Giant Cell Arteritis

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KEYWORDS

• Primary • Secondary • Vasculitis • Autoimmune • Nervous system

KEY POINTS

- Giant cell arteritis (GCA) or large-vessel GCA is a chronic, idiopathic, granulomatous vasculitis.
- Vascular complications are generally due to delay in diagnosis and initiation of effective treatment.
- Advancements have been made in MRI and MR angiography, computed tomography angiography, 18fluoro-deoxyglucose/PET and color duplex ultrasonography.
- Corticosteroids are the mainstay of therapy in GCA and tocilizumab is an alternative agent.

INTRODUCTION

In 1890, Hutchinson[1] described painful inflamed temporal arteries that prevented a man from wearing his hat. Giant cell arteritis (GCA) was characterized as a distinct entity by Horton and colleagues in 1932.[2] It is the most common primary systemic vasculitis of the Western world in people older than 50. The 2012 Revised Chapel Hill Consensus Conference nomenclature[3] categorizes GCA as a large-vessel vasculitis, prompting use of the equivalent term, large-vessel GCA. This article reviews the epidemiologic, clinicopathologic features, diagnosis, and treatment of GCA.

EPIDEMIOLOGY

The lifetime risk of developing GCA is estimated at 1% for women and 0.5% for men.[4] The disease rarely occurs in individuals younger than 50 years and peaks in the eighth decade of life. It more commonly affects Scandinavian individuals and North Americans of Scandinavian decent than Southern Europeans and rarely occurs in Black

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and Asian individuals. There is a genetic predisposition to the disease and an association with the HLA-DRB1*04 allele.[5]

PATHOLOGY

The classic histologic changes of GCA include arterial wall inflammation, internal elastic lamina fragmentation, and intimal thickening (**Fig. 1**). Although GCA derives its name from the presence of multinucleated giant cells, the latter are seen in only approximately one-half of positive temporal artery biopsies (TABs), in association with a granulomatous inflammatory infiltrate composed of CD4+ T-cells and macrophages located at the intima-media junction near fragments of the internal elastic lamina. Other TAB specimens manifest lympho-mononuclear–predominant panarteritis with occasional neutrophils and eosinophils without giant cells. In a minority of cases, inflammation may be seen in periadventitial vessels or the vasa vasorum. There is considerable variation in histopathology between patients and within a given TAB tissue sample. Arteritic involvement of a given artery may be focal and segmental, leading to skip lesions. There may be healed arteritis suggested by intimal thickening, fragmented elastic lamina, and scarred media, although these may in part be age-related changes. Arterial wall thickening can lead to partial or complete occlusion of the lumen and ischemic complications, such as anterior ischemic optic neuropathy (AION). A subset of patients had small-vessel vasculitis surrounding noninflamed temporal artery segments in TAB tissue specimens.[6] Arteritis of the temporal artery is not entirely specific for GCA, and can be encountered with polyarteritis nodosa, antineutrophil cytoplasm antibody–associated vasculitis, malignancy, and atypical polymyalgia rheumatica (PMR).

IMMUNOPATHOGENESIS

Inappropriate activation, maturation, and retention of antigen-presenting adventitial dendritic cells are early steps in the pathogenesis of GCA. These cells sample the surrounding environment for viral and bacterial pathogens through the action of toll-like receptors (TLRs) wherein particular TLR profiles appear to be vessel specific,[7] which may explain why some blood vessels are more prone to be targeted by GCA than others. Mouse models[8] show activated vessel wall–embedded dendritic cells that release chemokines that recruit CD4+ T-cells and macrophages. The pattern of

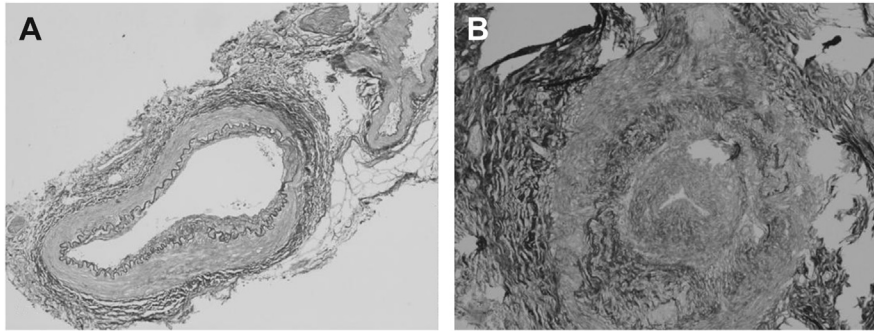

Fig. 1. TABs. (*A*) Normal. (*B*) Typical GCA showing inflammation of the arterial wall, fragmentation of the internal elastic lamina, intimal thickening, and luminal occlusion.

