Chapter

Giant Cell Arteritis: Current Advances in Pathogenesis and Treatment

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Abstract

Giant cell arteritis (GCA) is the most common vasculitis in adults, with the incidence increasing with the advancing age. The aorta and its branches, especially the carotid extracranial branches, are the classic targets of inflammation in GCA. Visual loss, upper limb ischemia, and stroke are complications described. Suspicion of GCA is a medical emergency, and patients need to be quickly diagnosed/treated to prevent irreversible damage. Headache is the most common symptom, and a new-onset headache in older adults should always raise the suspicion of GCA. Patients may also present with scalp tenderness or tongue/jaw pain. GCA is often found to be the cause of an obscure-origin fever in older patients. A positive temporal artery biopsy is considered the gold standard for the diagnosis, but imaging techniques enable the assessment of cranial and extracranial arteries and the aorta. Ultrasound of temporal arteries is recommended and noncompressible “halo” sign is the typical finding. PET, MRI, or CT may be useful for the detection of the disease in the aorta and other vessels. The treatment must be started promptly with prednisone 1 mg/kg/day. When visual symptoms/unilateral visual loss is present, methylprednisolone pulse is recommended. Methotrexate, leflunomide and tocilizumab may be effective and well-tolerated glucocorticoid-sparing agents in GCA. Cardiovascular diseases are the leading causes of death in patients.

Keywords: giant cell arteritis, T17, IL-6, pathogenesis, treatment, tocilizumab

1. Introduction

The first description of giant cell arteritis dates from 1890 by Hutchinson, who described an 80-year-old man with painful and inflamed temporal arteries which prevented him from wearing his hat [1]. Forty-seven years later Horton, Magath, and Brown described similar cases and called the syndrome temporal arteritis [2]. Originally thought to be a localized, self-limiting, and benign disorder, inflammation of the temporal arteries is now recognized as part of a widespread arteritis which untreated can lead to blindness and death.

Giant cell arteritis (GCA), previously called temporal arteritis and also known as Horton’s disease, is defined by the 2012 Chapel Hill Consensus Conference as “arteritis, often granulomatous, usually affecting the aorta and/or its major branches, with a predilection for the branches of the carotid and vertebral arteries; often involves the temporal artery; onset usually in patients older than 50; often
associated with polymyalgia rheumatica” [3]. It is the most common primary systemic vasculitis in adults, mostly seen in North America and Western Europe, with the incidence increasing with the advancing age. Women are more affected than men in a 2.5:1 ratio. GCA classically targets large vessels with predominance for the aorta and its branches. Arterial inflammation may lead to vascular damage which can result in stenosis, occlusions, and even aneurysms. Therefore, this condition is related to serious loss of function including visual loss, upper limb ischemia, and stroke. Suspicion of giant cell arteritis is a medical emergency, and patients need to be quickly diagnosed and treated to prevent irreversible consequences of vessel inflammation.

2. Pathogenesis

The immune and pathogenetic pathways responsible for the inflammation on the arterial walls in GCA are not fully understood yet. As in other autoimmune diseases, it is believed to be an environmental-triggered response occurring in genetic-predisposed individuals. The fact that it only affects older patients suggests that age-related damage on the vessel walls also plays a role in the development of the arteritis [4].

There is evidence of a cyclic pattern and yearly incidence of the onset of GCA, which led to the search for an environmental agent responsible for the initialization of the immune response. Many bacterial agents and viruses have been under research (Chlamydia pneumonia, Burkholderia, cytomegalovirus, erythrovirus B19, herpes simplex, and parainfluenzae 1, among others), but the studies failed in finding a causal correlation between infections and GCA so far [4].

GCA is associated with the major histocompatibility class II (MHC-II), particularly with HLA-DRB1*04 alleles [5]. Outside the MHC region, variants on the PTPN22 locus and other genes related to vascular response to inflammation and vascular remodeling, such as plasminogen and prolyl 4-hydroxylase subunit alpha 2, also increased the risk of GCA.

Age-related damage on the arterial wall also has a role on the pathogenesis. There are biochemical and structural modifications in the vessel leading to loss of self-tolerance. Differences in the DNA methylation level of several genes have been reported in temporal arteries from GCA patients comparing with non-GCA controls.

