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Large-vessel giant cell arteritis: diagnosis, monitoring and management

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Abstract

GCA is a chronic, idiopathic, granulomatous vasculitis of medium and large arteries. It comprises overlapping phenotypes including classic cranial arteritis and extra-cranial GCA, otherwise termed large-vessel GCA (LV-GCA). Vascular complications associated with LV-GCA may be due, in part, to delayed diagnosis, highlighting the importance of early identification and prompt initiation of effective therapy. Advancements in imaging techniques, including magnetic resonance angiography, CT angiography, PET and colour duplex ultrasonography, have led to improvements in the diagnosis of LV-GCA; however, the role imaging modalities play in the assessment of disease activity and long-term outcomes remains unclear. Glucocorticoids are the mainstay of therapy in LV-GCA, but their prolonged use is associated with multiple, sometimes serious, adverse effects. Recent data suggest that biologic therapies, such as tocilizumab, may be effective and safe steroid-sparing options for patients with GCA. However, data specifically evaluating the management of LV-GCA are limited.

Key words: biologic therapy, diagnosis, giant cell arteritis, glucocorticoids, imaging, prognosis, tocilizumab, vasculitis

Rheumatology key messages

- Large-vessel involvement of GCA is common and is associated with vascular complications.
- Imaging techniques may improve diagnosis, disease activity assessment and clinical outcome assessment in large-vessel disease.
- Biologic therapies show considerable promise for the reduction or replacement of glucocorticoids in GCA management.

REVIEW

Introduction

GCA is a chronic, idiopathic, granulomatous vasculitis of the medium and large arteries [1]. It comprises overlapping phenotypes, including classic cranial arteritis and extra-cranial GCA, otherwise known as large-vessel GCA (LV-GCA) [2]. Initially considered a form of vasculitis primarily involving the carotid and vertebral artery branches [3], autopsy studies have shown histological evidence of large-vessel involvement in 80% of cases [4, 5] and imaging studies of patients with GCA have demonstrated that extensive radiographic large-vessel involvement (e.g. aorta and its major branches) is present in up to 83% of patients [4–11]. Increased awareness of large-artery involvement is paramount because patients with GCA are 17 times more likely to develop aneurysms of the thoracic aorta compared with their age/sex-matched comparators [12], and occurrence of this complication is associated with a significant increase in mortality [13]. In addition, aortic aneurysm/dissection has been shown to occur in one in every five patients with GCA and large-artery stenosis in one in every eight [14]. The time from onset of large-artery symptoms to diagnosis may be prolonged [14], and the presence of active arterial inflammation appears to play a role in predicting aortic dissection/rupture [15], thus highlighting the importance of a timely diagnosis of LV-GCA to ensure prompt initiation of appropriate treatment.

Advances in non-invasive arterial imaging have led to greater understanding of the frequency of LV-GCA, but limited data are available to provide guidance on the modality best suited for either detection of large-vessel involvement or monitoring its response to treatment. While glucocorticoids have been the mainstay of GCA management for over six decades, their prolonged use

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is associated with adverse effects in up to 89% of patients [16]. Recent studies suggest that newly emerging biologic therapies, such as tocilizumab, can be effective and safe steroid-sparing options in patients with GCA [17–20]. However, data specifically evaluating the effectiveness of biologic therapies in the treatment of large-vessel involvement in GCA are limited. Herein, we describe current understanding and uncertainties related to LV-GCA, with particular focus on the diagnosis, monitoring and management of GCA.

Classification and nomenclature

Although investigators have identified that LV-GCA appears to produce a distinct clinical presentation compared with classic cranial GCA [21], there is a central challenge in understanding this variant because of the lack of a standardized definition. Even though a formal consensus has not been established, most studies consider LV-GCA to include inflammation of the aorta (aortitis) or its primary branches (arteritis) as evidenced by the presence of one or more of the signs listed in Table 1 [11, 22–28].

While efforts are underway to develop and validate criteria for the diagnosis of GCA [29], there are no endorsed or approved diagnostic criteria for this condition to date. Classification criteria, on the other hand, are available, but their intent is to provide standardized definitions of disease to create homogeneous cohorts for research purposes [30]. GCA disease classification is based on the 1990 ACR criteria [31], which primarily focus on cranial symptomatology. In particular, one of the five criteria for disease classification is the presence of an abnormal temporal artery biopsy (TAB), which is currently still considered the gold standard for a diagnosis of GCA [32]. In the absence of available diagnostic criteria, challenges may arise when clinicians incorrectly use classification criteria in routine daily practice to diagnose individual patients.

