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Extra-Cranial Involvement in Giant Cell Arteritis

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Abstract

Recent advances in imaging studies and treatment approaches have greatly improved our knowledge about Giant Cell Arteritis (GCA). Previously thought of as a predominantly cranial disease, we now know that GCA is a systemic disease that may involve other medium and large vessel territories. Several imaging studies have shown that between 30 and 70% of patients with GCA present with large-vessel vasculitis. Moreover, a significant proportion of patients present large-vessel disease in the absence of cranial involvement. Extra-cranial disease also poses management challenges as these patients may have a more refractory-relapsing disease course and need additional therapies. Aortic dilation and aneurysms are well-described late complications of GCA involving the large artery territories. In this chapter, we discuss the clinical picture of extra-cranial involvement in GCA, focusing on improved diagnostic protocols and suitable treatment strategies.

Keywords: giant cell arteritis, large-vessel vasculitis, polymyalgia rheumatica, vasculitis, diagnostic imaging

1. Introduction

Giant cell arteritis (GCA) is a systemic vasculitis that predominantly involves large and medium-size arteries [1]. It occurs almost exclusively in subjects aged 50 years or older, and is the most common form of systemic vasculitis among the elderly [2]. GCA is more common among caucasian female patients, with a female-male ratio of about 2–3:1. The GCA annual incidence varies with geographical location and ranges from 1.6 to 32.8 cases/100000 persons ≥ 50 years of age [3].

GCA is commonly defined as Large-Vessel (LV) GCA if the aorta and its branches are involved. The systemic nature of the disease was noted as early as the first cases described by Horton and colleagues in 1932 [4]. Later on, Gilmour suggested that the disease should be called “giant-cell chronic arteritis” as the temporal arteritis appeared to be only part of a more widespread vascular disease [5]. Despite this early reports, physicians have mainly focused on typical cranial symptoms and visual disturbances and have relied mostly on temporal biopsy for diagnosis. This focus is well reflected in the 1990 ACR classification criteria that emphasised the importance of headache as a cardinal symptom and temporal biopsy as its primary diagnostic tool [6]. Unfortunately, the concept of GCA as a limited cranial disease is inaccurate and obscures essential clinical features. Furthermore, the misuse of classification criteria for diagnostic purposes, may lead to underdiagnose LV-GCA [7].

In recent years there has been an increased awareness of the systemic large-artery nature of GCA. Necropsy studies have shown histologic evidence of systemic large-artery vasculitis in approximately 80% of patients [8, 9]. Recent advances in diagnostic imaging techniques have confirmed these figures, suggesting that imaging will have an increasing impact in the diagnosis and management of GCA [10–14]. Furthermore, patients with GCA are at increased risk of developing aortic dilation and aneurysms among other complications [15–17].

Altogether, these issues highlight the importance of the extra-cranial involvement of GCA which has been under-recognised and poorly managed.

2. Pathophysiology

GCA is an idiopathic inflammatory granulomatous vasculitis. The aetiology is unknown, and most probably, genetic, environmental, vascular, and age-related factors concur to the development of the disease [2, 18]. In GCA, a lymphocyte and plasma cell infiltrate originates at the *vasa vasorum* in the adventitia of large vessels, which then penetrates the vessel wall leading to an intimal and media hyperplasia and vessel wall thickening [19]. Multinucleated giant cells form a complex near the intima-media complex, but they are not a requisite for diagnosis. Inflammation can be segmental, circumferential, or transmural [9, 20]. The predominance of GCA by some vessel territories and the mechanisms behind the different phenotypes like LV-GCA are still unsolved questions. In fact, most studies have been performed in temporal artery biopsies, as large arteries are not as readily accessible for histologic examination. Animal models also present limitations regarding the expression of the disease in different vascular territories. The interaction of immunopathogenic mechanisms with the different functional and anatomic characteristics of the vessel walls in different parts of the body may explain the distinct aspects of LV-GCA pathophysiology.