arterial inflammation corresponds to TLR4 stimulation that induces panarteritis, and TLR5 that stimulates perivasculitis.[9]

CLINICAL FEATURES

The onset of GCA tends to be insidious over weeks to months, and abrupt in up to 20% of patients, with a spectrum of initial disease manifestations attributable to the localized effects of vascular and systemic inflammation, including new-onset headache, scalp tenderness, jaw claudication, fever, fatigue, malaise, anorexia, weight loss polymyalgia, and visual loss. The artificial separation of cranial and extracranial features is misleading, as postmortem studies show that the intracranial arteries are largely spared.[10] Although headache is a prominent feature, it is not universal. The headache is classically constant, sudden in onset, and located in the temporal region where it is severe enough to disturb sleep. It can vary greatly in intensity and location. It may become progressively worse, or wax and wane, temporarily subsiding in the absence of treatment. A key feature is that it typically differs from any other previously experienced headache, and for this reason, the patient may deny headache, instead calling the symptom head pain. The headache may be associated with scalp tenderness, especially on hair brushing/combing or wearing glasses. The slightest pressure on resting the head on a pillow may be intolerable. The pain may be generalized, spare the scalp altogether, or affect the eye, ear, face, jaw, or neck. Tenderness, prominence, and decreased temporal artery pulsation (**Fig. 2**) increase the likelihood of GCA, although a third of TAB-proven GCA cases have normal temporal arteries on clinical examination.

An estimated 15% of patients with GCA experience ophthalmologic complications, notably ischemic optic neuropathy (AION) due to arteritic involvement of the short posterior ciliary arteries supplying the optic nerve head, with the remainder composed mainly of retinal blindness due to central retinal artery involvement.[11,12] Visual loss is painless, partial or complete, and unilateral or bilateral; and once established it is

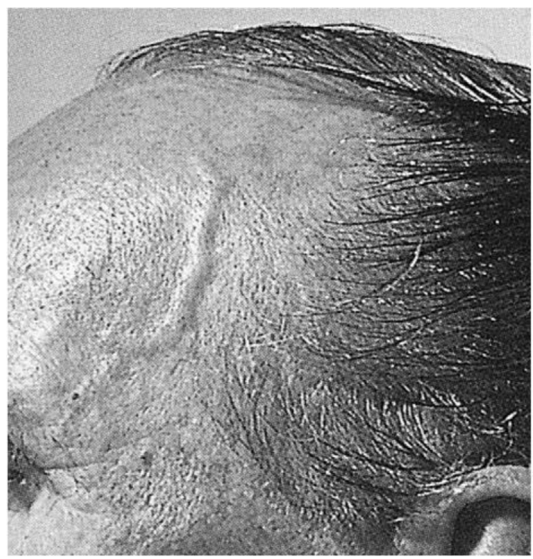

Fig. 2. Prominence of the temporal artery in GCA.

irreversible. It may be preceded by fleeting visual blurring with exercise, amaurosis fugax, or diplopia, but commonly occurs without warning and may be the presenting symptom. Ophthalmoplegia is usually due to a partial or complete oculomotor or abducens nerve palsy, and is a recognized complication of ischemia affecting the extraocular muscles, cranial nerves, or brainstem.

Other ischemic complications of GCA include transient ischemic attack and stroke, which may occur due to thrombosis, microembolism, or a combination of intimal hyperplasia and distal thrombosis. Although the vertebral arteries are inflamed in the large majority of patients at postmortem examination, clinically significant vertebrobasilar insufficiency is uncommon.

Large-Vessel Involvement

Aortic inflammation can be observed in surgical biopsies or at postmortem examination in GCA; however, the true frequency is difficult to ascertain. Computed tomography angiography (CTA) and helical aortic computed tomodensitometry discern aortic involvement in 45% to 65% of patients with GCA, with the thoracic aorta most often affected. The relationship between aortitis and subsequent aortic aneurysm remains unclear. In a cross-sectional study using CT, 12 (22.2%) of 54 patients with GCA developed aortic aneurysms after 4.0 to 10.5 years[13] with relative risks ranging from 3.0 to 17.3. Distal stenotic lesions of the subclavian, axillary, and brachial arteries occur in 3% to 15% of patients. Lower extremity arteries are infrequently affected; however, the identification of claudication and vascular bruits is important to ascertain before initiation of empiric corticosteroids (CS) because such findings, which add weight to the formal diagnosis of GCA, may resolve with effective treatment. The management of peripheral arterial involvement rarely requires surgical intervention.

