant is characterized by involvement of the great vessels and a higher likelihood of sparing the temporal arteries. Patients with this phenotype may develop upper extremity claudication because of subclavian and axillary artery disease (Figure 1). Brack et al (10) showed that the sensitivity of temporal artery biopsy for patients in the large-vessel subset was only 58%. This may account for many of the negative temporal artery biopsy samples in GCA patients who present with constitutional complaints and PMR. The approach to diagnosis of these patients includes a careful physical examination, with palpation of the peripheral pulses for asymmetry, auscultation for bruits (particularly in the subclavian and axillary regions), and selected imaging studies of the great vessels (e.g., magnetic resonance angiography or conventional angiography; see below).

### Are bilateral temporal artery biopsies essential?

Although a unilateral temporal artery biopsy is frequently sufficient to establish the diagnosis of GCA, at some institutions samples of both temporal arteries are taken during the same procedure. Boyev et al (11) performed a retrospective review of 186 patients who underwent bilateral temporal artery biopsies at the Wilmer Eye Institute of the Johns Hopkins Hospital (Table 3). Only 6 patients (3%) had arteritis on only 1 side, representing 20% of the total number diagnosed with GCA through biopsy. Another retrospective study by Pless et al (12), which involved 60 patients who underwent bilateral biopsies, reached similar conclusions. Of these 60 patients, 8 (13%) had temporal arteritis on only 1 side. Those 8 patients comprised 40% of the total number of patients diagnosed with GCA by biopsy. Considering the potential consequences of a missed diagnosis and the very low morbidity of the procedure, the routine performance of bilateral temporal artery biopsies is prudent, especially at institutions where frozen sections cannot be examined intraoperatively to determine if the first biopsy is diagnostic.

*Do the sites of symptoms correlate with the location of pathology identified by biopsy?* Not always. Among the 8 patients in the study by Pless et al (12) shown to have GCA



**Figure 1.** Angiography in giant cell arteritis with large-vessel involvement. Conventional angiogram shows long, tapered narrowings of several segments of the left subclavian artery. In association with the stenoses are tortuous, exuberant areas of collateral circulation.

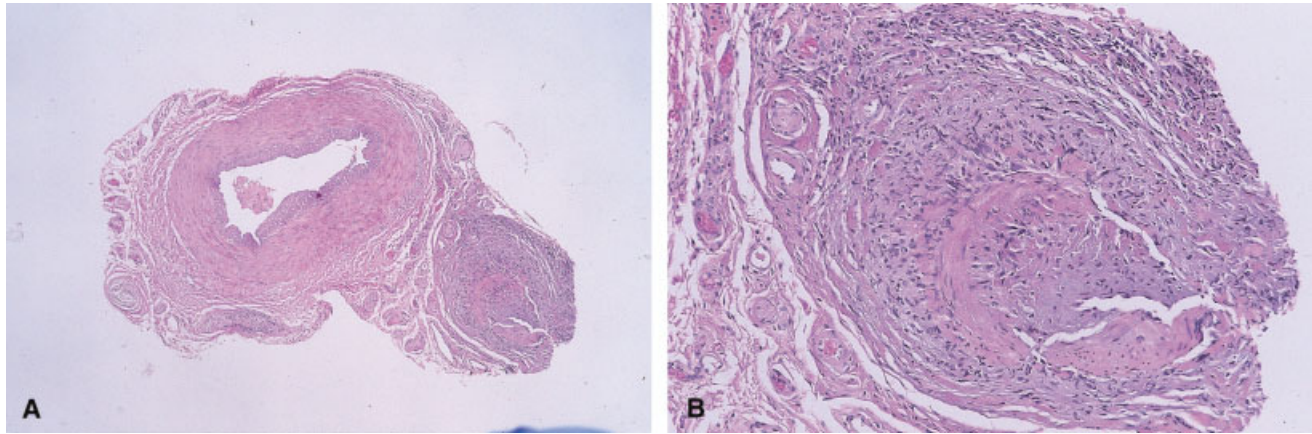
on only 1 side, symptoms (headache and scalp tenderness) were indeed more common on only 1 side, but not always the side that demonstrated pathology on biopsy. One patient had bilateral symptoms but pathology on only 1 side. Among the 7 patients with unilateral symptoms, 2 had symptoms that were contralateral to the abnormal temporal artery.

*What if temporal artery biopsies on both sides are negative but I still suspect GCA?* First, consider more strongly the possibility that the patient does not have GCA. If the clinical story is equivocal, then perhaps other diagnoses should be given more weight. Second, consider the possibility of GCA that involves only the great vessels (10) and evaluate the patient with an imaging study for signs of aortic, subclavian, carotid, or other large-vessel disease. Finally, a trial of glucocorticoid therapy for up to 1 week may be instructive. Failure of the patient's symptoms to resolve with 1 week of high-dose glucocorticoids argues strongly against the diagnosis of GCA. Conversely, resolution of symptoms after treatment with glucocorticoids supports the diagnosis but unfortunately does not confirm it. In the final analysis, the diagnosis of GCA must sometimes rely upon clinical intuition.

**Table 3. Comparison of concordance of bilateral temporal artery biopsies\***

	Boyev et al n = 182	Pless et al n = 60
Bilateral normal	152 (85)	40 (67)
Bilateral GCA	22 (12)	12 (20)
Discordant	6 (3)	8 (13)

\* Data presented as no. (%). GCA = giant cell arteritis. Data from refs. 11 and 12.



**Figure 2.** Temporal arteritis in microscopic polyarteritis. Focal arteritis consisting of lymphocytes and histiocytes involving the full thickness of a small branch off the main temporal artery segment. No giant cells are noted. This biopsy was obtained from a patient eventually diagnosed with microscopic polyangiitis who developed a vasculitic neuropathy (mononeuritis multiplex) and was found to have antibodies to myeloperoxidase, giving a perinuclear antinuclear cytoplasmic antibody pattern of immunofluorescence. **A**, Hematoxylin and eosin stained; magnification  $\times 100$ . **B**, Hematoxylin and eosin stained; magnification  $\times 400$ .