2.1 Immunologic mechanisms in large vessel giant cell arteritis

The critical event in initiating and sustaining the inflammatory response is thought to be the abnormal maturation and loss of tolerance of vascular Dendritic cells (DCs), which is triggered by toll-like receptors (TLRs) [21, 22]. Differentiated DCs drive T cell and macrophage recruitment [21]. Upon the maturation of DCs, CD4⁺ T cells are also stimulated by local cytokines, such as IL12, to polarise into T-helper 1 (Th1) and IL6 and IL23 to polarise into Th17 cells [23].

Th17 cells are responsible for implementing a strong acute IL17 mediated inflammatory response, which leads to the overproduction of a cluster of cytokines, namely IL1 β , IL6, IL23 and TNF- α [23]. Type II cytokine receptors (mainly IL6 and IL1 β) signal through JAK1 homo-dimers [24] promoting further cellular activation and inflammatory response. The IL17 pathway is therefore responsible for most of the inflammatory response in the acute phase and explains the systemic nature of the disease [25, 26].

Th1 cells differentiation induces an immune response where IFN- γ is the central cytokine [27]. IFN- γ receptor signals through JAK1–JAK2 heterodimers [28]. The INF- γ signature further enhances the inflammatory response (through IL1 β , IL6, and TNF- α), leading to macrophage differentiation and activation. Upon the stimulation by the granulocyte-macrophage colony-stimulating factor (GM-CSF) produced by T cells, macrophages act in sustaining inflammation and are key players in the interaction with the stromal and extracellular matrix [29, 30]. This interaction is mediated by matrix metalloproteinases (MMP) and several growth factors.

MMP are proteases with elastolytic activity, released and activated by inflammatory cells. Smooth muscle loss and proteolytic imbalance may contribute to elastic fibre rupture, weakening of the artery wall, and cell migration [29, 31]. The IFN- γ signature is responsible for the histiocytic reaction, myofibroblast differentiation, intimal hyperplasia, neoangiogenesis, vascular remodelling, damage, and fibrosis [32]. These aspects explain the vascular manifestations and the LV complications of GCA. Current treatments efficiently inhibit the Th17-mediated response, but not the Th1 mediated expression of IFN- γ [27, 33]. Thus, the current management of vascular manifestations like artery stenosis and aneurysms is suboptimal, as vascular remodelling processes may subsist even in the absence of raised inflammatory markers [34].

Patients with polymyalgia rheumatica (PMR) present activated DCs in focal vessel infiltrates with the expression of inflammatory cytokine production (IL1 β and IL6), but IFN- γ is absent [35]. Therefore, it is thought that it is the IFN- γ pathway, and not IL17 activation that marks the progression to overt vascular inflammation and remodelling.

It is not yet clear why some patients have only PMR while others progress to periadventitial or transmural vasculitis. Different TLR expression on DCs may partly explain such patterns as TLR4 activation induces transmural panarteritis, while TLR5 ligands promote adventitial perivasculitis [36]. Moreover, DCs exhibit distinct combinations of TLRs in different vascular beds [37]. Thus, the phenotype of the vasculitis may depend upon the profile of the TLR driven T cell activation, which is specific of each vascular territory.

The interaction between T cells and B cells might also be implicated in the expression of LV-GCA. Recent findings in aorta tissue samples from 9 LV-GCA patients who underwent aortic aneurysm surgery, showed massive infiltration of B-cells, which outnumbered T-cells. B-cells were mainly found in the adventitia and were organised into tertiary lymphoid organs [38]. This is an uncommon observation in temporal artery biopsies.

The interaction of immune mechanisms and the vascular matrix is also demonstrated by the MMP expression in singular vascular fields. MMP2 tissue expression was observed in active temporal artery lesions and in aortic aneurysm samples obtained in 2 GCA patients. However, MMP9 was present only in temporal artery lesions and faintly detectable in normal temporal arteries and GCA-related aneurysms [17]. While MMP9 is mainly produced by inflammatory cells, MMP2 may also be expressed in smooth muscle cells and be involved in reparative mechanisms. Therefore, the expression of MMPs on different vascular beds may also impact on the clinical features of GCA.