Although the ACR classification performs well for patients with cranial GCA symptoms, the current criteria underperform in classifying patients with LV-GCA because they have not yet been updated to account for more recent imaging findings in patients with GCA. For example, in a retrospective cohort study, ACR classification criteria for GCA were met by significantly fewer patients with radiographic evidence of LV-GCA than with cranial GCA (39% *vs* 95%; $P < 0.001$) [22]. In addition, despite the appropriate timing and performance of TAB, previous studies have also reported substantial proportions of patients with negative findings on initial biopsy subsequently receive clinical diagnoses of cranial GCA (19–30%) [33, 34] or LV-GCA (48%) [22]. Therefore, vascular imaging studies, such as magnetic resonance angiography (MRA), computed tomography angiography (CTA), PET and colour duplex ultrasonography (CDS), are often required to confirm a diagnosis of LV-GCA [35].

Epidemiology of large-vessel GCA

The estimated annual incidence of GCA varies with geographical location and ranges from 1.6 to 32.8 cases/100 000 persons $\geqslant$50 years of age [36]. The incidence appears to be highest in Scandinavian countries or in communities with Scandinavian ancestry, suggesting genetic factors may be important [36–38]. Studies of the epidemiology of GCA have historically focused on patients with predominantly cranial symptoms, which is, in part, due to the focus of the 1990 ACR classification criteria on cranial features (three of five criteria) [31]. However, the clinical spectrum of GCA includes patients with isolated cranial GCA, cranial GCA with LV-GCA and isolated LV-GCA [1]. Data are limited regarding the prevalence and incidence of LV-GCA, and it remains unknown whether the incidence of LV-GCA varies by geographical location.

Less is known about the incidence of LV-GCA because investigation of large-vessel involvement has been variable and dependent on disease stage and the methodological approach undertaken. In addition, the lack of a standard definition or of classification criteria for LV-GCA has resulted in marked heterogeneity among studies reporting the presence of this finding. Nevertheless, more recent epidemiological studies have begun to include patients in whom the diagnosis of LV-GCA was made on the basis of cross-sectional imaging [39].

Table 1 Signs of inflammation of the aorta (aortitis) or its primary branches (arteritis)

Signs of large-vessel involvement [22, 26–28]	Imaging modality
Circumferential wall thickening ($\geqslant$2- or 3-mm aorta)	CTA, MRA
Contrast enhancement	CTA, MRA
Wall gadolinium uptake	MRA
Wall oedema	MRA
Homogeneous wall hyper-metabolism	^{18}FDG-PET
Vascular stenosis/occlusion and/or vascular dilatation/aneurysm	CTA, MRA, conventional angiography
Dark, hypoechoic circumferential wall thickening (halo sign)	CDS

CDS: colour duplex ultrasonography; CTA: computed tomography angiography; ^{18}FDG-PET: ^{18}F-fluorodeoxyglucose positron emission tomography; MRA: magnetic resonance angiography.

Table 2 Clinical signs and symptoms of GCA subtypes and PMR

Signs and symptoms of GCA or PMR	LV-GCA	Cranial GCA	PMR
Headache	±	++	–
Temporal artery swelling/tenderness	±	+	–
Extra-cranial artery bruit	++	–	–
Jaw claudication or tongue pain	–	++	–
Visual symptoms or complications	–	++	–
Fever, weight loss	++	+	++
Limb claudication and/or blood pressure discrepancy	++	–	–
Polymyalgia symptoms	++	+	++
Acute-phase reactants	+	++	+
Peripheral arthritis/RS3PE syndrome	±	±	+

Signs and symptoms of GCA or PMR are summarized from [2] (personal communication, M. J. Koster, MD, 2016). ++: very common sign or symptom; +: common sign or symptom; –: uncommon sign or symptom; ±: sign or symptom may be present; LV: large-vessel; RS3PE: remitting seronegative symmetrical synovitis with pitting oedema.

Clinical features of large-vessel GCA

GCA is a heterogeneous disease with variable clinical presentations, depending on the area of arterial involvement. Although overlapping phenotypes are observed, distinguishable clinical patterns between cranial GCA and LV-GCA have been identified [21].

Classic cranial GCA symptoms of headache, jaw claudication, scalp tenderness and vision changes may be clinically absent or, if present, may occur significantly less often in patients with LV-GCA (Table 2) [2]. In addition, studies suggest that LV-GCA may have a stronger female predominance, younger age of disease onset, longer time to diagnosis and lower inflammatory markers than cranial GCA [21, 22, 28]. Clinical signs of large-vessel disease, including limb claudication, vascular bruits, pulse discrepancies and aortic regurgitation murmur, are more commonly noted in patients with LV-GCA [22, 28]. Clinicians unfamiliar with the location and frequency of large-vessel involvement may overlook examination findings identifying arterial insufficiency outside the cranial vessels. Hence, all patients with signs suspicious for, or confirmation of, GCA should undergo thorough vascular examination beyond the temporal arteries. At a minimum, bilateral upper extremity blood pressure, cardiac auscultation and assessment for vascular bruits or abnormal pulses in the carotid and limb arteries must be performed.