### Is vascular inflammation in the temporal artery specific for GCA?

The vasculitides are identified by their clinical presentations and their tendencies to affect characteristic organs and vascular beds. These associations are not absolute, however, and in some cases, they may lead physicians down the primrose path. In 1999, Génereau et al (13) confirmed that GCA is not the only form of vasculitis that can lead to inflammation of the temporal arteries, a fact noted in case reports by others (14,15). In a prospective study of 141 consecutive patients undergoing temporal artery biopsy for evaluation of GCA, 2 patients (1.4%) were diagnosed with non-GCA forms of vasculitis (i.e., Churg-Strauss syndrome and mixed essential cryoglobulinemia), accounting for nearly 5% of the abnormal temporal artery biopsy samples. The biopsy samples in those patients showed lymphocytic vascular inflammation, but not the classic pathologic hallmarks of GCA (e.g., multinucleated giant cells near the intimal-medial border). In the second part of this study, Genereau et al (13) performed a retrospective investigation at several centers to identify patients with histologic evidence of vasculitis on temporal artery biopsy who did not have GCA. Four of the 27 patients identified in this manner had been misdiagnosed with GCA before developing symptoms more characteristic of their true underlying disease (see Figure 2). Of the 27 non-GCA patients with inflammation in the temporal artery, polyarteritis nodosa (PAN) was the most common cause (11 patients). Other diagnoses included Churg-Strauss syndrome (6 patients), Wegener's granulomatosis (3 patients), hepatitis B-related PAN (2 patients), hepatitis C-related cryoglobulinemic vasculitis (1 patient), and rheumatoid vasculitis (1 patient).

In contrast to other systemic vasculitides, such as PAN and those associated with antineutrophil cytoplasmic antibodies, GCA is *not* associated with the histopathologic finding of fibrinoid necrosis (16). The presence of fibrinoid necrosis broadens the differential diagnosis to include diseases that may need other therapies in addition to pred-

nisone (17). In the setting of clinical features that are atypical for GCA, reexamination of the temporal artery specimen may be instructive.

### Do corticosteroids interfere with the results of temporal artery biopsy?

In a large, retrospective study nearly a decade ago, Achkar et al (18) debunked the notion that glucocorticoids interfere irretrievably with the interpretation of temporal artery biopsy specimens. Achkar et al grouped temporal artery biopsies from 535 consecutive patients according to the duration of glucocorticoid therapy prior to biopsy. Thirty-three percent of the specimens were positive. Of the 286 patients who had not been treated with glucocorticoids at the time of biopsy, 89 (31%) had positive specimens. Of the 32 patients who had received more than 15 milligrams of prednisone daily for longer than 14 days, 9 (28%) had evidence of temporal arteritis on biopsy ( $P =$  not significant). In the latter group, 1 patient's biopsy sample remained positive as long as 11 months after the start of treatment. Patients treated previously with glucocorticoids were more likely to have atypical histologic features, such as the absence of giant cells or the finding of "healed arteritis."

This issue was reexamined in a much smaller prospective study in 2002 by Ray-Chaudhuri et al (19). Eleven patients suspected of having GCA on clinical grounds were randomized to undergo temporal artery biopsy within 6 weeks after initiation of therapy with high-dose glucocorticoids. No patient was receiving  $<40$  mg of prednisone daily at the time of biopsy. Of the 7 patients with GCA who received between 4 and 6 weeks of glucocorticoids before their biopsies, 6 (86%) had histopathologic proof of this diagnosis on biopsy.

These studies confirm that even after the initiation of glucocorticoids, there remains a substantial window during which an informative temporal artery biopsy may be obtained. Therapy should never be delayed when the suspicion of GCA is high.

### Does a hypoechoic halo obviate the need for temporal artery biopsy?

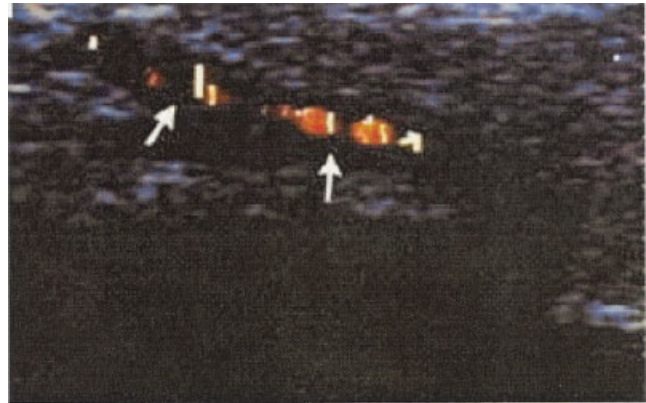
Temporal artery biopsy has been the gold standard for the diagnosis of GCA ever since Horton and colleagues reported 2 cases of “an undescribed form of arteritis of the temporal vessels” at a staff meeting of the Mayo Clinic in 1932 (20). Although the performance of temporal artery biopsy is an outpatient procedure associated with extremely low morbidity and excellent test characteristics for the diagnosis of GCA, the procedure is nevertheless invasive and—as discussed above—imperfect. In recent years, color duplex ultrasonography has been proposed as an alternative to biopsy in at least some circumstances.

