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Fenotipos de Arteritis de Células Gigantes Craneal y Extracraneal

Phenotypes of Cranial and Extracranial Giant cell Arteritis

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Abstract

Giant cell arteritis (GCA) is a large-vessel-vasculitis (LVV) that affects mainly elderly individuals. Two different clinical phenotypes of GCA have been described: the classic cranial pattern (C-GCA) and the extracranial large vessel pattern (LV-GCA). These phenotypes can occur in isolation or overlap. Although the pathophysiology seems to be the same, the two phenotypes, present with different clinical features. In addition, due to their distinct localization, C-GCA and LV-CGA lead to different complications and prognoses. Diagnosis and treatment are challenging, an early diagnosis and an appropriate treatment are fundamental for improving disease outcomes. EULAR published useful recommendations for the diagnosis and treatment of both C-GCA and LV-GCA in 2018. A careful diagnosis should be made in both C-GCA and LV-GCA to exclude other mimicking entities, such as infections, atherosclerosis, and tumors. While temporal artery biopsy is useful for the diagnosis of patients with the C-GCA phenotype, imaging techniques have shown to be more adequate for the diagnosis of patients with predominant LV-GCA features. Treatment for both C-GCA and LV-GCA are currently undifferentiated, further studies are necessary to confirm if a different treatment approach for each of them would be more appropriate.

Keywords: cranial giant cell arteritis, large-vessel giant cell arteritis, clinical features, diagnostic imaging, treatment guidelines

Resumen

La arteritis de células gigantes (GCA) es una vasculitis de grandes vasos (LVV) que afecta principalmente a personas de edad avanzada. Se han descrito dos diferentes fenotipos clínicos GCA: el patrón craneal clásico (C-GCA) y el patrón extracraneal (LV-GCA). Estos fenotipos pueden ocurrir de forma aislada o superponerse. Aunque la fisiopatología parece ser la misma, los dos fenotipos se presentan con características clínicas diferentes. Además, debido a su localización distinta, C-GCA y LV-CGA conducen a diferentes complicaciones y pronósticos. El diagnóstico y el tratamiento son un desafío, un diagnóstico temprano y un tratamiento adecuado son fundamentales para mejorar los resultados de la enfermedad. EULAR publicó recomendaciones útiles para el diagnóstico y tratamiento de C-GCA y LV-GCA en 2018. Se debe realizar un diagnóstico cuidadoso tanto en C-GCA como en LV-GCA para excluir otras entidades similares, como infecciones, aterosclerosis y tumores. Si bien la biopsia de la arteria temporal es útil para el diagnóstico de pacientes con fenotipo C-GCA, las técnicas de imagen han demostrado ser más adecuadas para el diagnóstico de pacientes con características predominantes de LV-GCA. Actualmente, el tratamiento para C-GCA y LV-GCA no está diferenciado, se necesitan más estudios para confirmar si sería más apropiado un enfoque de tratamiento diferente para cada uno de ellos.

Palabras claves: arteritis de células gigantes craneal, arteritis de células gigantes extracraneal, manifestaciones clínicas, diagnóstico por imágenes, guías de tratamiento

1. Background

Giant cell arteritis (GCA) is a large-vessel-vasculitis (LVV) that can affect medium and large arteries. GCA affects branches of the aortic artery, with a predilection for the branches of the extracranial carotid artery. This disease occurs almost exclusively in individuals older than 50 years with a prevalence of 1/750 individuals. The highest incidence rate, 52/100,000, is seen amongst the age group of 71-80 years old. Furthermore, CGA is more common among women than men (3:1) and shows a greater prevalence in Northern Europe and the Mediterranean region while being less common among native Americans and Asians [1,2,3].

Giant cell arteritis is a systemic chronic inflammatory disease characterized by an overexpressed immune system response in arterial tissue. This response is characterized by CD4+ T lymphocytic and macrophage proliferation with subsequent multinucleated giant cell formation. The result of said response is; inflammation, granulomatous formation, narrowing of the vessel lumen, impaired blood flow, and end-of-organ ischemia [4,5].

Although the etiology is not well understood, its association with the alleles HLA-DRB1*0401 and HLA-DRB1*0404 has been described in the medical literature [2,6,7]. Despite CGA being commonly known for its classical cranial artery affectation it is a far more heterogeneous disease. Another common pattern of presentation includes extracranial large-vessel GCA (LV-GCA) that can be presented independently of cranial artery involvement [6, 8]. Thus, patients with CGA can present with a clinical spectrum of the two phenotypes; the cranial GCA (C-GCA) and the large-vessel GCA (LV-GCA), that can overlap [9].