There is evidence that the inflammation starts in the adventitia and progresses to the other layers of the arterial wall, culminating in transmural damage. Activated dendritic cells (DCs) have a central role in the immune response of GCA. These cells are present in the adventitia and express Toll-like receptors, which are activated via pathogen-associated molecular patterns (PAMPs) or microorganism-associated molecular patterns (MAMPs). The activation of DC breaks immune tolerance and renders the arteries, considered otherwise an immune privileged site, susceptible to inflammatory injury. DCs activate CD4+ T lymphocytes through co-stimulatory molecules (CD80 and CD86) and class II MHC. DC depletion in mice models with GCA strongly decreased vasculitis lesions, emphasizing its importance on the immune response.

Activated DCs produce cytokines such as IL-6, IL-18, IL-23, IL-32, and IL-33, which are chemotactic for T lymphocytes. T cells that infiltrate the temporal arteries from GCA patients are enriched Th1, Th17, and Th9 cells. Th1-response polarization via IL-12 synthesizes IFN-γ, and Th17 cells produce IL-17. While Th17 cells are inhibited by glucocorticoids, the Th1 response is not, being this last one implicated in sustaining chronic disease activity in GCA [6].

IFN-γ seems to be important for the development of vasculitis. The cytokine panel described above is found in both GCA patients and PMR patients without
GCA, but INF-γ is only present in individuals with GCA. IFN-γ expression, in fact, is associated with increased risk of ischemic complications. Vascular smooth muscle cells, induced by IFN-γ, produce chemokines (CCL2, CXCL9, CXCL10, and CXCL11), leading to the recruitment of monocytes that merge to form multinucleated giant cells, the hallmark of GCA. The chemokines recruit more immune cells, amplifying the inflammatory response. Monocytes differentiate into macrophages in the arterial wall and produce IL-6, IL-1β, and TNF-α, responsible for the systemic inflammatory response which is characteristic of GCA. Toxic substances for the arteries are also produced by macrophages, such as reactive oxygen species, matrix metalloproteinase-2 (MMP-2), and MMP-9, which destroy cellular matrix proteins and cause destruction of the media and digestion of the internal elastic lamina.

Th17 cells appear to be important in the initial stages of the disease, producing IL-17, IL-21, IL-22, and CCL20. IL-17 leads to the recruitment of macrophages, while IL-21 enhances the differentiation of cytotoxic cells, and IL-22 mediates hepatocyte stimulation and acute-phase amplification. CCL20 facilitates the recruitment of more DCs and T cells.

The vascular smooth muscle cells in inflamed arteries are believed to acquire pro-inflammatory properties and produce several growth factors (vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF), among others), causing intimal hyperplasia and vascular occlusion.

B cells are not present in the arterial wall of all the patients with GCA, suggesting that its effect is not crucial in the pathogenesis. However, when present, they are activated and contribute for the amplification of the immune response and inflammation.

Finally, defects in immune checkpoints have also been studied and appear to play a role in the immune activation observed in GCA. T cells express programmed death-1 (PD-1), which binds to its receptor in antigen-presenting cells, inducing T cell anergy and apoptosis, and the production of IL-10 by T cells or their polarization into T-reg lymphocytes. A defect in the immunoprotective PD-1/PD-L1 immune checkpoint has been reported in GCA patients.

3. Clinical features

Headache is the most common symptom of GCA, and a new-onset headache (or worsening of a preexisting headache) in older adults should always raise the suspicion of this condition. The installation of the pain is usually acute/subacute. The typical pattern is a temporal headache, continuous throughout the day and resistant to standard analgesia, but it can also be felt over other cranial areas or be diffuse. Patients may also present with scalp tenderness or tongue/jaw pain. Jaw claudication, seen in 45% of the patients, is a relatively specific sign and correlates with temporal artery biopsy positivity.