DIAGNOSIS

Classification Criteria

The American College of Rheumatology (ACR) 1990 criteria for the classification of GCA[14] requires the presence of 3 or more of the following: age older than 50 years, new-onset localized headache, temporal artery tenderness or decreased pulsation, erythrocyte sedimentation rate (ESR) >50 mm/h, and abnormal TAB, yielding a sensitivity of 93.5% and specificity of 91.2% to discern GCA from other vasculitides. Jaw claudication in association with diplopia or decreased vision, or scalp tenderness and new headache are predictive of GCA (**Table 1**). The ACR Classification criteria have been mistakenly used for diagnosis, where they function poorly and (without TAB) are very insensitive.

Laboratory Studies

Blood studies

Acute-phase markers of inflammation are often significantly elevated, and a normocytic normochromic anemia and thrombocytosis may be present, as may elevation of liver transaminase levels with a reduced albumin level. The presence of rheumatoid factor, antinuclear and other autoantibodies are not present in greater frequency than in the general population. Although the ESR has historically been the acute-phase measure of choice in the diagnosis of GCA, up to a quarter of patients may have a normal value and elevation of the C-reactive protein (CRP) is a better predictor of obtaining a diagnostic TAB. The combination of an elevated CRP and positive TAB render the highest sensitivity and specificity for the diagnosis of GCA.

Table 1
Positive predictive value of clinical features of GCA

Clinical Features Associated With a Positive TAB	PPV, %	Percentage of Patients, %
New headache	46	49
Scalp tenderness	61	18
Jaw claudication	78	17
Double vision	65	10
Jaw claudication + Scalp tenderness + New headache	90	6
Jaw claudication + Double vision or decreased vision	100	0.7

Abbreviations: GCA, giant cell arteritis; PPV, positive predictive value; TAB, temporal artery biopsy.
Adapted from Younge BR, Cook BE, Bartley GB, et al. Initiation of glucocorticoid therapy: before or after temporal artery biopsy? Mayo Clin Proc 2004;79:486; with permission.

Temporal artery biopsy

TAB has been the gold standard test representing definitive pathologic diagnosis. Performed correctly, TAB carries a low procedural risk of significant complications and a positive result removes later doubts about diagnosis, particularly if treatment causes complications, or if the patient fails to respond promptly to therapy, whereas a negative biopsy is important in averting the long-term risk of empiric corticosteroid therapy.[15] The true sensitivity of unilateral TAB was 87% using Bayesian analysis with a variation in sensitivity of 24% to 94% in clinical cohorts.[16] The likelihood of a false-negative TAB may be influenced by the length of the specimen, the duration of prior glucocorticoid therapy, pathologic sectioning techniques, and the presence of predominantly noncranial disease. Retrospective reviews suggest a postfixation biopsy length of 1 to 2 cm is adequate. Whether bilateral biopsies should be performed depends on the rate of discordance, which in a pooled analysis of 4 studies looking at 439 synchronous bilateral biopsies was 5.9%.[17] The side selected for TAB should be the one, if present, with lateralizing symptoms or signs.

Temporal artery ultrasound

Temporal artery ultrasound studies, which are cost-effective, noninvasive, and lack significant complications, take approximately 5 minutes to perform, and render an image of the inflamed temporal artery characterized by edematous wall swelling. The latter conforms to a dark hypoechoic circumferential halo sign that represents continuous or segmental wall thickening (**Fig. 3**). Stenosis and occlusion common in elderly patients due to atherosclerosis, neither of which are specific or sensitive for GCA, also may be noted.

Three meta-analyses[18–21] demonstrated the usefulness of the halo sign in the diagnosis of GCA with a sensitivity of 68% and specificity of 91%, and 100% specificity for s bilateral halo sign.