Although signs and symptoms of vascular insufficiency are more common in LV-GCA, involvement of the aorta and its primary branches may be clinically silent, and patients with isolated LV-GCA may present only with constitutional symptoms, polymyalgia symptoms, elevated inflammatory markers or fever of unknown origin [2]. Such circumstances require a heightened clinical suspicion and additional imaging studies (e.g. CTA/MRA/PET) to confirm diagnosis and rule out other conditions that may present with similar non-specific symptoms (Table 3) [24, 40, 41]. An algorithm proposed by the authors for confirming the presence of GCA is suggested in Fig. 1.

Radiographic features and frequency of large-vessel GCA

Given the arterial distribution of large-vessel involvement, obtaining a surgical specimen or biopsy is often not feasible [35]. Advances in non-invasive imaging have improved the ability to identify large-vessel involvement in patients with GCA (Fig. 2); however, consensus is lacking regarding the timing of evaluation, the modality used and the definition of large-vessel involvement [26, 27]. Prospective studies using CTA to evaluate patients with recently diagnosed GCA have identified evidence of aortitis in 45–65% of patients [8, 11, 42]. Disruption of the medial layer within the elastic arteries in GCA suggests that aortic aneurysm/dissection may occur as a complication of aortic inflammation [43]. In CTA studies, aortic structural damage has been observed at diagnosis in 15–23% of patients with GCA [8, 11]. Additionally, retrospective and cross-sectional imaging studies have reported incident aortic structural damage in 10–33% of patients with GCA during the course of up to 10 years of follow-up [25, 44–47]. Because of the frequency of aortic involvement, medical and surgical thoracic guidelines have recommended a baseline CTA or MRA in all patients with newly diagnosed GCA to evaluate the presence and extent of thoracic disease [48].

Patients with GCA have also been evaluated with ^{18}F-fluorodeoxyglucose (^{18}FDG)-PET, which has demonstrated increased vascular hypermetabolism in large arteries in up to 83% of patients [6]. A meta-analysis has identified the presence of vascular ^{18}FDG uptake equal to or greater than liver uptake on PET to be the best criterion for the detection of vascular inflammation in patients with GCA compared with controls with a high degree of diagnostic accuracy (pooled sensitivity 90%, specificity 98%) [49]. Challenges encountered in the use of ^{18}FDG-PET in this condition include the lack of consensus agreement on the PET criteria to define cutoffs for vascular inflammation as well as the potential overestimation of vascular

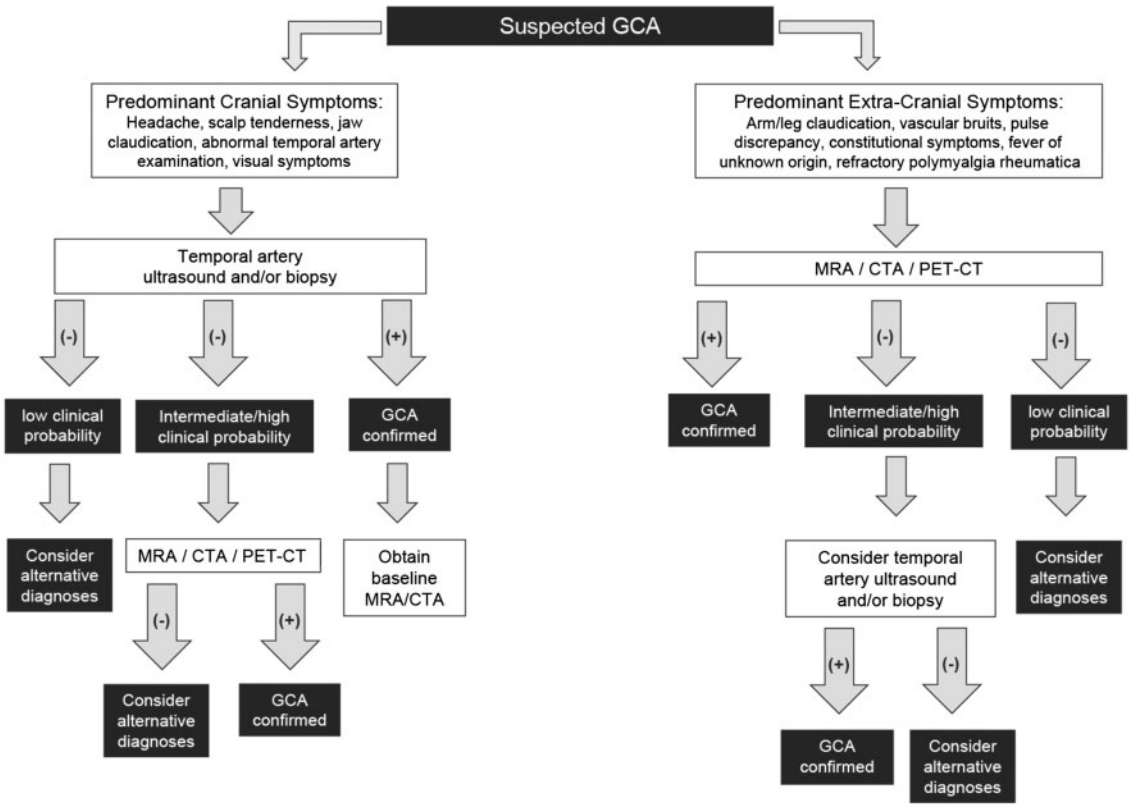
inflammation because of the increased presence of vascular uptake from arteriosclerosis in this older population [49]. In addition, the long-term clinical importance of detectable ^{18}FDG avidity in large vessels is incompletely understood; however, identification of increased ^{18}FDG uptake in the aortas of patients with GCA has been associated with an increased likelihood of future aortic dilatation [50].