2.2 Atherosclerosis, ageing and large vessel vasculitis

Atherosclerosis is highly prevalent among GCA patients as it is most present at an advanced age. The coexistence of these two diseases and the underlying immune mechanisms of both may tailor the phenotype of the vasculitis. It is known that patients with cardiovascular risk factors have a higher risk of developing severe ischaemic manifestations of GCA [39]. In fact, patients with ischemic complications have lower expression of IL6 suggesting that IL6 may play a protective angiogenic role to compensate for ischemia [40]. Furthermore, at the supra-aortic level, atherosclerosis most commonly affects the carotids, while LV-GCA predominantly affects the axillary arteries. Regardless of the immune profile, age and genetic factors also influence the development of atherosclerosis. In caucasians, atherosclerosis occurs later and less extensively in intracranial arteries compared to extra-cranial arteries. Interestingly, Asian and African populations are more affected by

intracranial atherosclerosis and also show a low prevalence of cranial GCA [3, 41]. Thus, atherosclerosis may alter vessel vulnerability or expression of GCA.

Age is an important factor that affects vascular and immune processes with a possible impact on disease vulnerability and manifestations [42]. Ageing induces significant changes in the expression of vascular MMP2 and MMP9 and reduces arterial smooth muscle proliferative capacity [43–45]. One of the main distinctions between LV-GCA and Takayasu arteritis (TAK) has been attributed to an age cut-off. Interestingly, TAK shows similar immunologic mechanisms with dysregulated activation of Th1 and Th17 pathways [46] and therefore age-related factors may be the key to explain the distinct manifestations between LV-GCA and TAK [20, 42].

3. Clinical features of large vessel giant cell arteritis

3.1 Clinical manifestations

LV-GCA usually presents with prominent constitutional symptoms and a marked increase in inflammatory markers. Systemic constitutional symptoms include fever, malaise, weight loss and night sweats. Symptoms are usually non-specific and, in up to 20% of the patients, systemic constitutional symptoms are the only clinical features of the disease with some cases being diagnosed following an investigation for fever of unknown origin [10, 18]. Aortitis is a common feature in LV-GCA. Aortitis is often pauci-symptomatic, but some patients may refer chest or back pain [18]. LV-GCA also affects the main arteries of the limbs, presenting most commonly as limb claudication. Limb claudication reflects intimal and muscular hyperplasia secondary to vascular inflammation, which leads to vessel wall thickening with lumen occlusion. Limb claudication involves the arms more frequently than the legs and may be present in up to 50% of LV-GCA patients. It can be intermittent and asymmetric despite vascular involvement being bilateral in around 80% of the patients [7, 10, 47].

The preferred vascular territories involved are the supra-aortic branches, particularly the axillary and subclavian arteries, which are involved in almost all patients with LV-GCA. Carotid and vertebral artery involvement are less frequent. Aortitis is present in around 50–65% of the patients with documented LV-GCA. Most commonly, it involves the aortic arch and the thoracic descending aorta. When the abdominal aorta is affected, there is usually involvement of the thoracic segment as well. Femoral arteries and inferior limb arteries are involved in only around 10–15% of the patients. Sometimes differential diagnosis with atherosclerosis, very commonly found in these arteries, may be difficult. Visceral arteries are rarely affected [7, 10, 12, 47–49].

3.2 Clinical overlap between large vessel vasculitis, cranial giant cell arteritis and polymyalgia rheumatica

There is a considerable clinical and epidemiologic overlap between GCA and PMR. PMR is a clinical syndrome characterised by bilateral shoulder pain, morning stiffness, shoulder or pelvic girdle weakness, and peripheral arthralgia/arthritis [2]. Approximately 20% of PMR patients have GCA, whereas PMR is present in up to 60% of GCA patients [2, 50, 51]. PMR is also the main form of relapse in up to 50% of GCA patients, while cranial symptoms are relatively uncommon at relapse [52]. Interestingly, Positron Emission Tomography (¹⁸FDG-PET) LV fluorodeoxyglucose increased uptake was noted in 30% of patients with isolated polymyalgia rheumatica at diagnosis [53]. Therefore, PMR patients with

incomplete response to corticosteroid treatment or a relapsing disease should be re-evaluated for LV involvement.