Schmidt et al (21) performed color duplex ultrasonography on the temporal arteries of 30 patients with known diagnoses of GCA. The comparison group consisted of 82 patients without GCA (37 had PMR, 30 had rheumatoid arthritis, and 15 had other conditions). Twenty-two of the 30 patients with GCA (73%) had hypoechoic “halos” (Figure 3) surrounding the temporal arteries, a finding the investigators attributed to inflammation-associated edema of the vessel wall. No such halos were identified in any of the 82 patients in the comparison group, suggesting that this finding was specific for GCA. Followup studies on the GCA patients demonstrated resolution of the halos over periods ranging from 1 to 8 weeks following the institution of glucocorticoid treatment.

The study by Schmidt et al (21) had several limitations. First, temporal artery biopsies were not performed on all patients in either the GCA or the comparison group, leading to the potential for misclassification in both groups. Second, the study was not masked: in many cases, the clinical investigators knew the ultrasound results. Third, the incremental value of ultrasound over the information provided by a thorough clinical evaluation, particularly physical examination, was not determined.

A subsequent evaluation of this technique was less sanguine about the utility of ultrasound in the diagnosis of GCA. Salvarani et al (22) evaluated the temporal arteries of 86 consecutive patients suspected of GCA or PMR using 3 methods: physical examination, ultrasound, and temporal artery biopsy. Temporal artery biopsies were performed in all cases, and the ultrasonographers were masked to the results of the clinical evaluations. In this blinded study, a hypoechoic halo had a sensitivity for biopsy-proven GCA of only 40% (95% CI 16–68%) and a specificity of 79% (95% CI 68–88%; Table 4). Moreover, ultrasound identified anomalies only in patients whose temporal arteries were abnormal on physical examination, leading to the conclusion that ultrasound was no better than the physical exam in the diagnosis of GCA. Finally, 5 patients (16% of all diagnosed GCA cases) had normal temporal arteries on both physical examination and ultrasound but were shown to have GCA on biopsy, and 4 patients with hypoechoic halos demonstrated by ultrasound had negative biopsy results and eventual clinical diagnoses of conditions other than GCA.

Time has illustrated shortcomings of ultrasound in GCA, particularly as a test to supplant temporal artery biopsy. Ultrasound is most effective in diagnosing new cases; it is substantially less effective in detecting cases of recurrent



**Figure 3.** A hypoechoic halo in giant cell arteritis. Color duplex ultrasonography demonstrates a hypoechoic, dark halo surrounding the lumen of the temporal artery. The halo probably represents edema of the vessel wall. Reproduced, with permission, from ref. 2.

disease and cases in which patients have been treated with glucocorticoids prior to the procedure. Color duplex ultrasonography is a highly operator-dependent technique; it is presently unclear how reliable this technique will be in general practice, once extrapolated from referral centers. Additional studies and perhaps technologic advances will be required before color duplex ultrasonography can pose a serious challenge to temporal artery biopsy in the diagnosis of GCA.

*What is the role of ultrasound in TA?* Based on several case studies (23–26), ultrasound may have some role in the early identification of TA in patients at risk. Correlation of radiologic findings with pathologic features of the disease will be challenging (as is the case with all noninvasive imaging modalities applied to this disease). In addition, because of the relative rarity of large-vessel vasculitis, the development of sufficient experience with the technique among radiologists poses another challenge to its widespread use. The utility of ultrasound in following the progression of known disease over time and the correlation between ultrasound findings and eventual clinical events (and therefore, the need for therapy) are still unknown. At this point, the technique remains investigational in large-vessel vasculitis.

### What other new approaches to imaging are available in large-vessel vasculitis?

The invasive nature of conventional angiography, as well as its inability to evaluate characteristics of the vessel wall other than luminal features, makes the search for alternative imaging approaches a worthy pursuit. Magnetic resonance angiography, positron emission tomography, and electron beam computed tomography (EBCT) all have both theoretical and practical advantages over conventional angiography, but the optimal means of using these techniques in the clinic still requires refinement.

*Magnetic resonance imaging/magnetic resonance angiography (MRI/A).* Tso et al (27) performed 77 electrocardiogram-gated “edema-weighted” MRI/A studies on 24 patients with TA. Evidence of vessel wall edema was noted in 94% of patients believed to have unequivocally active disease. Despite this technique’s apparently excellent sen-

Criteria for GCA diagnosis	Schmidt		Salvarani	
	Sensitivity	Specificity	Sensitivity	Specificity
ACR criteria	22/30 (73)	82/82 (100)	7/20 (35)	52/66 (79)
Biospy proven	16/21 (76)	24/26 (92)	6/15 (40)	56/71 (79)

\* Sensitivity is expressed as the number of positive tests/all tests (%); specificity is expressed as the number of negative tests/all tests (%). GCA = giant cell arteritis; ACR = American College of Rheumatology. Data from refs. 21 and 22.

sitivity for active disease, its positive predictive value for active disease was poor: vessel wall edema was also noted in 56% of patients who were believed to be in remission. More disturbing was the lack of correlation between the finding of vascular edema and new anatomic changes on subsequent studies. Among the 16 patients in the study who underwent serial MRI/A studies, 6 did not have disease progression despite the presence of vessel edema on consecutive MRI/A studies, and 3 developed new lesions at 1 or more sites in the absence of concurrent edema.

Experience with MRI/A in TA has shown that the presence of vessel wall edema may be the result of an early phase of inflammation, but this finding is not always associated with lesion progression or with the development of new lesions. Currently, because of its ability to image large portions of the great vessels and to provide information about both the luminal size and vascular wall, MRI/A is extremely useful in making the diagnosis of TA and in providing a safe, noninvasive means of assessing changes in vascular anatomy. Unfortunately, the poor correlation between MRI/A-determined vessel edema and disease progression make this imaging modality unreliable as the sole guide to disease activity and treatment decisions.