Colour duplex ultrasonographic findings of large-vessel involvement include evidence of stenosis/occlusion and increased intima-media thickness and the presence of a hypoechoic area around the vessel lumen (halo sign) [24, 51, 52]. Preliminary findings of an US study comparing patients with GCA with age- and sex-matched controls indicated that an intima–media thickness of $\geqslant$1 mm in the axillary artery correctly identified GCA patients with a sensitivity and a specificity of 100% [53]; additional studies are needed to confirm and validate these findings. A case–control study of patients with new-onset GCA identified large-vessel involvement in 29% of patients through the use of CDS [10]. Large-vessel involvement was also observed in 53 (30%) of 176 consecutive patients with GCA in which CDS was performed systematically to evaluate the temporal, subclavian, axillary and proximal brachial arteries [7]. In this study, axillary arteries were more frequently involved in confirmed cases of LV-GCA (98%) than were subclavian (61%) and proximal brachial arteries (21%). The benefits of US in the evaluation of large-vessel involvement of GCA include the absence of ionizing radiation and low cost [52]. However, because

Table 3 Differential diagnosis for patients evaluated for GCA without predominant cranial symptoms

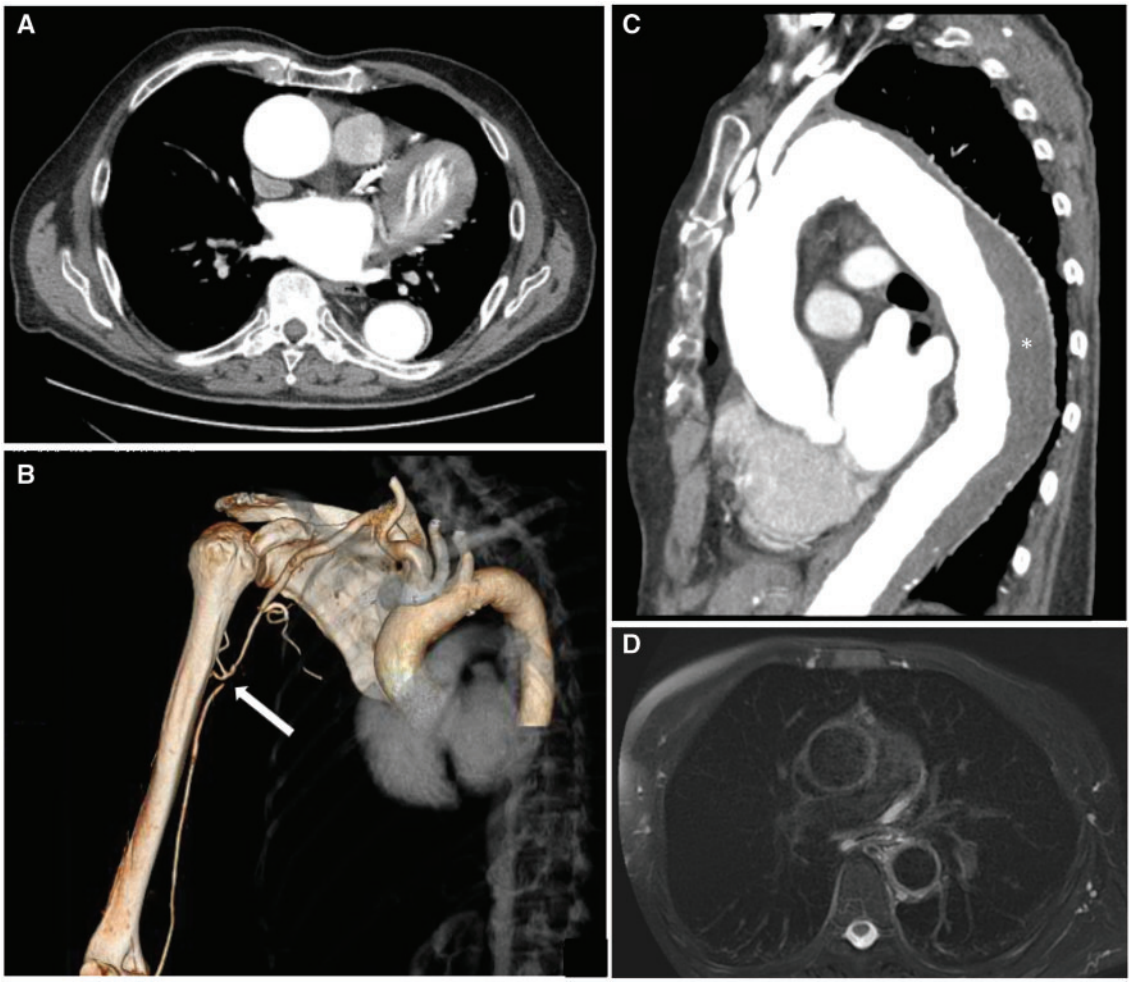
Haematological	**Rheumatic**
Amyloidosis	Idiopathic aortitis
Multiple myeloma	IgG4-related disease
Erdheim–Chester disease	Retroperitoneal fibrosis
Infection	Primary vasculitis
Syphilis	Takayasu arteritis
Herpes zoster	Polyarteritis nodosa
Epstein–Barr/ cytomegalovirus	ANCA-associated vasculitis
Endocarditis	Behçet's disease
Vascular	Vasculitis associated with autoimmune disease
Atherosclerotic disease	RA
	SLE
	Spondyloarthritis