Patients with LV-GCA are more frequently women and present at a younger age, whereas patients with cranial GCA are usually men and older [7, 10, 54]. When compared with cranial GCA, patients with LV-GCA present less frequently with headache (35% in LV-GCA vs. 60% in cranial GCA), jaw claudication (22% in LV-GCA vs. 50% in cranial GCA) and also with fewer cranial ischemic symptoms (permanent visual loss in 4% in LV-GCA vs. 20% in cranial GCA) [10, 55–57]. Although there may be specificities concerning the presentation of cranial GCA and LV-GCA, they are not distinct entities (**Table 1**). More likely, we are facing a different spectrum of the same disease (**Figure 1**). Depending on the different imaging techniques used, 32–83% of the patients with confirmed cranial GCA also have LV vasculitis [10–12, 14] and 10–30% of the patients with GCA have only LV vasculitis, with no clinical, histologic or Doppler evidence of temporal artery vasculitis [10, 48, 58, 59].

Symptoms and signs	Cranial GCA	LV-GCA	PMR
Headache	++	+	—
Jaw claudication	++	—	—
Visual disturbances	++	—	—
Limb claudication	+	++	—
Fever, night sweats, weight loss	+	++	+
Polymyalgic symptoms	+	++	++
Peripheral arthralgia/arthritis	+	+	++
Elevation of inflammatory markers	++	++	++

GCA, Giant Cell Arteritis; LV, Large Vessel; PMR, Polymyalgia Rheumatica; —, uncommon symptom or sign; +, common symptom or sign; ++, very common symptom or sign.

Table 1.
Clinical symptoms and signs in different subtypes of GCA and in PMR.

Figure 1.
The clinical spectrum of cranial GCA, LV-GCA and PMR.

Due to the more unspecific nature of the clinical presentation of LV-GCA, the diagnosis is often delayed or even missed. In general, patients with isolated LV-GCA have a delay in the diagnosis greater than one year compared with patients with cranial GCA [7]. It is still unknown whether this delay in diagnosis and treatment may impact the clinical course of the disease. However, LV-GCA patients relapse more frequently and earlier than those with cranial GCA and have higher corticosteroid cumulative doses and more frequently require additional immunosuppressive treatments [7, 54]. These facts suggest that patients with LV-GCA should be considered for a different management and treatment strategy, with a more tailored, eventually more aggressive approach.

4. Differential diagnosis

The systemic LV involvement in GCA may resemble the presentation of Takayasu arteritis (TAK). Patients with Takayasu's disease may present with raised inflammatory markers, vascular bruits, asymmetric blood pressure measurements and limb claudication, much like patients with LV-GCA. The recent widening of the concept of vascular involvement in GCA shows that there can be an overlap between these two conditions. However, some have proposed clear distinctions. Most importantly, the epidemiology is quite different. GCA is recurrent among northern European patients, whereas TAK is more prevalent among the Asian population [60]. Another difference is the age of disease onset. GCA is almost exclusively present in patients 50 years or older, whereas TAK is common under 40 [2, 61]. However, some argue age restriction to be arbitrary and without etiologic or pathophysiologic basis [20]. In a study of 96 Japanese patients with TAK, 22% were outside the proposed age cut-off [62]. Likewise, in the study that defined the 1990 ACR Classification Criteria for GCA, 23% of the patients had less than 50 years old at diagnosis [6]. Moreover, these definitions are elusive for patients with LV vasculitis aged between 40 and 50 years. So, distinguishing GCA and TAK based only on age and epidemiology may be difficult suggesting that we might, in fact, be looking at two forms of the same disease [63].