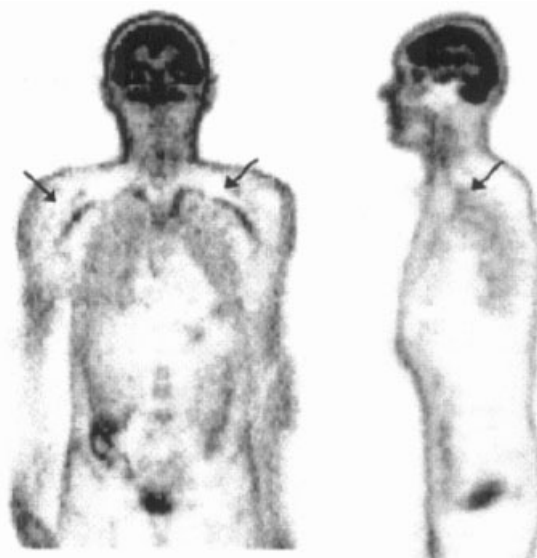
**Positron emission tomography (PET).** Striking images of large-vessel involvement in GCA have been generated through  $^{18}\text{F}$ -fluorodeoxyglucose (FDG) PET scans (Figure 4) (28). These images indicate the potential of this technique for studying large-vessel vasculitis, and imply that PET scans may soon be useful clinically. Because of high uptake of FDG in the brain, the small diameter of the temporal artery, and the relatively high background activity of the skin (Figure 4), direct evaluation of the temporal arteries is not possible with the current whole-body PET techniques. In the evaluation of the great vessels, however, there is promise. In a study of 25 patients with GCA and 13 patients with PMR, thoracic vascular FDG uptake had a sensitivity of 56% for the diagnoses of GCA or PMR, a specificity of 98%, and a positive predictive value of 93% (28).

In an ongoing followup study, Blockmans (23) studied 20 patients with GCA and 20 patients with PMR. Among the patients with PMR, vascular FDG uptake was visible in only 3 (15%), but 18 of the 20 showed intense shoulder and hip uptake. Among the GCA patients, 16 (80%) had intense FDG uptake in large vessels. At 3 months, uptake had disappeared in 7 of the 14 patients (50%) undergoing followup studies, and persisted (albeit with lower uptake) in the other 7. At 6 months, there was no further decrease in FDG uptake in the 6 patients reevaluated at that time.

PET scanning is an exciting modality for the study of

large-vessel vasculitis, yet many questions remain: Does persistent FDG uptake predict patients at risk for disease flares? How often is the diagnosis of large-vessel vasculitis confounded by the presence of other inflammatory processes involving large vessels, e.g., atherosclerosis? Should patients with PMR who demonstrate large-vessel FDG uptake be considered to have GCA (and treated accordingly)? The answers to these and other questions will come from additional studies.

**Electron beam computed tomography.** Some patients with TA have undergone aortic valve replacements, either because of valvulitis or valvular incompetence from dilatation of the ascending aorta. Most of these patients are unable to undergo MRI/A studies because of the metallic components in their prosthetic valves. In these patients, a reliable noninvasive means of monitoring their vasculature is not currently available. Technologic advances in the field of computed tomography may eventually address this problem. The short acquisition times used by EBCT improve resolution of the vasculature compared with conventional computed tomography techniques, and may make EBCT a useful modality for following disease pro-



**Figure 4.** Positron emission tomography scan in giant cell arteritis (GCA). Increased  $^{18}\text{F}$ -fluorodeoxyglucose uptake in the subclavian arteries of a patient with GCA. Reproduced, with permission, from ref. 28.

gression in patients with large-vessel vasculitis. In 2001, Paul et al (29) used serial EBCT to evaluate 16 patients with early TA. Of these patients, 6 had evidence of vascular changes. Only 1 of these patients had symptoms; EBCT detected evidence of vascular changes in the other 5 patients before they were clinically evident. More experience with this technique is required before broad recommendations can be made for clinical use.

*Where do we stand with alternatives to angiography in large-vessel vasculitis?* Ultrasound, MRI/A, PET, and EBCT all have the potential to provide information that conventional angiography cannot: namely, the status of the vascular wall (thickness, edema, biological activity, etc.). The major advantages and disadvantages of each technique are shown in Table 5. One principal advantage of angiography that should not be forgotten is the ability to measure the central aortic pressures directly during this procedure. Because of the propensity of large-vessel vasculitis—particularly TA—to involve the subclavian arteries, blood pressure measurements in the arms may be inaccurate. Patients with TA who have evidence of subclavian artery involvement should undergo a conventional angiogram to determine the degree to which arm pressures correlate with central aortic pressures. Even as noninvasive imaging procedures for large-vessel vasculitis continue to improve, it is likely that judicious use of conventional angiography will remain for the foreseeable future a cornerstone of the evaluation of these patients.

### Which patients with GCA lose vision?

The central concern of patients with GCA and their doctors is the prevention of vision loss. A quality-of-life study in GCA (30) indicated that anxiety about the potential threat to vision poses one of the greatest detractors from patients' quality of life. Not all patients with GCA may be subject to equal risk of this complication, however. The means of identifying those patients at greatest risk of vision loss and the question of whether or not some patients are relatively protected against this complication remain unresolved issues and areas of active investigation.

Cid et al (31) conducted a multicenter, retrospective study that identified 200 consecutive patients with biopsy-proven GCA. Thirty-two (16%) of those patients developed irreversible cranial ischemic complications, including blindness and cerebrovascular accidents. Surprisingly, the patients with the highest ESRs had the lowest risks of these events. Patients whose ESRs were  $>85$  mm/hour and whose hemoglobins were  $<11$  gm/dl had an odds ratio (OR) for ischemic events of 0.23 (95% CI 0.08–0.68). Patients with fever and weight loss also had a reduced risk of such events (OR 0.18, 95% CI 0.05–0.60). No patient with both constitutional symptoms and an ESR  $>85$  mm/hour suffered an ischemic event. In contrast, those without the classic features of inflammation (i.e., no fever or weight loss, ESR  $<85$  mm/hour, and hemoglobin  $>11$  gm/dl) had an OR for ischemic events of 5 (95% CI 2.05–12.2).