Fig. 1 Proposed algorithm for evaluating patients with suspected GCA



CTA: computed tomography angiography; MRA: magnetic resonance angiography.

Fig. 2 Evidence of large-vessel GCA manifestations on non-invasive cross-sectional imaging



(**A**) Aneurysm of the ascending thoracic aorta, 5.7 cm (computed tomography angiography, axial view). (**B**) Long tapered segment narrowing and occlusion (arrow) of the axillary artery with reconstitution of the brachial artery (3D reformatted computed tomography angiography, coronal view). (**C**) Dissection of the descending thoracic aorta with haematoma in the false lumen (asterisk) (computed tomography angiography, sagittal view). (**D**) Mural wall thickening, oedema and contrast enhancement of the ascending and descending thoracic aortas (magnetic resonance angiography, axial view, T2-weighted).

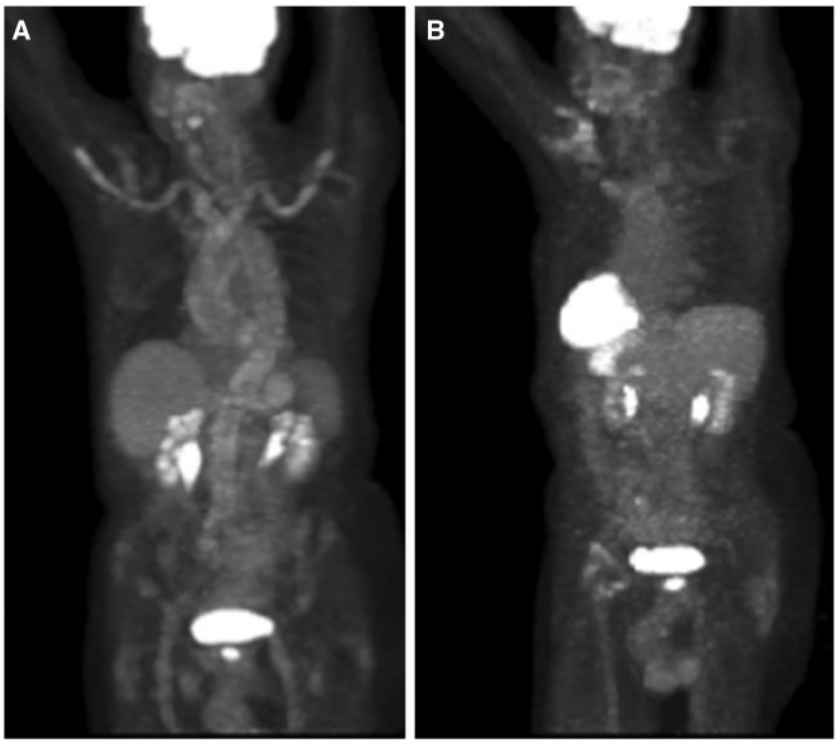
of relatively high inter-reader variability, it is recommended that these studies be performed by experienced ultrasonographers with training to detect the presence of findings indicative of GCA [52].