The histopathologic findings in both GCA and TAK show a lymphohistiocytic infiltrate in the vascular wall that may be indistinguishable [20]. However, this observation may be biased due to the small number of patients undergoing vascular biopsy in TAK. Pathophysiologic mechanisms also show common features between both diseases [42, 46]. Clinically, TAK presents with a more widespread vascular involvement. The carotid and mesenteric arteries are more frequently affected in patients with TAK than GCA, while subclavian and axillary artery involvement is more prevalent in LV-GCA [63, 64]. The aortic involvement is also distinct since stenotic/occlusive lesions are predominant in TAK, whereas aneurysmal disease is more common in GCA [64]. It is unclear, however, if the differences in imaging findings represent cumulative damage due to delay in TAK diagnosis or whether other age-related immunologic and vascular factors may explain these differences. Lastly, inflammatory markers seem to be higher in patients with GCA than in TAK. Around 44% of the patients with TAK may have active vascular inflammation despite normal inflammatory marker values [65].

Several cases of small and medium vessel vasculitis have been described with temporal artery involvement, particularly granulomatosis with polyangiitis and eosinophilic granulomatosis with polyangiitis [66]. However, the presentation of ANCA-associated vasculitis with aortitis is extremely rare [67] and even more so in other forms of primary vasculitis.

Infectious diseases Syphilis aortitis <i>Salmonella spp</i> <i>Staphylococcus spp</i> <i>Micobacterium tuberculosis</i> Sub-acute endocarditis	Immune-mediated diseases Systemic vasculitis Takayasu Arteritis ANCA-associated vasculitis Panarteritis nodosa
Haematological and oncological disorders Erdheim-Chester histiocytosis Amyloidosis Paraneoplastic retroperitoneal fibrosis	Autoimmune diseases Systemic lupus erythematosus Rheumatoid arthritis
Vascular disease Atherosclerosis	Inflammatory diseases HLA-B27 associated spondyloarthropathies Behçet disease Cogan disease Relapsing polychondritis
	Other Idiopathic aortitis IgG4-related disease Sarcoidosis

Table 2.
Differential diagnosis of large-vessel giant cell arteritis.

Other systemic diseases present with aortitis and may also be mistaken with LV-GCA (**Table 2**). Some infections like syphilis or sub-acute endocarditis may evolve with aortitis [68, 69]. In these cases, serologic and microbiologic studies often guide the diagnosis. Other immune-mediated diseases also have aortitis as a prominent clinical feature such as Behçets disease, IgG4-related disease, and Erdheim-Chester disease. These entities often have other distinctive organ involvement and typical histologic findings pointing to a different diagnosis [69–71]. Also, in IgG4-related and Erdheim-Chester diseases, aortic involvement occurs as peri-aortitis and retroperitoneal fibrosis which is different from vascular inflammation. Aortitis may also be a late complication of ankylosing spondylitis. It often involves the aortic root or the iliac periaortic peritoneum. It presents late in the disease, and articular symptoms often precede it by years. With recent advances in treatment, it is expected that it will become a less common manifestation of the disease [72].

5. Imaging features of large-vessel giant cell arteritis

Several imaging techniques have contributed to significant improvements in the assessment and management of LV-GCA, yet no single method is considered preferable (**Table 3**).

5.1 Ultrasonography

Ultrasonography has become widely used in GCA as it can be comparable to biopsy in the diagnosis of temporal arteritis [48, 73]. The presence of a regular hypoechoic non-compressible area around the lumen (the “halo sign”) that reflects an oedematous inflammatory intima-media thickening is considered diagnostic of medium and large vessel vasculitis [74]. It is distinguished from atherosclerotic plaques since atherosclerosis presents as irregular iso- or hyper-echoic extrusions. Ultrasonography identifies aspects compatible with LV-GCA in 29–48% of patients when axillary-subclavian arteries are systematically analysed, and this standard evaluation is particularly important as 13–33% of patients have LV-GCA in the absence of temporal involvement [10, 11, 48, 58, 59]. The identification in the axillary arteries of a smooth hypoechoic increase in the intima-media thickness (IMT)

