Chapter

Extra-Cranial Involvement in Giant Cell Arteritis

João Fernandes Serôdio, Miguel Trindade, Catarina Favas and José Delgado Alves

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 Ddendritic 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 IL1β, IL6, IL23 and TNF-α [23]. Type II cytokine receptors (mainly IL6 and IL1β) 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 IL1β, 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 (IL1β and IL6), but IFN-y 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 extracranial 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 (^{18}FDG-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.

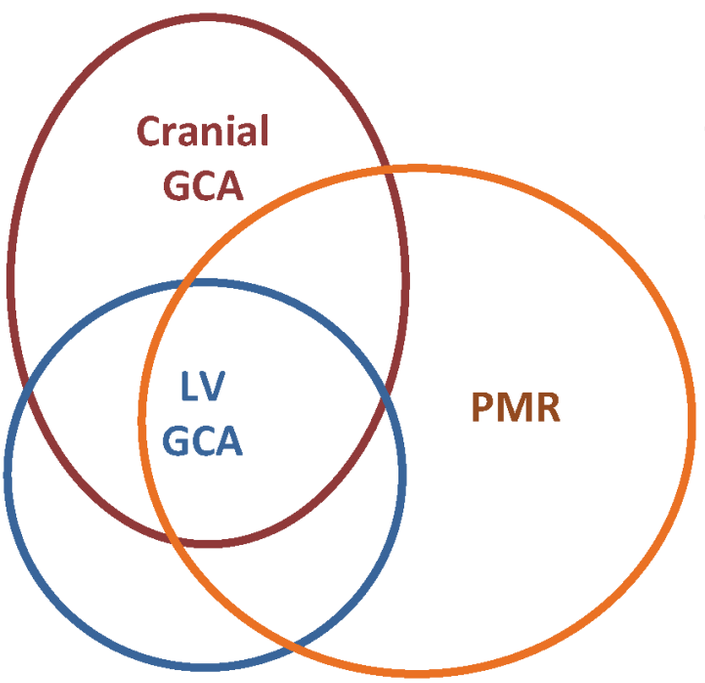

Figure 1.
The clinical spectrum of cranial GCA, LV-GCA and PMR.

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	**Immune-mediated diseases**
Syphilis aortitis	**Systemic vasculitis**
Salmonella spp	Takayasu Arteritis
Staphylococcus spp	ANCA-associated vasculitis
Micobacterium tuberculosis	Panarteritis nodosa
Sub-acute endocarditis	**Autoimmune diseases**
Haematological and oncological disorders	Systemic lupus erythematosus
Erdheim-Chester histiocytosis	Rheumatoid arthritis
Amyloidosis	**Inflammatory diseases**
Paraneoplastic retroperitoneal fibrosis	HLA-B27 associated spondyloarthropathies
Vascular disease	Behçet disease
Atherosclerosis	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 periaortitis and retroperitoneal fibrosis which is different from vascular inflammation. Aortitis may also be a late complication of ankylosing spondylitis. It often involves de 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	• Hypoechoic wall thickening (halo)	29–48% [10, 48, 58, 59]	2 weeks
CT and CTA	• Circumferential wall thickening • Wall contrast enhancement.	45–68% [12, 77, 78]	3 days
MRI	• Circumferential wall thickening • T2 sequence enhanced wall oedema	~54% [82]	—
^{18}FDG-PET	• Increase vascular ^{18}FDG uptake	58–83% [14, 49, 83]	10 days

CT, Computed tomography; CTA, CT angiography; MRI, magnetic resonance; ^{18}FDG-PET, ^{8}F-deoxyglucose positron emission tomography; –, unavailable data.