Disease activity assessment of large-vessel GCA

Despite the availability of several non-invasive modalities to detect evidence of large-vessel abnormalities in patients with GCA, assessment of disease activity over time remains a challenge. Long-term surveillance and monitoring of disease activity is important given the risk for vascular complications in patients with GCA, particularly those with large-vessel involvement at the time of diagnosis [35]. However, consensus guideline recommendations on the necessity, timing and duration of follow-up imaging for patients with evidence of LV-GCA are lacking [48, 54].

Laboratory parameters including ESR and CRP are commonly used to determine ongoing activity in patients with GCA but, on their own, are insufficient to determine the presence of ongoing vascular inflammation [55, 56]. Furthermore, the use of CRP as a marker of activity in patients on treatment, particularly with anti-IL-6 therapy, is further complicated as evidenced by active vasculitis being seen in a pathological specimen at autopsy from a patient receiving tocilizumab who appeared to be in both clinical and biochemical remission [57].

Fig. 3 Response of vascular hypermetabolism in large-vessel GCA to therapy



(**A**) Increased hypermetabolic vascular uptake involving the bilateral carotid and subclavian vessels as well as diffuse increased activity from the ascending aorta to the iliac bifurcation (PET, coronal oblique view). (**B**) Repeat PET 3 years after treatment initiation, demonstrating resolved vascular hypermetabolism.

It is unknown whether the progression of aortic dilatation is the result of subclinical aortic inflammation that may be responsive to chronic immunosuppression or the result of previous vascular damage. Histopathological findings from a population-based cohort of patients with GCA revealed active aortitis in four of seven patients with aortic dissection/rupture related to GCA [15]. In contrast, a prospective CTA study of newly diagnosed GCA observed destruction of the medial fibres in all six surgical resection specimens obtained at the time of surgical aortic repair, with minimal residual inflammatory infiltrates evident in only two of six patients [11]. Although histological evaluations of the large vessels are only available in the context of surgery or autopsy, these discordant findings highlight the incongruity between non-invasive methods and direct arterial investigation.

Arterial wall and lumen changes (vascular signs of inflammation) may be visualized by CDS, MRA and CTA, but these vascular signs may lag behind clinical improvement and remission [26, 35]. Although some studies have shown that arterial wall changes identified by CT can improve or resolve in the vast majority of patients within 6–12 months [42, 58], another study noted complete disappearance of aortic thickening at 6 months in only 8.8% of patients [59].

^{18}FDG-PET has been evaluated as a tool for the diagnosis and assessment of disease activity (^{18}FDG uptake) [6, 46] and can be used to detect early therapeutic response (Fig. 3). The use of serial PET examinations has not shown definitive benefit, however, when repeated over time because it is unknown whether the presence of persistent low-level subclinical vascular uptake results from ongoing arterial inflammation or vascular repair/remodelling [6].

MRI combined with ^{18}FDG-PET may also be a useful tool for the assessment of disease extent and disease activity [60]. In an evaluation of 25 consecutive patients with complicated courses of GCA, PET and MRI were considered inadequate to assess LV-GCA activity in those currently receiving immunosuppressive therapy [61]. Furthermore, the usefulness of PET in monitoring disease activity is limited by its availability and cost; therefore, it is not recommended for routine monitoring.

The presence of a halo on CDS may also be considered evidence of active disease [26]. The presence of a hypoechoic halo in the temporal artery may resolve within as few as 2 days after glucocorticoid initiation [62], but resolution of halo in the axillary artery may take 1–2 months [52]. Although it has not been prospectively validated in therapeutic clinical trials, some experts suggest US of the

axillary arteries every 6 months demonstrates a decrease or stability in the intima–media thickness of the axillary artery over time, denoting presumed disease control [52].

In the absence of conclusive, long-term, prospective studies, the surveillance of aortic damage and the timing of vascular intervention have been based on the recommended treatment of patients with degenerative or atherosclerotic aneurysms [48]. Until patients with GCA and large-vessel involvement are systematically evaluated with a standardized imaging, laboratory, clinical and therapeutic approach for a sufficient duration of follow-up (5–10 years), it will remain difficult to determine which non-invasive studies will provide clinically meaningful findings. Given the prevalence of structural aortic damage at baseline and the increase in detection seen ~5–7 years after diagnosis [14, 25], a reasonable protocol for screening of thoracic aortic aneurysm includes baseline imaging (CTA/MRA) at the time of GCA diagnosis. If the initial cross-sectional study results are normal, repeat surveillance imaging 3–5 years later can be considered. If aortic dilatation is present at baseline, then serial monitoring based on aortic diameter and rate of growth should be followed. The incorporation of such elements into large, multicentre, international clinical trials will be paramount for further understanding of this condition.