Imaging technique	Findings of LV vasculitis	GCA with LV vasculitis	Diagnostic accuracy under treatment
Ultrasonography	<ul style="list-style-type: none">• Hypoechoic wall thickening (halo)	29–48% [10, 48, 58, 59]	2 weeks
CT and CTA	<ul style="list-style-type: none">• Circumferential wall thickening• Wall contrast enhancement.	45–68% [12, 77, 78]	3 days
MRI	<ul style="list-style-type: none">• Circumferential wall thickening• T2 sequence enhanced wall oedema	~54% [82]	—
¹⁸ FDG-PET	<ul style="list-style-type: none">• Increase vascular ¹⁸FDG uptake	58–83% [14, 49, 83]	10 days

CT, Computed tomography; CTA, CT angiography; MRI, magnetic resonance; ¹⁸FDG-PET, ¹⁸F-deoxyglucose positron emission tomography; —, unavailable data.

Table 3.
Imaging methods in the diagnosis of large vessel inflammation in giant cell arteritis.

Figure 2.
Doppler ultrasonography of a right axillary artery in a patient with Large Vessel Giant Cell Arteritis. White line shows a smoothly increased hypo-echoic intima-media thickness of around 1.5 mm.

(with a local cut-off for IMT ≥ 1 mm) correctly identified LV-GCA (**Figure 2**) with a sensitivity and a specificity of close to 100% [75].

Ultrasonography has the advantage of being inexpensive, not using ionising radiation and can be readily accessible to use, as demonstrated in the implementation of fast track clinics [55, 57], though it requires experienced sonographers. Ultrasonography may also be useful in disease monitoring, as most patients show the disappearance of wall thickening over the course of steroid treatment [76]. This is why ultrasonographic signs are accurate for diagnosis purposes only within the first two weeks of corticosteroid treatment, losing sensitivity thereafter [74, 76], whilst thoracic aorta examination is not easily accessible by ultrasound.

5.2 Computed tomography

Computed tomography (CT) and CT angiography (CTA) are useful for LV imaging; they have a short scanning time yet allowing for a comprehensive vascular assessment, including the thoracic and abdominal aorta. Prospective studies of newly diagnosed

Figure 3.
 Computed tomography (CT) and CT angiography (CTA) revealing Large Vessel Vasculitis in Giant Cell Arteritis (GCA). Left image shows a CTA image with circumferential wall thickening >2 mm of the thoracic aorta. Central CTA image shows the extent of thoracic aorta wall thickening in the same patient, predominantly involving posterior wall. Right image reveals thoracic wall thickening in CT of another GCA patient. Arrow depicts vasculitic wall thickening, arrowhead depicts atherosclerotic calcified plaque.

GCA patients assessed by CTA have revealed LV involvement in 45–68% of subjects [12, 77, 78]. Typical findings of LV include circumferential wall thickening and vessel wall contrast enhancement. However, CTA findings may be attenuated by an as short as three-day course of corticosteroid treatment [12]. Nevertheless, up to 43% of patients still present significant arterial wall thickening one year after treatment [79]. The simultaneous assessment of aortic dilation and the adequate distinction between vasculitis and atherosclerosis, which appears as focal calcifications, are other advantages of CTA. Ionising radiation is of concern when repetitive evaluations are performed, but novel low-dose CTA techniques may reduce radiation exposure (**Figure 3**) [80].

5.3 Magnetic resonance

Magnetic Resonance (MRI) conveys a wide vascular assessment with vasculitis appearing as a mural thickening or wall oedema, enhanced in T2 sequences. High-resolution MRI has been extensively used to assess temporal arteritis, but there is little experience with MRI in LV-GCA [13, 81, 82]. In contrast, and as MRI does not require iodinated contrast or ionising radiation, it has been exhaustively used for periodic assessment in younger patients with TAK [80].