Total or partial visual loss affects 15–20% of patients, mostly at disease onset. The main cause is anterior ischemic optic neuropathy due to vasculitis of the posterior ciliary arteries, which are branches of the ophthalmic artery and responsible for the blood supply of the optic nerve and the choroid. The optic neuropathy leads to visual loss, which is usually painless and with rapid onset. Occasionally, posterior ischemic optic neuropathy, occlusive vasculopathy of the central artery of the retina, or cortical ischemia can cause visual loss too. Blindness is irreversible in most cases, and when one eye is affected, the other one will likely (in half of the cases) be diseased too in a few days if the treatment is not promptly started. About 10% of patients develop amaurosis fugax, visual hallucinations, or diplopia, which are considered premonitory signs and can progress to blindness in half of the cases.
Systemic manifestations, such as fever, weight loss, and fatigue, are frequent (42, 50, and 40%, respectively). Some patients present only with constitutional symptoms, without headache or visual changes, and in those cases, the diagnosis can be challenging. GCA can be the cause of an obscure-origin fever in older patients.

Polyarthritis rheumatica (PMR) is the most common extracranial manifestation of GCA, and it may also be the first clinical sign of a vasculitis relapse. It is defined by pain/tenderness in proximal arms and legs, with morning stiffness and fast improvement with low-dose glucocorticoid treatment. PMR is seen in 50% of the patients with GCA, while only 20% of the patients with PMR have clinical signs of GCA. However, in patients with PMR with persistently high inflammatory markers and insufficient response to glucocorticoids, a careful investigation may reveal an oligo-symptomatic GCA requiring more aggressive treatment. GCA and PMR are different conditions that share many common features: they occur almost exclusively in patients aged 50 years or older, have similar gender ratios, are associated with the HLA-DRB1*04 alleles and increased levels of serum acute-phase reactants, and respond to glucocorticoid therapy.

GCA is a systemic vasculitis with predominance for the aorta and its branches. Therefore, the patients may also present with chest pain and limb claudication. Large-vessel disease may complicate with aneurysms or stenosis development, resulting in increased mortality due to cardiovascular disease. Many patients with GCA develop clinical manifestations of large-vessel involvement, such as arm claudication (4%) and arterial bruits (21%).

Cerebrovascular events are less common ischemic complications, seen in 15% of the patients. They are mostly due to occlusive vasculitis of the carotid or verteobasilar arteries. Transitory or persistent ischemic attacks are the most common neurologic manifestations, but cognitive impairment and neuropathy are other possible complications. Neuropsychiatric symptoms (dementia, mood disorders, and psychosis) affect 3% of the patients. Audio vestibular dysfunction leading to sensorineural hearing loss has also been described in GCA.

Infrequent clinical manifestations include tongue, scalp or lip necrosis, and facial/submandibular swelling. Unlike visual loss, ischemic necrosis tends to improve after the glucocorticoid treatment is started. Peripheral synovitis is found in 15% of the patients.

Physical examination is frequently normal, but it may also reveal temporal artery abnormalities such as thickness, tenderness, and hyperemia, with normal, decreased, or absent pulse. Even though temporal artery abnormality is one of the five ACR classification criteria for GCA, it is seen in less than 30% of the patients. Peripheral pulses in arms and legs may be decreased or absent as well in large-vessel disease, and arterial bruits can be heard in such patients.

4. Diagnosis

The American College of Rheumatology classification criteria for GCA, published in 1990, requires three or more of the following five criteria [1]: age 50 years and older [2], new onset of localized headache [3], temporal artery tenderness on palpation or decreased pulsation [4], an abnormal temporal artery biopsy, and [5] an erythrocyte sedimentation rate (ESR) of 50 mm/h or more (Table 1) [7]. These criteria are designed to be classificatory and not diagnostic, with sensitivity and specificity of 81.1% and 64.2%, respectively [8]. In the last years, new imaging techniques have emerged and can be helpful tools on diagnosis and disease activity assessment.
4.1 Acute-phase reactants

ESR higher than 50 mm/h is one of the five criteria for GCA classification according to the ACR. However, in recent years alternative acute-phase reactants have been proposed as more sensitive markers. Recently one study analyzed 26 markers in GCA and PMR comparing with healthy controls and found that three serum markers (B cell-activating factor [BAFF], CXCL9, and IL-6) were increased in both newly diagnosed GCA and newly diagnosed PMR patients. Serum BAFF and IL-6, but not CXCL9, were attenuated upon glucocorticoid-induced remission and showed the strongest association with disease activity in both GCA and PMR patients [9]. BAFF is an important regulator of B cell responses and has been linked to the development of many autoimmune diseases. Even though these markers are not used routinely in clinical practice yet, they are promising new tools in the diagnostic approach and disease activity assessment in GCA.