Short- and long-term outcomes of large-vessel GCA

Short- and long-term outcomes in patients with LV-GCA are variable and depend on the pattern of vascular involvement. Morbidity related to impaired vision is generally lower in patients with LV-GCA than with cranial GCA because of the reduced prevalence of visual symptoms or permanent vision loss [21, 22]. Large-vessel stenosis can also result in ischaemic complications such as limb claudication; however, the development of collateral circulation in most patients is sufficient to maintain tissue viability [63]. Critical limb ischaemia is distinctly uncommon [64, 65], and vascular bypass surgery is rarely necessary [63]. If performed, revascularization should be undertaken only in the quiescent phase of the disease [63].

To date, long-term prospective studies comparing patients with isolated cranial GCA *vs* cranial GCA with evidence of large-vessel involvement *vs* isolated LV-GCA have not been performed. As a result, limited information is available about the true effects of large-vessel involvement on long-term outcomes. Although some cohorts have shown patients with LV-GCA without cranial features may have a lower risk for relapse [28], others have noted a higher rate of relapse, longer duration of therapy, higher cumulative glucocorticoid exposure and more frequent use of additional immunosuppressive therapy [22]. In addition, patients with intense inflammation in the thoracic aorta (as demonstrated by ^{18}FDG uptake) at diagnosis appear to be more prone to the subsequent development of aortic dilatation [50].

There is significant variability between epidemiological studies evaluating risk factors of aortic aneurysms. Prognostic factors for the development of aortic aneurysm/dissection include aortic insufficiency murmur at GCA diagnosis, hyperlipidaemia, coronary artery disease and laboratory markers indicative of an inflammatory response in combination with symptoms of PMR [14, 25, 44]. The presence of inflammatory aortic involvement at the onset of GCA may also predict a more chronic/relapsing course of GCA, with an increased need for glucocorticoid use and a higher risk for long-term vascular events [66]. A recent cohort study comparing outcomes in patients with LV-GCA and cranial GCA also reported a higher prevalence of aortic aneurysms in patients with LV-GCA during follow-up (15 *vs* 3% at 5 years) [22].

Aortic involvement in LV-GCA may also be associated with increased risk for death [14]. A population-based cohort study comparing LV-GCA patients with those without large-vessel disease reported a 2.4-fold increase in risk for death in patients with LV manifestations, decreased survival rates in those with aortic aneurysm/dissection and higher than expected cardiovascular- and pulmonary-related deaths in patients with aortic aneurysm/dissection compared with the general population [25].

Treatment of large-vessel GCA

To date, no study has been published comparing different glucocorticoid doses or immunosuppressive treatment regimens specifically in patients with LV-GCA or comparing LV-GCA with cranial GCA. In general, patients with evidence of LV-GCA should receive the same treatment that patients with cranial GCA receive, with the goal of suppressing systemic and vascular inflammation [54, 67].

Glucocorticoids

Glucocorticoids remain the treatment of choice to induce remission in patients with GCA and evidence of large-vessel involvement. Initial doses of 0.75–1.0 mg/kg/day followed by gradual tapering are recommended. Recently, a prospective, longitudinal study of 40 patients with biopsy-proven GCA confirmed signs of improvement in patients with large-vessel inflammation after treatment with glucocorticoids (decreased number of affected segments and decreased wall thickness) after a median follow-up of 13.5 months through the use of CTA [3]. Furthermore, contrast enhancement was completely resolved in most evaluable patients. Although this study demonstrates the effect of glucocorticoids on radiographic signs of LV-GCA, longer follow-up in studies with adequate sample sizes is required to determine whether these improvements translate to reductions in relapse risk and/or a decrease in the progression or development of aortic damage.

Non-biologic and biologic therapies

MTX has been evaluated in patients with GCA in three randomized clinical trials, reporting inconsistent efficacy results with regards to reductions in observed relapse and overall glucocorticoid exposure [68–70]. However, the use of MTX has not been prospectively evaluated in patients

with GCA and large-vessel involvement. In a large, retrospective, single-institution cohort, 42% of patients with LV-GCA received MTX during the course of follow-up compared with only 14% of patients with cranial GCA, although outcomes related to this treatment were not assessed [22].

More recently, biologic therapies have been evaluated for the management of GCA. Ustekinumab, an IL-12/IL-23-blocking mAb, was recently evaluated in an open-label, prospective study treating patients with refractory GCA [20]. Among the 14 patients enrolled, 50% had evidence of large-vessel disease on CTA. After a median follow-up of 13 months, repeat imaging was performed in five of the seven patients. Improvement in wall thickening was observed in all five patients, two of whom demonstrated full resolution of inflammatory changes. No new stenoses or aneurysms were observed. Though preliminary, these results are promising, and a larger phase 2 open-label study is under way (ClinicalTrials.gov, NCT02955147).