5.4 Positron emission tomography

^{18}F FDG-PET has become widely used in LV-GCA as it allows broad vascular assessment of inflamed vascular territories that have an increased glucose metabolism. Accordingly, 58–83% of patients with GCA show LV involvement in ^{18}F FDG-PET studies [14, 49, 83]. ^{18}F FDG-PET also has the advantage of suggesting possible differential diagnoses such as infectious or neoplastic disease. However, it is not as accurate in assessing vascular stenosis or occlusions and distinction with atherosclerotic plaques that also show increased vascular uptake may be troublesome in older patients. Furthermore, a consensus agreement regarding ^{18}F FDG-PET criteria of LV vasculitis is lacking. ^{18}F FDG uptake equal to or greater than liver uptake on PET has been proposed as the best criterion of LV inflammation in GCA [84]. The vascular uptake in LV is also attenuated after three-day corticosteroid treatment but nevertheless, maintains an adequate sensitivity for diagnostic purposes. Notwithstanding, after ten days of treatment, sensitivity may diminish considerably (**Figure 4**) [85].

Figure 4.

¹⁸F-FDG-PET scans of Large vessel GCA. Left panel shows aortitis with involvement of the thoracic and abdominal aorta. Central panel shows inflammatory uptake of the ascending aorta and subclavian arteries. Right panel reveals inflammatory uptake of the aorta and common carotid arteries. Arrows reveal areas of increased vascular ¹⁸F-FDG uptake.

6. Treatment particularities

There are no studies specifically addressing the treatment of LV-GCA. As such, LV-GCA is currently managed in the same fashion of GCA. Corticosteroids remain the mainstay of treatment. Induction of remission should be started with 40-60 mg/day of prednisone equivalent to suppress systemic and vascular inflammation and prevent ischaemic complications such as blindness, and then followed by progressive tapering [2, 56, 86]. However, GCA relapses are frequent and corticosteroids account for significant complications. Therefore, adjunctive therapy should be considered in selected patients. Methotrexate (MTX) has been used as an adjunctive treatment with modest efficacy [87, 88]. TNF inhibitors have proven to be ineffective in GCA [89–91]. By contrast, the IL6-receptor blocker tocilizumab (TCZ) proved to be an effective and safe adjunctive therapy in GCA. Treatment with TCZ induced remission in over 50% of patients at 52 weeks, compared to less than 20% with placebo, and markedly reduced cumulative corticosteroid doses [92]. Recent results from real-life data corroborate the efficacy of TCZ shown in clinical trials [93].

There is some indirect evidence that LV vasculitis responds equally to standard treatment. This is corroborated by prospective imaging studies that show a decrease in LV inflammation over the course of treatment [76, 79, 85]. In a small study MTX was effective in corticosteroid-resistant LV-GCA [94]. However, it is widely accepted that patients with LV-GCA have a more relapsing disease course and receive higher doses of corticosteroids and more concomitant immunosuppressive therapy [7, 95].

In the GIACTA trial, 119 out of 251 patients included had evidence of LV vasculitis [96]. The outcomes measured did not include vascular imaging, and there is no sub-analysis directly aimed at patients with LV involvement. However, weekly TCZ was superior to biweekly TCZ or placebo in relapsing disease [92]. Being LV-GCA a more relapsing disease, it is possible that TCZ might be a preferred treatment option in this subgroup of patients [97].

Two other drugs have been studied in small GCA trials with data regarding LV-GCA. Ustekinumab, an IL-12/IL-23-blocking monoclonal antibody, was

prospectively studied in 25 patients with refractory GCA, 10 of them with LV-GCA shown on CTA. Eight of these ten patients had multiple image assessments, and all of them showed improvement of wall thickening including four that had a complete resolution of the lesions [98]. However, in another prospective open-label trial with 13 patients with newly diagnosed or relapsing GCA, enrolment was prematurely closed due to lack of efficacy and high relapse rates [99]. Abatacept, an IgG1-CTLA4 fusion protein, was evaluated in a trial with 41 patients, (22% had LV vasculitis) and showed an improvement in relapse-free rate and duration of remission as compared to placebo [100]. Both these drugs need to be further evaluated in prospective and more extensive trials to further assess their efficacy.