Platelets are also considered a serum marker for inflammation in GCA. The postulated mechanism of thrombocytosis in promoting inflammation stems from their early interaction with the endothelium in inflammatory states during which they provide adhesion molecules and chemotactic stimulation to aid in the recruitment of leukocytes and enhance the release of different inflammatory mediators [10].

The most used tests for measuring inflammation in clinical practice are ESR and CRP. One study showed that the optimal cutoff value for CRP in GCA was 26.9 mg/L (sensitivity 75% and specificity 51%) and for ESR was 53 mm/h (sensitivity 66% and specificity 55%) [11].

4.2 Temporal artery biopsy (TAB)

Even though temporal artery biopsy is not essential for the diagnosis, one study found that sensitivity and specificity of ACR criteria for diagnosis of GCA before performing TAB were 68.5 and 58%, respectively, while sensitivity and specificity of ACR criteria after performing TAB biopsy were 89.8 and 64.5%, respectively [12]. The sensitivity rates are lower in the large-vessel phenotype of GCA, and even in patients with the temporal artery affected, skip lesions may contribute to a negative TAB.

TAB showing transmural inflammation is still considered the gold standard for the diagnosis of GCA and remains the most specific diagnostic test. It is a minimally invasive and well-tolerated surgical procedure that is generally performed in an outpatient surgery setting and carries a low risk of complications in experienced hands. The length of the artery needed for optimal histopathological analysis is 2 cm. For all these reasons, TAB is still recommended in all patients with a clinical suspicion of GCA. In addition to their diagnostic role, histological findings of positive TAB may have clinical and prognostic significance and thus implications for the patients’ management.

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| 1. Age ≥ 50 years | 1 |
| 2. New-onset headache | 1 |
| 3. Temporal artery tenderness/decreased pulsation | 1 |
| 4. Abnormal temporal artery biopsy | 1 |
| 5. ESR ≥ 50 mm/1st hour | 1 |
| **Total** | 1 |

**Table 1.**

ACR classification criteria for GCA (1990).
GCA is characterized histopathologically by mononuclear infiltrates in all layers of the arterial wall. Macrophages and T cells are present in granuloma formation, and multinucleated giant cells are localized close to the fragmented internal elastic lamina. Neutrophils, eosinophils, and plasma cells are rare. Proliferation of the intima results in occlusive vasculopathy. Neoangiogenesis is frequent and at times prominent, and fibrinoid necrosis is typically absent (Figures 1 and 2) [13].

The positivity of TAB declines after glucocorticoid treatment is started, and the biopsy should ideally be performed within 2 weeks from the onset of the therapy.
Importantly, the therapy should never be delayed for the performance of a biopsy, especially when visual symptoms are present [14].

For patients with a negative temporal artery biopsy, clinical assessment remains a mainstay of diagnosis.

4.3 Imaging techniques

In 2018, the European League Against Rheumatism (EULAR) published recommendations about the use of imaging techniques in large-vessel vasculitis (LVV), which included GCA and Takayasu’s arteritis. According to these recommendations, in patients with suspected GCA, an early imaging test is recommended to complement the clinical criteria for diagnosing GCA, assuming high expertise and prompt availability of the imaging technique [15]. However, imaging should not delay initiation of treatment. The choice of the individual imaging method depends on the predominant clinical symptoms and local settings. In settings where imaging modalities are not readily available or expertise with imaging in GCA is questionable, a biopsy should still be favored in first place. Besides, if positive histology is already available, additional imaging may not be needed for the diagnosis. In centers, however, where imaging (and TAB) is readily available and performed with high quality, the task force recommends that imaging should be preferred as the first test because of low invasiveness, ready availability of imaging results, and assessment of a larger extent of potentially inflamed arteries at the same examination, therefore contributing to a lower number of false-negative results. Imaging should be performed before or as early as possible after initiation of therapy, best within 1 week, because treatment with glucocorticoids rapidly reduces the sensitivity of imaging [15].

Figure 3.
Temporal artery duplex scan of a patient from the Rheumatology Division of the University of Sao Paulo, School of Medicine with GCA showing thickness in the vascular wall and the noncompressible “halo” sign.
In patients in whom there is a high clinical suspicion of GCA and a positive imaging test, the diagnosis of GCA may be made without an additional test (biopsy or further imaging). In patients with a low clinical probability and a negative imaging result, the diagnosis of GCA can be considered unlikely [15].