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

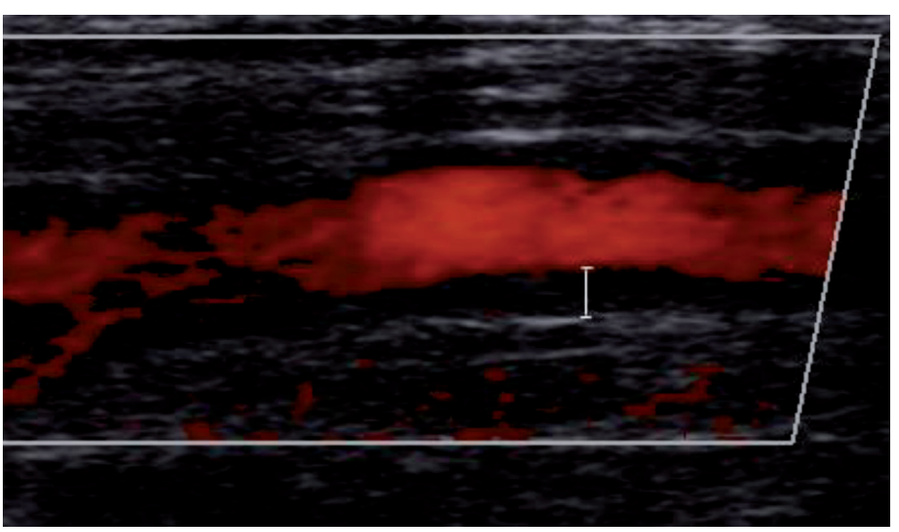

Figure 2.
Doppler ultrasonography of a right axillary artery in a patient with Large Vessel Giant Cell Arteritis. White line shows a smoothly increased hypo-echoic intima-media thickness of around 1.5 mm.

(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

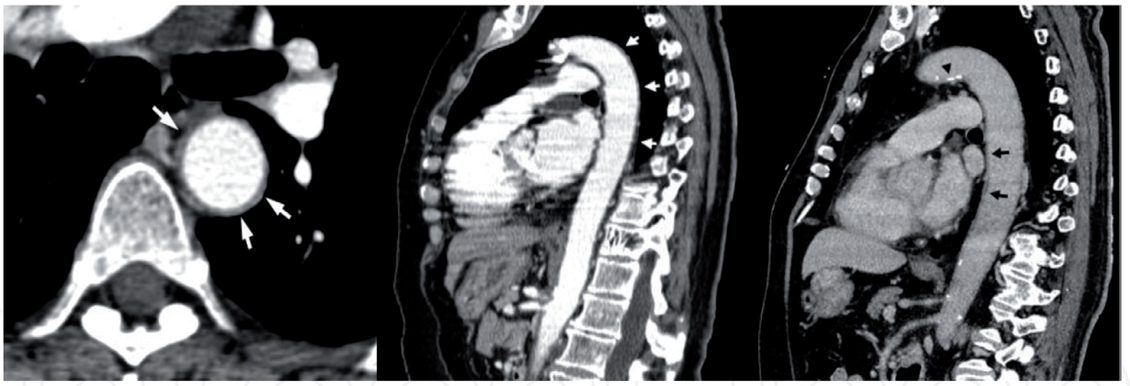

Figure 3.
Computed tomography (CT) and CT angiography (CTA) revealing Large Vessel Vasculitis in Giant Cell Arteritis (GCA). Left image shows a CTA image with circumferential wall thickening >2 mm of the thoracic aorta. Central CTA image shows the extent of thoracic aorta wall thickening in the same 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}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}FDG-PET studies [14, 49, 83]. ^{18}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}FDG-PET criteria of LV vasculitis is lacking. ^{18}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].

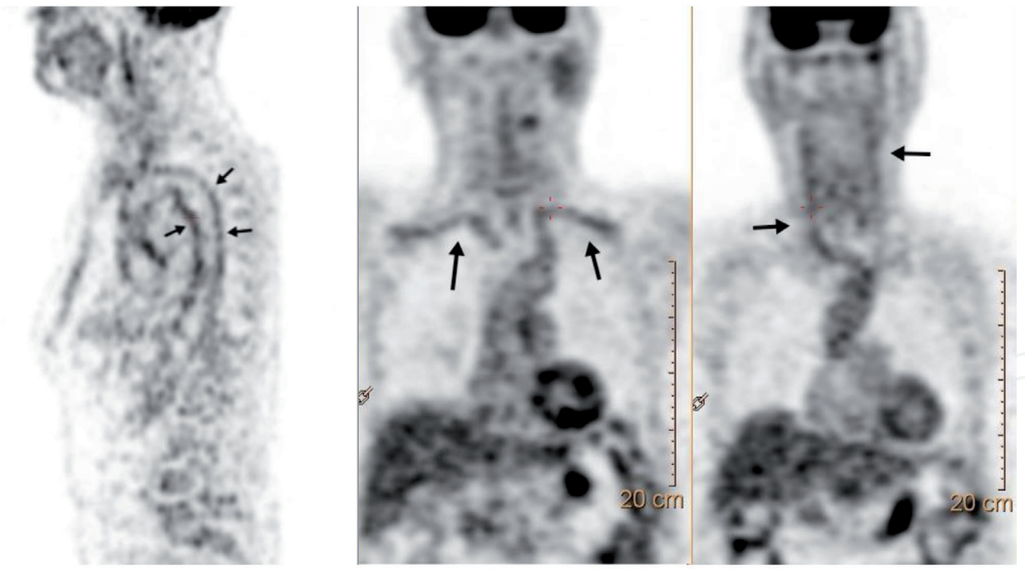

Figure 4.
^{18}FDG-PET scans of Large vessel GCA. Left panel shows aortitis with involvement of the thoracic and abdominal aorta. Central panel shouws inflammatory uptake of the ascendeing aorta and subclavian arteries. Reight panel reveals inflammatory uptake of the aorta and common carotid arteries. Arrows reveal areas of increased vascular ^{8}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 mavrilumab, 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 subgroups (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