Other imaging studies

Conventional angiography has little if any role unless a surgical intervention is contemplated. Ultrasound of the thoracic aorta is generally inadequate but it may provide useful information in proximal upper limb arteries to increases the diagnostic yield of GCA. Both MRI, MR angiography (MRA), and contrast-enhanced CTA provide useful images of mural and luminal changes suggestive of large-vessel vasculitis in GCA that include circumferential wall swelling, smoothly tapered luminal narrowing of aortic branches, and aortic aneurysm formation. Moreover, MRI and MRA are favored over CTA by

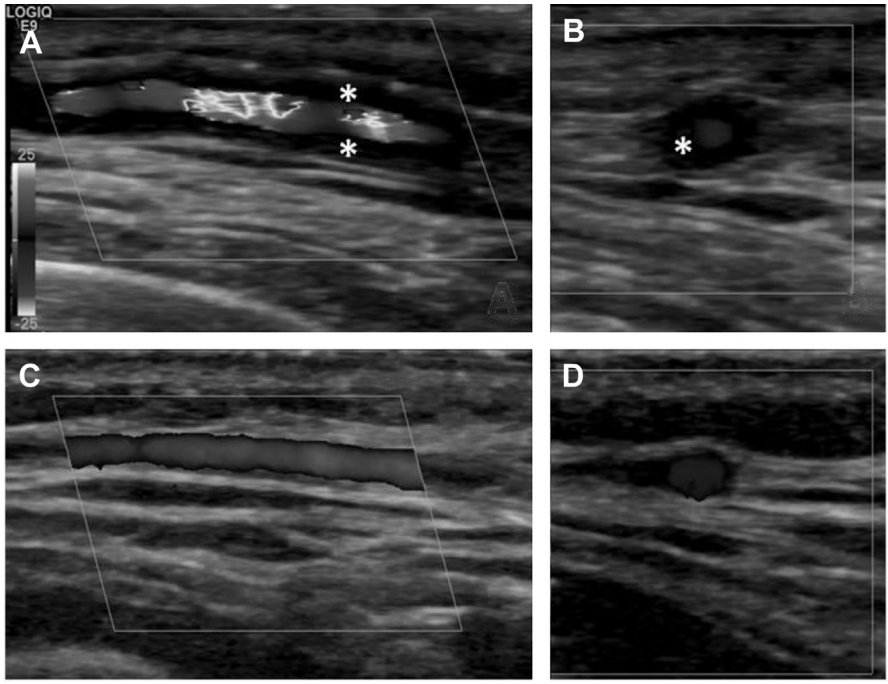

Fig. 3. TAUS. The hypoechoic "halo" sign (*asterisks*) on (*A*) longitudinal and (*B*) transverse section. (*C*) and (*D*) Normal artery.

most experts. Bright mural enhancement of the temporal artery on contrast-enhanced high-resolution MRI had comparable sensitivity and specificity to temporal artery ultrasound (TAUS) in the diagnosis of GCA in one retrospective single-center analysis, the latter of which decreased in sensitivity over the first few days of corticosteroid treatment (85% after 0–1 days, 64% after 2–4 days, 56% after >4 days).[12,22]

Whole-body ^{18}Fluorodeoxyglucose (FDG)-PET increases the overall diagnostic accuracy of large-vessel involvement in GCA from 54% to 70%.[23] One meta-analysis[24] found that the absence of FDG uptake conferred a negative predictive value of 88% of GCA, whereas thoracic vascular uptake was highly suggestive of GCA. However, there have not been properly designed trials to assess the sensitivity and specificity of ^{18}F-FDG PET in GCA, nor does it reliably distinguish between atherosclerosis and vasculitis.[25] The radiographic features of large-vessel involvement so noted in CTA and PET imaging decrease rapidly after the initiation of CS treatment; features of large-vessel vasculitis including concentric wall thickening were significantly more frequent in treatment-naïve patients compared with patients treated with CS for 1 to 3 days (77% vs 29%, $P = .005$).[26] The diagnostic accuracy of PET in detecting large-vessel involvement was significantly higher in patients not receiving immunosuppressive therapy (93.3% vs 64.5%).[23]

PROGNOSIS

Clinical studies have not validated the relation of existent classification criteria for GCA to clinical and laboratory measures to prognosticate relapse likelihood and outcome. It seems reasonable to consider a return to higher-dose treatment to improve prognosis

in patients experiencing a returning headache, PMR-like symptoms, jaw claudication, and visual symptoms. Since the advent of CS for GCA, the long-term outcome and survival rates have been similar to age-matched population including those with large-vessel complications,[26] although before CS, the estimated mortality was 12.5%.[27]

TREATMENT AND OUTCOME

Most experts recommend early initiation of high-dose CS therapy. The case can be made for early intervention with empiric treatment in patients with visual loss because untreated, the other eye is at heightened similar risk in up to one-third of cases for the ensuing 3 weeks, moreover partial visual improvement in vision is more likely if treatment commences within the first day of visual loss. A similar approach is advocated in those with features of impending visual loss, such as amaurosis fugax, diplopia, and jaw claudication. However, if the likelihood of GCA is low to moderate, withholding treatment and awaiting TAB that later returns negative would avoid unnecessary treatment.