Ultrasound of temporal ± axillary arteries is recommended as the first imaging modality in patients with suspected predominantly cranial GCA. A noncompressible “halo” sign is the ultrasound finding most suggestive of GCA (Figure 3). High-resolution MRI of cranial arteries to investigate mural inflammation may be used as an alternative for GCA diagnosis if ultrasound is not available or inconclusive. Ultrasound, PET, MRI, and/or CT may be used for the detection of mural inflammation and/or luminal changes in extracranial arteries to support the diagnosis of large-vessel GCA (Figure 4). Ultrasound is of limited value for the assessment of aortitis [15].

In patients with a suspected flare, imaging might be helpful to confirm or exclude it. Imaging is not routinely recommended for patients in clinical and biochemical remission. In patients with large-vessel vasculitis, MRA, CTA, and/or ultrasound may be used for long-term monitoring of structural damage, particularly to detect stenosis, occlusion, dilatation, and/or aneurysms [15].

5. Treatment

Treatment with oral glucocorticoid (GC) effectively induces remission and reduces the evolution to visual loss, and it should be started as early as possible.
when there is a clinical suspicion of GCA. The GC therapy cannot be postponed to after confirmation of the diagnosis, because once the visual loss is installed, it is rarely reversible [16].

Oral prednisone in a daily single dose of 40–60 mg usually resolves the symptoms and normalizes acute inflammation reactants within the first 2–4 weeks of the treatment. When premonitory visual signs are present (amaurosis fugax) or when visual loss is installed, pulse therapy with daily intravenous methylprednisolone (500–1000 mg) for 3 days can be tried, even though its superiority compared to the oral prednisone regimen has not been proven in clinical trials.

Glucocorticoids are effective in inducing clinical remission, but the side effects of its chronic use are undesirable, especially in elderly individuals. Therefore, synthetic or biological immunosuppressants have been used as GC-sparing adjuvants to reduce the cumulative GC dose and to maintain remission after the prednisone withdrawal [17]. There is no consensus on the timing of initiating GC-sparing therapy, but indications to start it early in the disease course include the presence of significant premorbid diseases (diabetes mellitus, osteoporosis, obesity), the emergence of significant glucocorticoid-related side effects, and a relapsing course necessitating protracted CS use. After clinical remission is achieved (symptoms resolved and laboratory inflammation markers normalized), the GC taper can be started. It has to be slow, especially with lower doses. The dose can gradually be reduced by 5 mg every 2 weeks to 20 mg/day and then by 2.5 mg every 2 weeks to 10 mg/day if there are no flares of disease activity. After achieving a daily dose of 10 mg, the prednisone taper should be slowed, such that patients remain on progressively decreasing doses over the ensuing 6–12 months. Tapering by 1 mg decrements each month once the daily dose is less than 10 mg can be considered. Disease relapses are more frequent in this final phase of the GC tapering regimen [18].

5.1 Glucocorticoid-sparing therapy

**Methotrexate** (MTX) is the conventional immunosuppressive drug most commonly used for the management of refractory GCA. However, the efficacy of this drug in GCA is modest. The trials yielded a role of MTX (10–15 mg/week) to reduce the frequency of relapses (by 35% of a first relapse and by 51% of a second relapse) and decrease the cumulative prednisone dose. However, the optimum efficacy of MTX becomes manifest only after 24–36 weeks [19].

**Leflunomide** may also be an effective and well-tolerated glucocorticoid-sparing agent in GCA, but there are no randomized controlled trials to confirm it yet. In one prospective observational study with 76 newly diagnosed GCA patients, 10 mg daily leflunomide was compared with glucocorticoid only in a follow-up period of at least 48 weeks. During the follow-up 13.3% patients in the leflunomide group flared versus 39.1% in the GC-only group (p = 0.02). Furthermore, 56.7% patients in the leflunomide were able to stop GC at week 48 but none in the GC-only group [20].