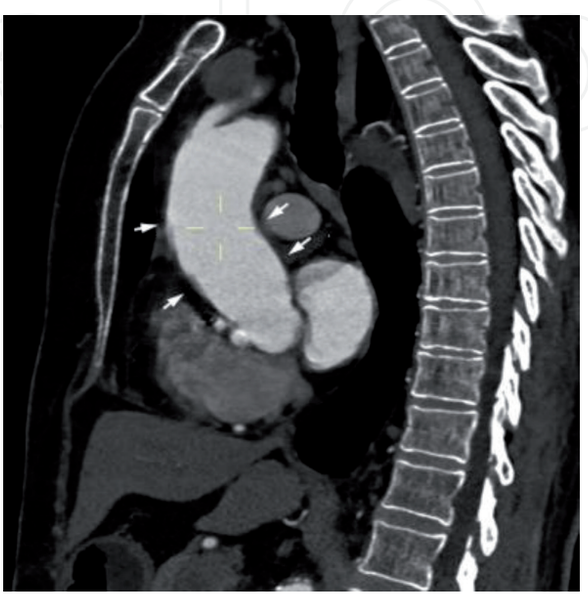

Figure 5.
Computed tomography angiography showing ascending aortic dilation in a patient with Giant Cell Arteritis.

[104]. 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}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 on relapse [52] and up to 86% of patients will develop at least on 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.

Acknowledgements

We kindly thank Dr. Pedro Marques, from the Department of Radiology, Hospital Prof. Doutor Fernando Fonseca, for his collaboration with computed tomography image selection and editing.

We kindly thank Dr. Ângelo Ferreira Silva, from the Department of Nuclear Medicine, Champalimaud Foudation, for his collaboration with ^{18}FDG-PET image selection and editing.

Ultrasound images collected by the authors (Serôdio and Trindade) during the assessment of GCA patients with Siemens Acuson X300 equipment, VF13-5 probe, bandwidth 4,4-13,0 MHz.

Conflict of interest

The authors declare no conflict of interest.

Author details

João Fernandes Serôdio[1*], Miguel Trindade[1], Catarina Favas[1,2] and José Delgado Alves[1,2]

1 Department of Internal Medicine IV and Immune-Mediated Systemic Diseases Unit, Hospital Prof. Doutor Fernando Fonseca, Amadora, Portugal

2 Immune Response and Vascular Disease Unit, Chronic Diseases Research Centre CEDOC, Nova Medical School, Lisbon, Portugal

*Address all correspondence to: jserodio@campus.ul.pt

References

[1] Jennette JC, Falk RJ, Bacon PA, et al. 2012 Revised International Chapel Hill consensus conference nomenclature of vasculitides. Arthritis Rheum. 2013; 65:1-11.

[2] Salvarani C, Pipitone N, Versari A, Hunder GG. Clinical features of polymyalgia rheumatica and giant cell arteritis. Nat Rev Rheumatol; 2012. 8;509-521.

[3] Gonzalez-Gay MA, Vazquez-Rodriguez TR, Lopez-Diaz MJ, et al. Epidemiology of giant cell arteritis and polymyalgia rheumatica. Arthritis Rheum; 2009. 61:1454-1461.

[4] Horton BT, Magath TB, Brown GE. An undescribed form of arteritis of the temporal vessels. Staff Meet Mayo Clin Proc. 1932;7:700-701.

[5] Gilmour JR. Giant-cell chronic arteritis. J Pathol Bacteriol. 1941;53(2):263-277.

[6] Hunder GG, Bloch DA, Michel BA, et al. The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. Arthritis Rheum. 1990;33(8): 1122-1128.

[7] Muratore F, Kermani TA, Crowson CS, et al. Large-vessel giant cell arteritis: A cohort study. Rheumatol. 2015; 54(3):463-470.

[8] Östberg G. Morphological changes in the large arteries in polymyalgia arteritica. Acta Med Scand Suppl. 1979;533:135-159.

[9] Ostberg G. Temporal arteritis in a large necropsy series. Ann Rheum Dis. 1971; 30:224-235.