A subsequent study by Cid's group (32) offered a potential explanation for the inverse association between inflammatory symptoms and risk of visual loss that they observed. Using histologic techniques, Cid et al (32) quantified the degree of angiogenesis in temporal artery speci-

mens obtained from 31 patients with biopsy-proven GCA. Greater degrees of angiogenesis were noted in patients with a strong systemic inflammatory response. These findings support the concept that angiogenesis, occurring in response to inflammation, leads to the development of collateral circulation that protects patients from ischemic events.

These conclusions were partially supported by the findings of a prospective study by Liozon et al (33), who examined 174 GCA patients identified between 1978 and 2000. Thirty-five of the 174 patients (20%) experienced transient visual symptoms, and 23 (13%) suffered permanent vision loss. Both constitutional symptoms (defined in that study as a temperature  $>38^{\circ}\text{C}$  for longer than 1 week, severe asthenia, or weight loss  $>5\%$  of baseline body weight) and elevated C-reactive protein levels were protective against visual events, with ORs of 0.14 and 0.35, respectively. Interestingly, the ESR was not helpful, with an OR of 1.0. There was one other discordant fact: thrombocytosis, typically a marker of systemic inflammation, was second only to transient vision loss (OR 6.3; 95% CI 1.4–29.0) as a predictor of permanent vision loss (OR 3.7, 95% CI 1.8–7.9).

There is one other possible explanation for the apparent protective effect of inflammatory symptoms against vision loss: patients manifesting such symptoms are likely to present for medical care earlier, and are therefore more likely to receive prompt, vision-sparing therapy. This may explain why the population-based study by Salvarani and Hunder (7) found no difference in the incidence of vision loss between GCA patients with low ( $<50$  mm/hour) and high ( $\geq 50$  mm/hour) ESRs.

*How can I not treat acute vision loss in an elderly patient as GCA?* Confronted with such a clinical dilemma, one should remember the entity of nonarteritic anterior ischemic optic neuropathy (NAAION). This poorly understood disorder is the most common cause of optic neuropathy, with the exception of glaucoma (34). As with GCA, NAAION tends to affect white people older than 60 years of age. Unlike GCA, however, NAAION is not an inflammatory disorder—constitutional symptoms and elevated acute phase reactants are usually absent. NAAION tends to be associated with hyperemic disc swelling and a morphologically small optic disc with no cup (Figure 5A and 5B). In contrast, arteritic AION, the most common mechanism of vision loss in GCA, is associated with disc pallor, disc swelling, cotton wool spots, and a normal optic cup size (Figure 5C and 5D; Table 6).

Patients with NAAION typically report visual loss discovered soon after awakening. The underlying etiology of the vision loss is not clear, but is presumably related to microvascular ischemia (35). The damage to the optic nerve head ranges from subclinical to devastating. In some cases, both eyes are affected (36). Diabetes is a known risk factor for NAAION. The importance of other traditional risk factors for vascular dysfunction (e.g., hypertension, atherosclerosis) is not clear. Treatment is largely supportive. There is no role for glucocorticoids or surgical decompression of the optic nerve (37).

### Do patients with GCA who lose vision ever recover it?

The response of vision loss in GCA to treatment after the fact is a point of controversy in the literature. In 2002,

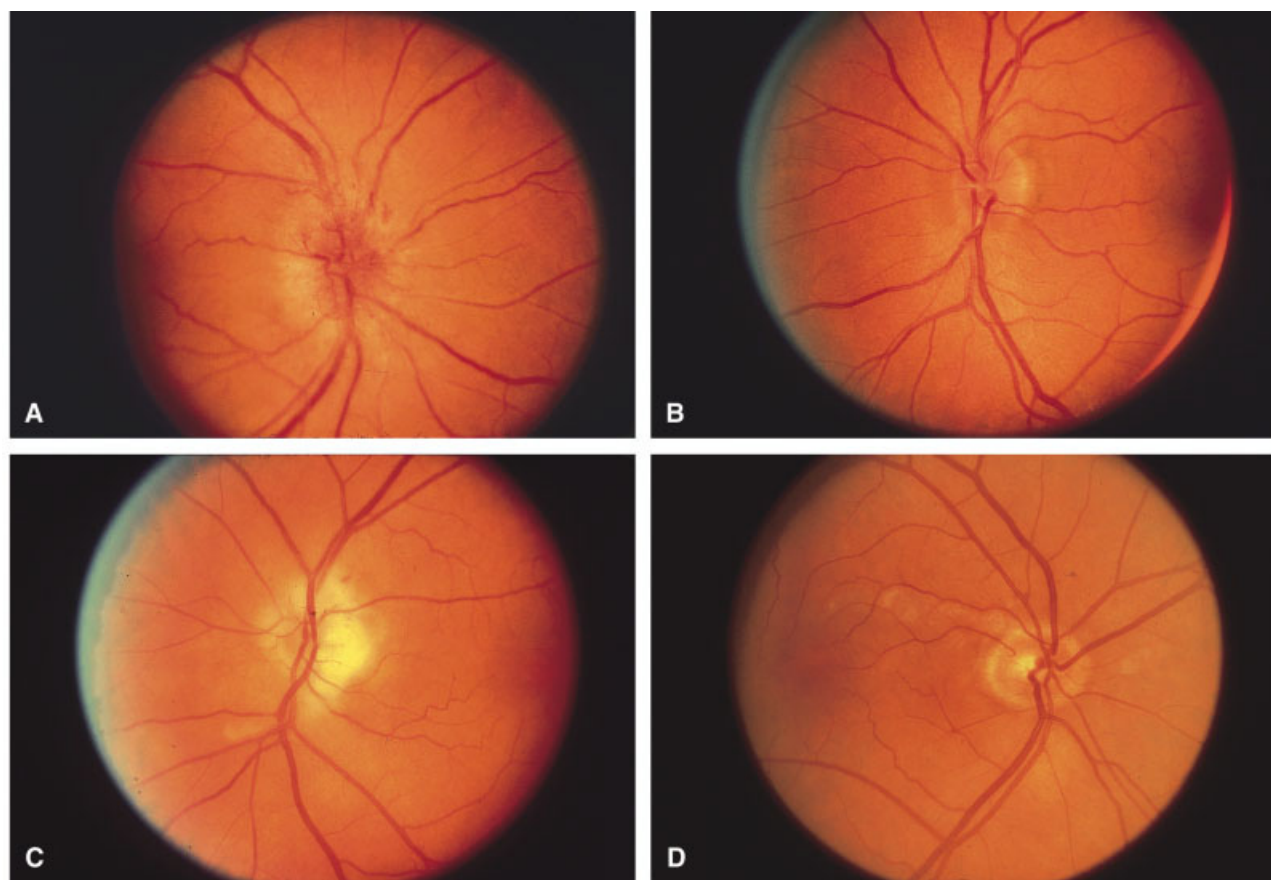
**Table 5. Advantages and disadvantages of angiography and noninvasive imaging techniques in large-vessel vasculitis\***