**Tocilizumab** is a humanized monoclonal antibody that binds to the soluble and membrane-bound forms of the IL-6 receptor (IL-6R). IL-6 has a key role in the pathogenesis of GCA, and elevated levels of IL-6 are present and correlate with disease activity. Efficacy of tocilizumab in GCA has been proved in a multicenter, randomized, double-blind, placebo-controlled, phase 3 trial with 251 patients (119 newly diagnosed and 132 with relapsing disease). The patients were randomized to receive subcutaneous tocilizumab (162 mg) weekly or every other week combined with a 26-week prednisone taper or placebo, combined with a prednisone taper over a period of either 26 or 52 weeks. Both groups of patients treated with tocilizumab achieved sustained remission more commonly than those placebo-treated at week 52. Patients who underwent tocilizumab therapy had fewer relapses of disease than
those in the placebo arms [21]. Tocilizumab use was associated with a powerful glucocorticoid-sparing effect, and this effect was stronger in those patients who had experienced relapses before randomization. Tocilizumab in a subcutaneous weekly dose of 162 mg was approved by the US FDA and the European Commission for the treatment of GCA. However, there is concern about the characterization of a relapse in patients that are under tocilizumab therapy, because tocilizumab is very effective in normalizing CRP and ESR and some patients can be oligo-symptomatic during a flare. Periodic imaging in these patients is recommended for accessing vascular activity or progression of the vascular damage during the treatment.

**Ustekinumab** is a human monoclonal antibody that binds to the p40 subunit of both IL-12 and IL-23 preventing their binding to their shared cell surface receptor chain, IL-12Rβ1. The inhibition of IL-12 signaling abrogates Th1 response with reduction in TNF-α, IFN-γ, and IL-12 production. The inhibition of IL-23 signaling abrogates Th17 response with the reduction on IL-6, IL-17, IL-21, IL-22, and TNF-α production. Th1 and Th17 responses both have important roles in the pathogenesis of GCA. A prospective open-label 52-week trial with 25 patients with relapsing GCA showed that ustekinumab may be effective for the treatment of GCA: at week 52 the median daily dose of prednisolone decreased from 20 to 5 mg (p < 0.0001), and no patient experienced a relapse of GCA while receiving ustekinumab [22]. No randomized controlled trial with ustekinumab in GCA patients has been performed yet.

**Abatacept** is a fully human fusion protein that binds to CD80/CD86 on antigen-presenting cells preventing these molecules from binding to their ligand, CD28, on T cells, and is moderately effective in the treatment of GCA. In a multicenter, randomized, double-blind trial, 49 patients with GCA were treated with 10 mg/kg intravenous abatacept on days 1, 4, and 29 and week 8 and monthly after that. The relapse-free survival rate at 12 months, the primary endpoint, was 48% for those receiving abatacept and 31% for those receiving placebo (p = 0.049) [23]. Further studies encompassing larger number of patients are needed to confirm the utility of abatacept as adjunctive therapy in GCA.

Anti-TNFα agents have been tested and yielded disappointing results, showing no efficacy in reducing GC dose or relapse rates in GCA. There are other promising target therapies being tested, such as the JAK/STAT inhibitors, but the results are not available, and there is no data to support their use in clinical practice yet.

### 5.2 Preventing complications

Patients with GCA are elderly and frequently have multiple comorbid conditions that can be worsened by the use of GC and immunosuppressants. Therefore, the levels of vitamin D must be higher than 30 ng/mL for all patients, and the dietary intake of calcium must be stimulated (or supplementation, if the dietary intake is insufficient) for bone protection, as well as the use of bisphosphonates if indicated.

Low-dose aspirin (80–100 mg/day) should be prescribed for prevention of cardiovascular events, which represent the main cause of death in this population.

### 6. Prognosis

The most frequent causes of death in GCA patients are cardiovascular diseases followed by cancer. Combined, these conditions account for approximately two thirds of all deaths. A Norwegian cohort of 881 patients with GCA and 2577 population controls found no significant difference in the overall cumulative survival or survival at any specific time after diagnosis. In this study the mean age of death was
83.6 (SD 7.5) years for GCA patients, and survival was more than 80% in 5 years and approximately 50% in 10 years [24]. The same study found that even though the overall mortality was not reduced in GCA, these patients have an increased risk of death due to circulatory diseases and infections but a decreased risk of death due to cancer over time. The increased risk of death by circulatory diseases may be related to aneurysms and dissections, which are recognized as large-vessel complications of GCA. Therefore, it is extremely important in the management of these patients to identify and to treat other contributing risk factors for circulatory disease.

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