Although there are no randomized controlled trials (RCTs) of the use of CS in GCA, most experts agree with daily morning treatment of prednisone at dosages of 40 mg to 60 mg until symptoms and laboratory abnormalities resolve. Alternate daily CS is not as effective as a daily regimen, alone or in association with adjuvant methotrexate for GCA. In fact, the symptomatic response that follows CS treatment is so striking and rapid in GCA, that it is a diagnostic criterion of the disease. Patients with PMR experience improvement in symptoms related to systemic inflammation over 2 to 3 days, whereas symptoms related to impaired blood flow, such as jaw claudication and visual disturbance, generally take longer to respond and resolve. Although sustained visual loss may be permanent and unresponsive to therapy, the risk of further progression is low. Although prednisone in the dose range of 10 mg to 40 mg per day was effective in several cohorts,[28,29] the results were not considered conclusive because of small sample sizes and apparent selection bias. Pulsed intravenous methylprednisolone was advocated in patients with GCA and visual disturbances[30,31]; however, one observational study[32] and another RCT[33] failed to demonstrate improved efficacy in preventing visual loss compared with high-dose oral therapy. Moreover, intravenous pulsed methylprednisolone, which demonstrated no significant long-term CS-sparing effects in the treatment of simple forms of GCA, was reserved for complicated forms of GCA. One small RCT[34] that administered 3 consecutive days of 1 g intravenous pulsed methylprednisolone induction, followed by oral CS found higher rates of remission, fewer relapses, and more rapid tapering compared with patients treated with oral high-dose CS. The CS dose can be gradually tapered in the first month after the resolution of reversible clinical symptoms and the levels of acute-phase reactants falls by 50%. Treatment should be continued for at least 2 years, with most patients weaned off of medication by 4 to 5 years. A minority of them may need continued low-dose CS.

A multicenter RCT[35] concluded that tocilizumab, received weekly or every other week, combined with a 26-week prednisone taper, was superior to either 26-week or 52-week prednisone tapering plus placebo with regard to sustained CS-free remission in patients with GCA. Longer follow-up is necessary to determine the durability of remission and safety of tocilizumab. Sustained remission at week 52 occurred in 56% of the patients treated with tocilizumab weekly and in 53% of those treated with tocilizumab every other week, as compared with 14% of those in the placebo group who underwent the 26-week prednisone taper and 18% of those in the placebo group who underwent the 52-week prednisone taper ($P<.001$ for the comparisons of either active

treatment with placebo). The cumulative median prednisone dose over the 52-week period was 1862 mg in each tocilizumab group, as compared with 3296 mg in the placebo group that underwent the 26-week taper ($P<.001$ for both comparisons) and 3818 mg in the placebo group that underwent the 52-week taper ($P<.001$ for both comparisons). Serious adverse events occurred in 15% of the patients in the group that received tocilizumab weekly, 14% of those in the group that received tocilizumab every other week, 22% of those in the placebo group that underwent the 26-week taper, and 25% of those in the placebo group that underwent the 52-week taper.

SUMMARY

GCA is a common, serious, and treatable vasculitis that affects older adults. Rapid access and management care pathways ensure the early referral of untreated suspected patients for readily available TAB especially warranted in those with low to moderate probability of disease, and appropriate primary and secondary care to prevent excess morbidity and mortality associated with empiric and often unwarranted high-dose CS therapy. Published guidelines for GCA diagnosis and management need to be rigorously examined to assess the impact of CRP, TAUS signs, large-vessel imaging, and TAB in any given patient, especially those who warrant empiric high-dose CS due to impending visual loss. Moreover, guidelines need to reflect a unified definition of clinical relapse. Studies assessing the link among clinical symptoms, inflammatory markers, imaging techniques, and mimicking conditions will be very valuable. Finally, long-term vascular complications are increasingly recognized in GCA, and this is blurring the margin between atherosclerosis and vasculitis, which may improve our understanding of both these conditions (65). Biological agents, including tocilizumab, are emerging as effective and safe CS-sparing therapy in treating GCA.

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