Technique	Advantage	Disadvantages
Angiography	Measurement of CAP possible	Invasive
Ultrasound	Noninvasive	Noninformative about the vascular wall
Magnetic resonance imaging	Noninvasive	Operator dependent
Positron emission tomography	Noninvasive	Interpretation of hypoechoic halo finding frequently problematic
Electron beam computed tomography	Noninvasive	Cannot measure CAP
	Measures metabolic activity	Poor correlation of MRI/A-determined vessel edema with clinical events
	Can be used in some individuals with contraindications to MRA	Cannot measure CAP
		Expense
		Potential confounding by atherosclerosis
		Cannot measure CAP
		Radiation exposure
		Cannot measure CAP

\* CAP = central aortic pressure; MRI/A = magnetic resonance imaging/ magnetic resonance angiography; MRA = magnetic resonance angiography.

Hayreh et al (38) addressed this question systematically in a retrospective review of 84 patients evaluated for variable degrees of GCA-associated vision loss. In each case, the diagnosis of GCA was confirmed by temporal artery biopsy

and the vision loss correlated temporally with the onset of other GCA symptoms. Among the 84 patients, 114 eyes were affected. Patients who presented with complete vision loss in 1 eye, a history of amaurosis fugax, or evidence



**Figure 5.** Arteritic versus nonarteritic anterior ischemic optic neuropathy (AION): fundoscopic appearances. **A and B**, Nonarteritic AION: A hyperemic, swollen optic disc with a few scattered peripapillary hemorrhages on one side (left eye, **5A**) with a small contralateral optic disc that has no central cup (right eye, **5B**) is consistent with a diagnosis of nonarteritic AION. If there were a clinical history consistent with giant cell arteritis (GCA), however, it would be difficult to exclude arteritic AION based on these ophthalmoscopic findings alone. **C and D**, Arteritic AION: The combination of a pale, swollen optic disc on one side (right eye, **5C**) with a disc that has a normal central cup in the contralateral eye (left eye, **5D**) makes the diagnosis of arteritic AION. The presence of cotton wool spots in this setting is virtually pathognomonic for GCA. Courtesy of Dr. Neil R. Miller, Wilmer Eye Institute, Johns Hopkins University.

**Table 6. Comparison of features of arteritic and nonarteritic anterior ischemic optic neuropathy\***

Feature	Arteritic	Nonarteritic
Age, mean, years	70	60
Sex distribution	Female > male	Male = female
Associated symptoms	Headache, scalp tenderness	Pain occasionally noted
Visual acuity	Up to 76% < 20/20	Up to 61% > 20/20
Disc	Pale > hyperemic edema	Hyperemic > pale edema
Cup size	Cup normal	Cup small
Mean ESR, mm/hour	70	20–40
Natural history	Improvement rare	Improvement in up to 43%
Contralateral involvement	Fellow eye in 95%	Fellow eye in <30%
Treatment	Glucocorticoids	None proved

\* ESR = erythrocyte sedimentation rate (59).

of bilateral or rapidly progressive visual involvement received 150 mg of dexamethasone intravenously every 8 hours for 1–3 days before starting treatment with oral glucocorticoids (generally 60–80 mg/day of prednisone). All patients underwent detailed serial examinations, including tests of visual fields (Goldman perimeter) and visual acuity (Snellen).

Arteritic AION was responsible for the vision loss in >90% of the patients studied (Table 7). Only 12 eyes (10%) belonging to 10 patients showed improvement in visual acuity (defined as an improvement of at least 2 lines of the Snellen chart). Moreover, only 5 eyes (4%) belonging to 5 patients had improvement in the central visual field function as well as visual acuity. The discrepancy in results is likely due to a combination of factors, including the subjectivity of the visual field test (which relies heavily on both cooperation from the patient and the skill of the clinician interpreting the results), the inability of the Goldman perimeter test to detect small amounts of visual improvement, and learning by the patient (e.g., by fixating eccentrically on the letters in the Snellen chart). In short, improvement perceived by patients and noted on visual acuity tests may not reflect true improvement in retinal or optic nerve function, but rather the patients' compensation for acquired, permanent vision deficits.