Encouraging preliminary results were reported from a randomised controlled trial with mavrimumab, an anti-GM-CSF receptor α monoclonal antibody, which has shown sustained remission at week 26 in 83% of the patients, compared to 50% in the placebo group. These results were consistent across the different disease sub-groups (final report is still pending) [101].

Another open question is whether current treatment significantly improves vascular remodelling and long-term LV-GCA complications such as aneurysms. The inhibition of both Jak1 and Jak2 may be a reasonable target to reduce the activation of the Th1 and Th17 pathways present in LV-GCA. Two Jak1 and Jak2 inhibitors are currently under investigation in clinical trials: baricitinib and upadacitinib [102, 103].

7. Complications and prognosis

Vascular complications of LV-GCA include the formation of arterial stenosis, occlusions and aneurysms [15, 16]. Involvement of the aorta commonly occurs as dilation or aneurysm, as aortic stenosis is unlikely. Stenosis presents as limb claudication, involving more commonly the superior extremities, although the involvement of the inferior extremity is also possible [7, 47]. GCA patients are at an increased risk of developing aortic aneurysms/dissection or large artery stenosis (**Figure 5**). While stenosis mostly occur during the first year, the incidence of aortic aneurysms/dissection increases over the five years following the GCA diagnosis [104].

Figure 5.
Computed tomography angiography showing ascending aortic dilation in a patient with Giant Cell Arteritis.

In the long-term, 10–33% of the patients may develop aortic aneurysms/dissection and around 13% may develop large-artery stenosis [16, 104, 105].

Interestingly, aortic dilation is already present in 15% of the newly diagnosed GCA patients [12] with the thoracic aorta being the most commonly involved [105]. Aortic aneurysms are more frequently found among male patients with identified cardiovascular risk factors that include hypertension, dyslipidaemia and coronary artery disease [16, 17, 106]. It is unlikely that aortic aneurysms result from the persistent inflammatory activity as patients with aortic dilation/aneurysms were found to have lower serum acute-phase reactants and a lower relapse rate [17, 105]. However, increased ^{18}F FDG uptake in the aorta on PET performed at the GCA diagnosis was associated with the subsequent development of aortic dilation [107, 108]. It is thus conceivable that a strong inflammatory response at the beginning of the disease followed by remodelling vascular factors and hemodynamic factors (like hypertension), may be more relevant to the development of aortic dilation and aneurysms than a continuous inflammatory process.

Despite all the possible complications, the overall prognosis of GCA is good, with a mortality rate similar to the general population [109]. However, GCA is responsible for a significant morbidity. Around 64% of the patients will have at least one relapse [52] and up to 86% of patients will develop at least one steroid-related complication [110]. Initially it would be thought that LV-GCA patients would not contribute to an increased morbidity as they have fewer ischaemic cranial events that classically have been responsible for the most relevant morbidity associated with GCA [10, 11].

However, LV-GCA patients have a more relapsing disease-course, have higher corticosteroid cumulative doses, and require additional immunosuppressive treatments [7, 95]. Moreover, patients with LV inflammation are at increased risk of developing large-artery stenosis and aortic arch syndrome [54, 105, 106]. In fact, when compared to the general population, survival is decreased in GCA patients with an aortic aneurysm/dissection [104], confirming the negative impact the involvement of large arteries has on both mortality and morbidity associated to GCA.

8. Conclusions

LV-GCA has been previously misregarded and underdiagnosed. However, there is consistent evidence confirming that large arteries are involved in around two-thirds of patients with GCA and one-third of patients with PMR. Classification criteria are inadequate for LV-GCA. A revision of the current criteria is required in the near future. LV-GCA presents a more relapsing-disease course and an increased risk of vascular complications, with LV inflammation being responsible for a considerable increment in the morbidity and mortality associated to this condition. This chapter emphasises the importance of carefully considering the large artery aspects in the management and treatment of patients with GCA.

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Conflict of interest

The authors declare no conflict of interest.

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