[10] Schmidt WA, Seifert A, Gromnica-ihle E, et al. Ultrasound of proximal upper extremity arteries to increase the diagnostic yield in large-vessel giant cell arteritis. Rheumatology. 2008;47(1):96-101.

[11] Aschwanden M, Kesten F, Stern M, et al. Vascular involvement in patients with giant cell arteritis determined by duplex sonography of 2x11 arterial regions. Ann Rheum Dis. 2010;69(7):1356-1359.

[12] Prieto-González S, Arguis P, García-Martínez A, et al. Large vessel involvement in biopsy-proven giant cell arteritis: Prospective study in 40 newly diagnosed patients using CT angiography. Ann Rheum Dis. 2012;71(7):1170-1176.

[13] Narváez JA, Narváez JA, Nolla JM, et al. Giant cell arteritis and polymyalgia rheumatica: Usefulness of vascular magnetic resonance imaging studies in the diagnosis of aortitis. Rheumatology. 2005; 44(4):479-483.

[14] Blockmans D, De Ceuninck L, Vanderschueren S, et al. Repetitive 18F-fluorodeoxyglucose positron emission tomography in giant cell arteritis: A prospective study of 35 patients. Arthritis Care Res. 2006;55(1):131-137.

[15] Evans JM, O'Fallon WM, Hunder GG. Increased incidence of aortic aneurysm and dissection in giant cell (temporal) arteritis: A population-based study. Ann Intern Med. 1995;122(7):502-507.

[16] Nuenninghoff DM, Hunder GG, Christianson TJH, et al. Incidence and Predictors of Large-Artery Complication (Aortic Aneurysm, Aortic Dissection, and/or Large-Artery Stenosis) in Patients with Giant Cell Arteritis: A Population-Based Study over 50 Years. Arthritis Rheum. 2003;48(12):3522-3531.

[17] García-Martínez A, Hernández-Rodríguez J, Arguis P, et al. Development of aortic aneurysm/dilatation during the followup of patients with giant cell arteritis: A cross-sectional screening of fifty-four prospectively followed patients. Arthritis Care Res. 2008;59(3):422-430.

[18] Dejaco C, Duftner C, Buttgereit F, et al. The spectrum of giant cell arteritis and polymyalgia rheumatica: Revisiting the concept of the disease. Rheumato logy. 2017; 56(4):506-515.

[19] Harky A, Fok M, Balmforth D, Bashir M. Pathogenesis of large vessel vasculitis: Implications for disease classification and future therapies. Vasc Med 2019; 24(1):79-88.

[20] Koster MJ, Warrington KJ. Classification of large vessel vasculitis: Can we separate giant cell arteritis from Takayasu arteritis? Press Medicale. 2017;46(7-8 Pt 2):e205–e213.

[21] Krupa WM, Dewan M, Jeon MS, et al. Trapping of misdirected dendritic cells in the granulomatous lesions of giant cell arteritis. Am J Pathol. 2002;161(5):1815-1823.

[22] Ma-Krupa W, Jeon MS, Spoerl S, et al. Activation of Arterial Wall Dendritic Cells and Breakdown of Self-tolerance in Giant Cell Arteritis. J Exp Med. 2004; 199(2):173-183.

[23] Dejaco C, Brouwer E, Mason JC, et al. Giant cell arteritis and polymyalgia rheumatica: Current challenges and opportunities. Nat Rev Rheumatol. 2017;13(10):578-592.

[24] Müller M, Briscoe J, Laxton C, et al. The protein tyrosine kinase JAK1 complements defects in interferon-α/β and -γ Signal transduction. Nature. 1993;366(6451):129-135.

[25] Espígol-Frigolé G, Corbera-Bellalta M, Planas-Rigol E, et al. Increased IL-17A expression in temporal artery lesions is a predictor of sustained response to glucocorticoid treatment in patients with giant-cell arteritis. Ann Rheum Dis. 2013;72(9):1481-1487.

[26] Hernández-Rodríguez J, Segarra M, Vilardell C, et al. Tissue production of pro-inflammatory cytokines (IL-1beta, TNFalpha and IL-6) correlates with the intensity of the systemic inflammatory response and with corticosteroid requirements in giant-cell arteritis. Rheumatology. 2004;43(3):294-301.

[27] Brack A, Rittner HL, Younge BR, et al. Glucocorticoid-mediated repression of cytokine gene transcription in human arteritis-SCID chimeras. J Clin Invest. 1997; 99(12):2842-2850.

[28] Kohlhuber, F. Rogers NC, Watling D, et al. A JAK1/JAK2 chimera can sustain alpha and gamma interferon responses. Mol Cell Biol. 1997; **17**, 695-706.