### Should patients with acute vision loss in GCA receive pulsed glucocorticoids?

In the setting of acute vision loss in GCA, many practitioners advocate the use of high-dose, intravenous glucocorticoids, e.g., 1 gm of methylprednisolone daily for 3 days. The value of this regimen compared with that of prednisone 60–80 mg daily in this scenario has not been studied rigorously. In Hayreh's retrospective review (38), the glucocorticoid regimen did not impact prognosis: among the patients with evidence of vision improvement, more than half were treated with intravenous dexamethasone (150 mg every 8 hours for 1–3 days). In a small minority of patients, however, there remains some residual circulation within the retinal or posterior ciliary artery circulatory beds within a day or so of vision loss (38). It is conceivable that the immediate institution of glucocorticoid therapy

and the maintenance of an adequate perfusion pressure could be associated with at least partial vision recovery in some patients. For this reason, pulse glucocorticoids is a reasonable intervention if the vision loss is extremely acute.

### Should we prescribe aspirin in addition to prednisone for GCA?

Liozon et al (33) reported that the *degree* of thrombocytosis correlated with the risk of permanent vision loss: 10 of 43 patients (23%) with platelet counts  $>500 \times 10^9$ /liter experienced this complication in at least 1 eye, as did 6 of the 18 (33%) with platelet counts  $>600 \times 10^9$ /liter. This correlation raises the possibility that antiplatelet agents, such as aspirin, may be effective adjunctive therapy in the treatment of GCA.

A laboratory model of GCA supports the notion that aspirin may have a role in the treatment of this disease. Studies of the severe combined immune deficient (SCID) mouse chimera model of GCA (in which temporal arteries from humans with GCA are grafted onto SCID mice) indicate that glucocorticoids decrease vascular inflammation by downregulating the nuclear factor  $\kappa$ B (NF- $\kappa$ B) pathway (39). In theory, other agents that block this pathway may also decrease vascular inflammation. One such agent is acetylsalicylic acid (ASA). In fact, the combined use of

**Table 7. Ocular ischemic lesions in 84 patients with visual loss from GCA\***

Ocular diagnosis	Unilateral no. (%)	Bilateral no. (%)
Arteritic anterior ION	50 (60)	27 (32)
Arteritic posterior ION	5 (6)	0 (0)
Central retinal artery occlusion	10 (12)	1 (1)
Cilioretinal artery occlusion	9 (11)	1 (1)
Choroidal ischemia	1 (1)	0 (0)

\* The numbers add up to > 84 patients because some had more than one coexisting ocular diagnosis as the cause of vision loss. GCA = giant cell arteritis; ION = ischemic optic neuropathy (38).

ASA and dexamethasone in vitro synergistically inhibits interferon- $\gamma$ , a cytokine believed to be central to GCA (40). Weyand et al (41) treated SCID mouse chimeras with intraperitoneal injections of ASA, indomethacin, dexamethasone, or saline for 3 weeks. The investigators then harvested the temporal arteries and quantified cytokine messenger RNA through polymerase chain reaction (PCR)/enzyme-linked immunosorbent assays. ASA, but not indomethacin, was an effective inhibitor of interferon- $\gamma$ , indicating that ASA achieves its effect through inhibition of a pathway not mediated by cyclooxygenase. Additional in vitro studies demonstrated that although dexamethasone inhibits the production of interleukin-1 $\beta$  by monocytes, ASA is a very effective inhibitor of interferon- $\gamma$  production by T cells. Electrophoretic mobility shift assays demonstrated that in contrast to dexamethasone, which suppresses the nuclear translocation of NF- $\kappa$ B, ASA inhibits the production of activator protein 1.

*Can these in vitro findings be extrapolated to patients with GCA?* This is not clear. The dose of aspirin administered to the laboratory mice is approximately equivalent to prescribing an oral dose of 325 mg 3 times per day in humans (Weyand CM: personal communication). This is substantially higher than the doses of aspirin recommended now as prophylaxis against cardiovascular events, but considerably lower than the doses not long ago used to treat rheumatoid arthritis. Adjunctive therapy with aspirin in patients who have no contraindications may help prevent ischemic complications of this diagnosis. The use of aspirin, however, is not without risk. Patients who take low-dose (i.e., <325 mg daily) aspirin have a 2.5 times greater risk of gastrointestinal hemorrhage than those who do not (42). Caution should be exercised before prescribing daily aspirin for patients who are at high risk of gastrointestinal hemorrhage, renal dysfunction, or other untoward effects of this medication.

### What are the current steroid-sparing options in large-vessel vasculitis?

A number of clinical trials and case series of new therapies have been reported in the medical literature (43,44). The greatest amount of attention, however, has been paid to the role of methotrexate (MTX) in the treatment of GCA.

*Methotrexate.* Two randomized, double-masked trials of MTX as a glucocorticoid-sparing agent have reached disparate conclusions about the value of this agent in GCA (45,46). In a single-center study from Spain, Jover et al (45) randomized 42 GCA patients to receive either 10 mg of oral MTX weekly (in addition to glucocorticoids), or glucocorticoids alone. Approximately 25% of patients in the MTX group withdrew from the study due to adverse effects, but those 15 patients who tolerated MTX for the entire length of the study (24 months) appeared to derive significant benefits. Among these 15 patients, there were 8 relapses. These patients were treated with a mean cumulative dose of prednisone of 4.2 gm and had an average length of treatment with prednisone of 29 weeks. The group treated with prednisone alone had 24 relapses ( $P = 0.02$ ), a total cumulative dose of 5.5 gm of prednisone ( $P = 0.009$ ), and an average of 94 weeks of prednisone treatment ( $P = 0.0016$ ). Despite the lower quantities of prednisone used in

the MTX group, patients in that group had a rate of glucocorticoid-induced side effects similar to that seen in the group treated with glucocorticoids alone, including fracture, neuropsychiatric disorders, cataracts, diabetes, hypertension, weight gain, and myopathy. The results of this trial support the use of MTX in GCA but indicate that MTX is not a definitive solution to the treatment of this disease.