Abatacept, a selective T cell co-stimulation modulator [71], was recently evaluated in a multicentre, randomized, double-blind, phase 2 trial of 49 patients with GCA who were receiving a standardized prednisone taper [18]. Patients were required to have a temporal artery abnormality or biopsy results of a temporal artery or a large vessel demonstrating evidence of vasculitis or characteristic changes of large-vessel stenosis or aneurysm on arteriography. Patients with large-vessel involvement underwent MRI of the aorta and branches at 6-month intervals. Overall, 61.0% of patients in the study had a positive TAB result, and 12.2% had evidence of large-vessel involvement (new vascular stenosis or aneurysm). At 12 months, the relapse-free rate was significantly higher in the abatacept group than in the placebo group (48 *vs* 31%; $P = 0.049$), and a longer median duration of remission was achieved with abatacept (9.9 *vs* 3.9 months; $P = 0.023$). Despite the small number of patients with large-vessel involvement in this study population, the findings suggest that abatacept may be an efficacious treatment option for reducing relapse in patients with GCA. Prospective studies evaluating abatacept in patients with evidence of LV-GCA will determine whether this biologic therapy is an effective option for these patients.

Improvements in clinical manifestations and relapse-free survival have been reported in small studies and case series evaluating tocilizumab, an IL-6 receptor alpha antagonist, in GCA patients [10, 72, 73]. Long-term clinical response and steroid-sparing efficacy were also demonstrated with tocilizumab in eight cases of refractory LV-GCA [74]. A randomized, double-blind, placebo-controlled, phase 2 trial demonstrated the efficacy of tocilizumab compared with prednisolone in the induction and maintenance of remission in patients with newly diagnosed or relapsing GCA [19]. Complete remission at 12 weeks was achieved by 85% of patients receiving tocilizumab compared with 40% of patients receiving placebo ($P = 0.03$), and the relapse-free survival rate at 52 weeks was 85% compared with 20%. In this study, large-vessel involvement (abnormal thoracic-abdominal angiography) was observed at baseline in 55% of patients in the tocilizumab group and 60% of patients in the placebo group. However, given the small sample size of this study ($n = 30$), subgroup analysis of therapeutic response in patients with large-vessel involvement was not reported.

A recent multicentre, randomized, double-blind, placebo-controlled, phase 3 trial assessing the efficacy and safety of tocilizumab in patients with GCA (GiACTA) demonstrated superior clinical efficacy and a glucocorticoid-sparing effect in patients with GCA treated with tocilizumab and a blinded prednisone taper compared with prednisone taper alone [17]. Enrolment in GiACTA was based on a modification of the 1990 ACR classification criteria for GCA, specifically allowing inclusion of patients with evidence of large-vessel vasculitis by angiography or imaging (MRA, CTA, PET/CT). With 251 patients recruited, GiACTA is the largest prospective study evaluating treatment in patients with GCA. A total of 138 patients underwent cross-sectional imaging, of whom 119 (86%) had findings consistent with large-vessel involvement [75]. As a result, more than one-third of the GiACTA patient population received diagnoses of GCA based on imaging evidence of large-vessel vasculitis [75]. As with all GCA treatments, open questions include how long this treatment should be continued and whether normalization of CRP and resolution of vessel inflammation on imaging reflect actual reductions in the inflammatory burden observed on histopathological examination and subsequent complication rates. Subgroup analysis of GiACTA patients with large-vessel involvement will provide valuable clinical data for this particular GCA phenotype and is eagerly awaited.

Conclusions

Large-vessel involvement in GCA is common and is associated with vascular complications, which may be due, in part, to the delay in diagnosis of the disease. Advancements in imaging techniques have resulted in improvements in the diagnosis of large-vessel involvement in GCA; however, their performance and usefulness in assessing and monitoring ongoing disease activity require further evaluation in long-term studies. In addition, there is uncertainty about and limited evidence-based guidance for the timing and cost-effectiveness of interval imaging for the evaluation of large-vessel involvement and its complications, particularly aneurysm development. Long-term outcome data about these vascular lesions are needed to determine whether patients with evidence of large-vessel involvement require different treatment regimens or durations. Although glucocorticoids are the mainstay of therapy for patients with LV-GCA, their prolonged use is associated with morbidity related to adverse effects. Effective approved glucocorticoid-sparing therapies have been lacking for these patients, but recent studies of biologic therapies such as tocilizumab suggest that these treatments may offer patients with LV-GCA an effective and safe glucocorticoid-sparing therapeutic option.

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