[29] Cid MC, Prieto-Gonzalez S, Arguis P, et al. The spectrum of vascular involvement in giant-cell arteritis: Clinical consequences of detrimental vascular remodelling at different sites. APMIS Suppl; 2009. 27:10-20.

[30] Cid MC, Gandhi R, Corbera-Bellalta M, et al. THU0008 GM-CSF pathway signature identified in temporal artery biopsies of patients with giant cell arteritis. Ann Rheum Dis 2019;78:271-272.

[31] Rodríguez-Pla A, Bosch-Gil JA, Rosselló-Urgell J, et al. Metalloproteinase-2 and -9 in giant cell arteritis: Involvement in vascular remodeling. Circulation. 2005; 112(2):264-269.

[32] Weyand CM, Goronzy JJ. Immune mechanisms in medium and large-vessel vasculitis. Nat Rev Rheumatol; 2013. 9:731-740.

[33] Deng J, Younge BR, Olshen RA, et al. Th17 and Th1 T-cell responses in giant cell arteritis. Circulation. 2010 Feb;121(7):906-915.

[34] Visvanathan S, Rahman MU, Hoffman GS, et al. Tissue and serum markers of inflammation during the follow-up of patients with giant-cell arteritis--a prospective longitudinal study. Rheumatology. 2011; 50(11):2061-2070.

[35] Weyand CM, Hicok KC, Hunder GG, Goronzy JJ. Tissue cytokine patterns in patients with polymyalgia rheumatica and giant cell arteritis. Ann Intern Med. 1994;121(7):484-491.

[36] Deng J, Ma-Krupa W, Gewirtz AT, et al. Toll-like receptors 4 and 5 induce distinct types of vasculitis. Circ Res. 2009; 104(4):488-495.

[37] Pryshchep O, Ma-Krupa W, Younge BR, et al. Vessel-specific toll-like receptor profiles in human medium and large arteries. Circulation. 2008; 118(12):1276-1284.

[38] Graver JC, Boots AMH, Haacke EA, et al. Massive B-Cell Infiltration and Organization Into Artery Tertiary Lymphoid Organs in the Aorta of Large Vessel Giant Cell Arteritis. Front Immunol 2019; 10: 83.

[39] Gonzalez-Gay MA, Piñeiro A, Gomez-Gigirey A, et al. Influence of traditional risk factors of atherosclerosis in the development of severe ischemic complications in giant cell arteritis. Medicine. 2004; 83(6):342-347.

[40] Hernández-Rodríguez J, Segarra M, Vilardell C, et al. Elevated production of interleukin-6 is associated with a lower incidence of disease-related ischemic events in patients with giant-cell arteritis: Angiogenic activity of interleukin-6 as a potential protective mechanism. Circulation. 2003 ;107(19):2428-2434.

[41] Campbell BCV, De Silva DA, Macleod MR, et al. Ischaemic stroke. Nat Rev Dis Prim. 2019 ;5(1):70.

[42] Maksimowicz-Mckinnon K, Clark TM, Hoffman GS. Takayasu arteritis and giant cell arteritis: A spectrum within the same disease? Medicine. 2009; 88(4):221-226.

[43] McNulty M, Spiers P, McGovern E, Feelty L. Aging is associated with increased matrix metalloproteinase-2 activity in the human aorta. Am J Hypertens. 2005; 18(4):504-509.

[44] Ma Y, Chiao YA, Clark R, et al. Deriving a cardiac ageing signature to reveal MMP-9-dependent inflammatory signalling in senescence. Cardiovasc Res. 2015 Jun 1;106(3): 421-431.

[45] Najjar SS, Scuteri A, Lakatta EG. Arterial aging: Is it an immutable cardiovascular risk factor? Hypertension. 2005; 46:454-462.

[46] Saadoun D, Garrido M, Comarmond C, et al. Th1 and Th17 cytokines drive inflammation in Takayasu arteritis. Arthritis Rheumatol. 2015; 67(5):1353-1360.

[47] Kermani TA, Matteson EL, Hunder GG, Warrington KJ. Symptomatic lower extremity vasculitis in giant cell arteritis: A case series. J Rheumatol. 2009; 36(10):2277-2283.

[48] Diamantopoulos AP, Haugeberg G, Hetland H, et al. Diagnostic value of color doppler ultrasonography of temporal arteries and large vessels in giant cell arteritis: A consecutive case series. Arthritis Care Res. 2014; 66(1):113-119.

[49] Walter MA, Melzer RA, Schindler C, et al. The value of [18F] FDG-PET in the diagnosis of large-vessel vasculitis and the assessment of activity and extent of disease. Eur J Nucl

Med Mol Imaging. 2005 Jun;32(6):674-681.