The results of the study by Jover et al (45) were contradicted by those of a larger, double-masked, placebo-controlled trial that also addressed the efficacy of MTX as a steroid-sparing agent. In the second trial (46), 98 patients—more than twice the number enrolled in the study by Jover et al—were randomized to receive either MTX (median dosage achieved 15 mg/week) or placebo in addition to prednisone. At the end of only 1 year of treatment, 77.3% in the placebo group and 57.5% in the MTX group had failed therapy (i.e., experienced disease flares;  $P = 0.26$ ). The difference in failure rate between the 2 treatment groups was not statistically different. Approximately 300 patients (3 times the number enrolled) would have been required to demonstrate that the observed difference between the 2 treatment groups was statistically significant. Moreover, in this trial, the use of MTX did not lead to a significant reduction in prednisone use.

The reasons for the great disparities in outcomes for these 2 trials have been debated in detail (47–49). The difference may reflect the use of an aggressive prednisone taper by the latter group (entailing a reduction in prednisone dose of 5 mg every 4 days on an alternate-day schedule, leading to a dosage of 60 mg every other day at the end of 3 months), but in fact *both* protocols were designed to wean the patient completely from corticosteroids at the end of 6 months. In the final analysis, the reasons for the different findings remain unclear. The benefit of MTX as an adjunct agent to glucocorticoids in the treatment of GCA (if any) appears to be modest.

### Do infections cause large-vessel vasculitis?

A recent laboratory model of large-vessel arteritis suggests that the media of the elastic arteries is an inherently immunoprivileged site, supporting the plausibility of an infectious etiology for GCA (50,51). Candidate pathogens in GCA have been investigated using both broad-range and microbe-specific PCR techniques.

*Parvovirus.* Gabriel et al (52) performed PCR for parvovirus B19 DNA on temporal artery specimens obtained from 50 consecutive patients suspected of having GCA. Thirteen of those patients had histologic proof of temporal arteritis, and 1 had a clinical diagnosis of GCA despite a negative temporal artery biopsy. Parvovirus B19 DNA was found in the temporal arteries of 8 of the 14 patients (57%) diagnosed with GCA, compared with only 3 of 36 arteries (8%) from patients without GCA ( $P = 0.0013$ ), consistent with a role for parvovirus in the pathophysiology of GCA.

Salvarani et al (53) reexamined this question by performing PCR on temporal artery specimens from 31 consecutive patients with biopsy-positive GCA, 43 consecutive patients with biopsy-negative PMR, and 19 age-matched controls. Patients in the control group were suspected (incorrectly) of having GCA and were diagnosed later with a variety of other disorders, including sepsis,

cancer, polyarteritis nodosa, hypersensitivity vasculitis, psoriatic arthritis, and adult-onset Still's disease. Similar to the study by Gabriel et al (52), 64% of temporal artery specimens from patients with GCA had evidence of parvovirus B19 infection by PCR. In contrast with the previous study, however, 77% of temporal artery samples from patients with PMR and 74% of temporal artery samples from age-matched controls also demonstrated evidence of parvovirus B19 infection. Although there was no difference in the percentages of GCA patients and controls whose biopsies were positive for parvovirus by PCR, differences in messenger RNA expression were not evaluated. The study by Salvarani et al makes a role for parvovirus appear less likely, but does not exclude it entirely.

*Chlamydia pneumoniae*. Case reports and small controlled studies have suggested a role for *C. pneumoniae* in GCA (54–57). Regan et al (58) performed a case-control study involving 90 patients diagnosed with GCA based on clinical and histologic criteria and 90 control patients matched for age, sex, and year of biopsy. The investigators employed 2 validated sets of PCR primers that target 2 different *C. pneumoniae* genes. Only 1 case sample (1% of all case samples) was positive for the *ompA* gene using the CP1-CP2/CPC-CPD primer set. One control sample was also positive using these primers. With the Cpn90/Cpn91 primers, none of the cases and none of the controls were positive for the 16S rRNA gene. The validity of these negative findings was documented by confirmation of the presence of human DNA in the samples (using primers for the beta-globin gene) and appropriate spiking experiments with *C. pneumoniae* DNA. The results of these investigations argue strongly against any role for *C. pneumoniae* in the propagation of GCA.

## Summary

- GCA almost never occurs in a patient younger than 50 years of age.
- One of every 10 patients with GCA has negative temporal artery biopsy specimens, even if bilateral biopsies are performed.
- One of every 10 patients with GCA has an ESR <50 mm/hour.
- By itself, a highly elevated ESR (e.g., >100 mm/hour) is not a powerful predictor of GCA.
- Jaw claudication and diplopia are extremely useful in predicting which patients will have a positive temporal artery specimen. Classic GCA symptoms, such as headache, PMR, and visual symptoms other than diplopia, are not.
- Temporal artery biopsies may confirm the diagnosis of GCA even weeks after therapy with glucocorticoids has begun.
- The presence of fibrinoid necrosis on a temporal artery biopsy should prompt the search for forms of systemic vasculitis other than GCA, such as PAN or the ANCA-associated vasculitides.
- Ultrasound of the temporal arteries adds little to a thorough physical examination when evaluating a patient for GCA.
- MRI/A is useful in identifying the vascular abnormalities associated with TA, but the presence of vessel edema alone is not an accurate gauge of disease activity.
- PET and EBCT should still be considered experimental modalities in the evaluation of the large-vessel vasculitides.
- GCA patients with highly elevated ESRs may be less likely to experience vision loss. The specific reasons for this observation, if true, remain under investigation.
- Patients with hyperacute vision loss from GCA (e.g., within 24–48 hours) should be treated with high-dose, intravenous glucocorticoids.
- GCA patients without contraindication to aspirin therapy may benefit from adjunctive therapy with dosages as high as 325 mg 3 times per day.

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