[50] Salvarani C, Gabriel SE, O'Fallon WM, Hunder GG. Epidemiology of polymyalgia rheumatica in Olmsted county, Minnesota, 1970-1991. Arthritis Rheum. 1995;38(3):369-373.

[51] González-Gay MA, García-Porrúa C, Vázquez-Caruncho M. Polymyalgia rheumatica in biopsy proven giant cell arteritis does not constitute a different subset but differs from isolated polymyalgia rheumatica. J Rheumatol 1998; 25(9):1750-1755.

[52] Alba MA, García-Martínez A, Prieto-González S, et al. Relapses in patients with giant cell arteritis: Prevalence, characteristics, and associated clinical findings in a longitudinally followed cohort of 106 patients. Medicine; 2014; 93(5):194-201.

[53] Blockmans D, Ceunick L, Vanderschueren S, et al. Repetitive 18-fluorodeoxyglucose positron emission tomography in isolated polymyalgia rheumatica: a prospective study in 35 patients. Rheumatology. 2007; 46:672-677

[54] Schmidt WA, Moll A, Seifert A, et al. Prognosis of large-vessel giant cell arteritis. Rheumatology. 2008; 47(9):1406-1408.

[55] Patil P, Williams M, Maw WW, et al. Fast track pathway reduces sight loss in giant cell arteritis: results of a longitudinal observational cohort study. Clin Exp Rheumatol. 2015 ;33(2):S-103.

[56] González-Gay MA, Blanco R, Rodríguez-Valverde V, et al. Permanent visual loss and cerebrovascular accidents in giant cell arteritis: Predictors and response to treatment. Arthritis Rheum. 1998; 41(8):1497-1504.

[57] Diamantopoulos AP, Haugeberg G, Lindland A, Myklebust G. The fast-track ultrasound clinic for early diagnosis of giant cell arteritis significantly reduces permanent visual impairment: Towards a more effective strategy to improve clinical outcome in giant cell arteritis? Rheumatology. 2016; 55(1):66-70.

[58] Ghinoi A, Pipitone N, Nicolini A, et al. Large-vessel involvement in recent-onset giant cell arteritis: A case-control colour-doppler sonography study. Rheumatology. 2012; 51(4):730-734.

[59] Monjo I, Fernández E, Peiteado D, et al. OP0180 Diagnostic validity of ultrasound including extra-cranial arteries in Giant Cell Arteritis. Ann Rheum Dis. 2020; 79-112.

[60] Onen F, Akkoc N. Epidemiology of Takayasu arteritis. Press Medicale. 2017;46(7-8 Pt2):e197-203.

[61] Mason JC. Takayasu arteritis advances in diagnosis and management. Nat Rev Rheumatol. 2010;6(7):406-415.

[62] Ishikawa K. Diagnostic approach and proposed criteria for the clinical diagnosis of Takayasu's arteriopathy. J Am Coll Cardiol. 1988;12(4):964-972.

[63] Grayson PC, Maksimowicz-McKinnon K, Clark TM, et al. Distribution of arterial lesions in Takayasu's arteritis and giant cell arteritis. Ann Rheum Dis. 2012 Aug;71(8):1329-1334.

[64] Kermani TA, Crowson CS, Muratore F, et al. Extra-cranial giant cell arteritis and Takayasu arteritis: How similar are they? Semin Arthritis Rheum. 2015; 44(6):724-728.

[65] Kerr GS, Hallahan CW, Giordano J, et al. Takayasu arteritis. Ann Intern Med. 1994 Jun 1;120(11):919-929.

[66] Esteban MJ, Font C, Hernández-Rodríguez J, et al. Small-vessel vasculitis

surrounding a spared temporal artery: Clinical and pathologic findings in a series of twenty-eight patients. Arthritis Rheum. 2001;44(6):1387-1395.

[67] Chirinos JA, Tamariz LJ, Lopes G, et al. Large vessel involvement in ANCA-associated vasculitides: Report of a case and review of the literature. Clin Rheumatol. 2004; 23(2):152-159.

[68] Koster MJ, Matteson EL, Warrington KJ. Large-vessel giant cell arteritis: Diagnosis, monitoring and management. Rheumatology. 2018; 57(suppl_2):ii32–ii42.

[69] Gornik HL, Creager MA. Aortitis. Circulation. 2008; 117:3039-3051.

[70] Stone JH, Zen Y, Deshpande V. Mechanisms of disease: IgG4-related disease. N Engl J Med. 2012;366(6):539-551.

[71] Haroche J, Arnaud L, Amoura Z. Erdheim-chester disease. Current Opinion in Rheumatology. Curr Opin Rheumatol. 2012; 24:53-59.

[72] Palazzi C, Salvarani C, D'Angelo S, Olivieri I. Aortitis and periaortitis in ankylosing spondylitis. Joint Bone Spine. 2011; 78:451-455.

[73] Luqmani R, Lee E, Singh S, et al. The role of ultrasound compared to biopsy of temporal arteries in the diagnosis and treatment of giant cell arteritis (TABUL): A diagnostic accuracy and cost-effectiveness study. Health Technol Assess. 2016; 20(90):1-270.

[74] Schmidt WA, Kraft HE, Vorpahl K,et al. Color Duplex Ultrasonography in the Diagnosis of Temporal Arteritis. N Engl J Med. 1997; 337(19):1336-1342.

[75] Schäfer VS, Juche A, Ramiro S, et al. Ultrasound cut-off values for intima-media thickness of temporal, facial and axillary arteries in giant cell arteritis. Rheumatology. 2017; 56(9):1479-1483.

[76] De Miguel E, Roxo A, Castillo C, et al. The utility and sensitivity of colour Doppler ultrasound in monitoring changes in giant cell arteritis. Clin Exp Rheumatol. 2012; 30(1Suppl 70):S34-S38.

[77] Agard C, Barrier JH, Dupas B, et al. Aortic involvement in recent-onset giant cell (temporal) arteritis: A case-control prospective study using helical aortic computed tomodensitometric scan. Arthritis Care Res. 2008; 59(5):670-676.

[78] Hervé F, Choussy V, Janvresse A, et al. Aortic involvement in giant cell arteritis. A prospective follow-up of 11 patients using computed tomography. Rev Med Interne. 2006; 27(3):196-202.

[79] Prieto-González S, García-Martínez A, Tavera-Bahillo I, et al. Effect of glucocorticoid treatment on computed tomography angiography detected large-vessel inflammation in giant-cell arteritis. A prospective, longitudinal study. Medicine. 2015; 94(5):e486.

[80] Prieto-González S, Arguis P, Cid MC. Imaging in systemic vasculitis. Curr Opin Rheumatol. 2015; 27:53-62.

[81] Klink T, Geiger J, Both M, et al. Giant cell arteritis: Diagnostic accuracy of mr imaging of superficial cranial arteries in initial diagnosis-results from a multicenter trial. Radiology 2014;273(3):844-582.

[82] Quinn KA, Ahlman MA, Malayeri AA, et al. Comparison of magnetic resonance angiography and 18 F-fluorodeoxyglucose positron emission tomography in large-vessel vasculitis. Ann Rheum Dis. 2018; 77(8):1166-1172.

[83] Lariviere D, Benali K, Coustet B, et al. Positron emission tomography and computed tomography angiography for

the diagnosis of giant cell arteritis: A real-life prospective study. Medicine. 2016; 96(30):e4146.

[84] Soussan M, Nicolas P, Schramm C, et al. Management of large-vessel vasculitis: a systematic literature reviwe and meta-analysis with FDG-PET. Medicine. 2015; 94(14):e622

[85] Nielsen BD, Gormsen LC, Hansen IT, et al. Three days of high-dose glucocorticoid treatment attenuates large-vessel 18F-FDG uptake in large-vessel giant cell arteritis but with a limited impact on diagnostic accuracy. Eur J Nucl Med Mol Imaging. 2018; 45(7):1119-1128.

[86] Hellmich B, Agueda A, Monti S, et al. 2018 Update of the EULAR recommendations for the management of large vessel vasculitis. Ann Rheum Dis. 2020;79(1):19-30.

[87] Hoffman GS, Cid MC, Hellmann DB, et al. A multicenter, randomized, double-blind, placebo-controlled trial of adjuvant methotrexate treatment for giant cell arteritis. Arthritis Rheum. 2002;46(5):1309-1318.

[88] Jover JA, Hernández-García C, Morado IC, et al. Combined treatment of giant-cell arteritis with methotrexate and prednisone: A randomized, double-blind, placebo-controlled trial. Ann Intern Med. 2001;134(2):106-114.

[89] Hoffman GS, Cid MC, Rendt-Zagar KE, et al. Infliximab for maintenance of glucocorticosteroid-induced remission of giant cell arteritis a randomized trial. Ann Intern Med. 2007;146(9):621-630.

[90] Martínez-Taboada VM, Rodríguez-Valverde V, Carreño L, et al. A double-blind placebo controlled trial of etanercept in patients with giant cell arteritis and corticosteroid side effects. Ann Rheum Dis. 2008;67(5):625-630.

[91] Seror R, Baron G, Hachulla E, et al. Adalimumab for steroid sparing in patients with giant-cell arteritis: Results of a multicentre randomised controlled trial. Ann Rheum Dis. 2014;73(12):2074-2081.

[92] Stone JH, Tuckwell K, Dimonaco S, et al. Trial of Tocilizumab in Giant-Cell Arteritis. N Engl J Med. 2017;377(4):317-328.

[93] Calderón-Goercke M, Castañeda S, Aldasoro V, et al. Tocilizumab in giant cell arteritis: differences between the GiACTA trial and a multicentre series of patients from the clinical practice. Clin Exp Rheumatol. 2020;38(2):112-119.

[94] Camellino, D; Morbelli S, Sambuceti GCM. Methotrexate treatment of polymyalgia rheumatica/ giant cell arteritis associated large vessel vasculitis. Clin Exp Rheumatol. 2010;28:288-289.

[95] Muratore F, Bolardi L, Restuccia G, et al. Relapses and long-term remission in large vessel giant cell arteritis in northern Italy: Characteristics and predictors in a long-term follow-up study. Sem Arthritis Rheum. 2020; 50(4):549-558.

[96] Tuckwell K, Collinson N, Klearman M, et al. FRI0377 Classification Criteria for Giant Cell Arteritis: Data from Giacta Informing The Need for Revision. Ann Rheum Dis 2016;75:571.

[97] Leuchten N, Aringer M. Tocilizumab in the treatment of giant cell arteritis. Immunotherapy. 2018;10(6):465-472.

[98] Conway R, O'Neill L, O'Flynn E, et al. Ustekinumab for the treatment of refractory giant cell arteritis. Ann Rheum Dis. 2016; 75:1578-1579.

[99] Matza MA, Fernandes AD, Stone JH, Unizony SH. Ustekinumab for

the Treatment of Giant Cell Arteritis. Arthritis Care Res. 2020; doi: 10.1002/acr.24378.

[100] Langford CA, Cuthbertson D, Ytterberg SR, et al. A Randomized, Double-Blind Trial of Abatacept (CTLA-4Ig) for the Treatment of Giant Cell Arteritis. Arthritis Rheumatol. 2017; 69(4):837-845.

[101] Cid M, Unizony S, Pupim L, et al. Mavrilimumab (anti GM-CSF Receptor α Monoclonal Antibody) Reduces Time to Flare and Increases Sustained Remission in a Phase 2 Trial of Patients with Giant Cell Arteritis. Arthritis Rheumatol. 2020;72(Suppl 10).

[102] Baricitinib in Relapsing Giant Cell Arteritis C.incialTrials.gov: clinicaltrials.gov/ct2/show/NCT03026504

[103] A Study to Evaluate the Safety and Efficacy of Upadacitinib in Participants With Giant Cell Arteritis. ClinicalTrials.gov:clinicaltrials.gov/ct2/show/NCT03725202

[104] Kermani TA, Warrington KJ, Crowson CS, et al. Large-vessel involvement in giant cell arteritis: A population-based cohort study of the incidence-trends and prognosis. Ann Rheum Dis. 2013;72(12):1989-1994.

[105] García-Martínez A, Arguis P, et al. Prospective long term follow-up of a cohort of patients with giant cell arteritis screened for Aortic structural damage (aneurysm or dilatation). Ann Rheum Dis. 2014;73(10):1826-1832.

[106] Gonzalez-Gay MA, Garcia-Porrua C, et al. Aortic aneurysm and dissection in patients with biopsy-proven giant cell arteritis from northwestern Spain: A population-based study. Medicine. 2004;83(6):335-341.

[107] Blockmans D, Coudyzer W, Vanderschueren S, et al. Relationship between fluorodeoxyglucose uptake in the large vessels and late aortic diameter in giant cell arteritis. Rheumatology. 2008;47(8):1179-1184.

[108] De Boysson H, Liozon E, Lambert M, Parienti JJ, Artigues N, Geffray L, et al. 18 F-fluorodeoxyglucose positron emission tomography and the risk of subsequent aortic complications in giant-cell arteritis. Medicine. 2016;95(26):e3851.

[109] Matteson EL, Gold KN, Bloch DA, Hunder GG. Long-term survival of patients with giant cell arteritis in the American College of Rheumatology giant cell arteritis classification criteria cohort. Am J Med. 1996;100(2):193-196.

[110] Proven A, Gabriel SE, Orces C, et al. Glucocorticoid Therapy in Giant Cell Arteritis: Duration and Adverse Outcomes. Arthritis Care Res. 2003;49(5):703-708.