2. Objectives

2.1. Primarily objective

The objective of this work is to present the most recent literature review on Giant Cell Arteritis aiming to provide information to help understand the different phenotypes of both C-GCA and LV-GCA, their complications, prognosis, and outcomes. In addition, it aims to present novel elements in the imaging techniques for an early diagnosis and advance on treatment to control symptoms, inflammation, and to avoid clinical relapses.

2.2. Secondary objective

It aims to identify shortcomings in diagnosis, monitoring, and current treatment guideline. Identifying where further studies are necessary to provide a better understanding of the disease, and greater control of its outcomes. This would help to improve the quality of life for the patients and increase survival rates.

3. C-GCA and LV-GCA phenotypes of GCA

The cranial GCA phenotype is characterized by new onset temporal or occipital headache (70-85%), jaw claudication (30-40%), scalp tenderness (20-40%), tender temporal artery (30-60%), and visual disturbances that can lead to blindness (15-45%). Meanwhile, patients with the LV-GCA phenotype may present with constitutional symptoms (30-60%) including; fever, weight loss, malaise, and polymyalgia rheumatica (20-65%), as well as limb claudication due to large-vessel involvement (Table 1) [(1)]. C-GCA and LV-GCA can occur in isolation or overlap.

Table 1: Signs and symptoms of GCA, Nesher G., 2014 [(1)].

	Clinical feature	Frequency
Cranial arteritis	Headache, facial pain	70–85%
	Scalp tenderness	20–40%
	Prominent or tender temporal arteries	30–60%
	Jaw claudication	30–40%
	Eye symptoms: sudden vision loss (transient or permanent), diplopia or other ophthalmic manifestations	15–45%
	Stroke, transient ischemic attacks and other neuropsychiatric manifestations	<15%
	Vestibulo-auditory manifestations: hearing loss, tinnitus, vertigo	5–25%
	Tongue or scalp infarction	<5%
Extracranial arteritis	Aortic arch syndrome, aortic-valve insufficiency, aortic aneurysm or dissection.	5–20%
	Clinically significant involvement of other arteries	5–20%
	Peripheral neuropathies	<15%
	Respiratory symptoms (cough, sore throat, hoarseness)	<15%
Systemic symptoms	Fever, malaise, fatigue, anorexia, weight loss	30–60%
PMR	Bilateral aching and stiffness of the shoulder girdle, sometimes the neck and hip girdle.	20–65%

Polymyalgia rheumatica (PMR) is a frequent manifestation in GCA patients, particularly in patients with the LV-GCA phenotype. On average, 46% of patients with GCA present pain in the neck, shoulders, and pelvic region, associated with morning stiffness, symptoms of PMR. Nevertheless, just 16-21% of patients with PMR have GCA [(8)]. Both GCA and PMR are common diseases in elderly patients. Patients presenting PMR may be an indicator of who already has or will later develop GCA, thus screening should be considered, especially for those refractories to the treatment [(8,10)]. Patients with isolated PMR and those with PMR associated with GCA have similar symptoms. The inflammation response, however, is more severe in patients with PMR associated with GCA, thus requiring more aggressive management [(11)].

The differences between C-GCA and LV-GCA patterns can be observed on the Table 2. As forementioned the predominant cranial pattern mainly has a later onset and more cranial ischemic manifestations, and the predominant extracranial pattern despite the earlier onset also presents with greater constitutional symptoms and PMR [12].

Table 2: Differences between GCA with a predominant cranial pattern and GCA with a predominant extracranial pattern, González-Gay M, Prieto-Peña D, Martínez-Rodríguez I, 2019 [12].

Differences between GCA with a predominant cranial pattern and GCA with a predominant extracranial (LVV) pattern.

	Disease Pattern	
Main features	Predominant cranial	Predominant LVV
Age of disease onset	65–85 years	50–70 years
Constitutional symptoms	++	+++
Cranial ischemic manifestations	+++	+
Positive temporal artery biopsy	++	+/−
Visual ischemic complications	+	+/−
Polymyalgia rheumatica	++	++/+++
Intermittent limb claudication	+/−	+

3.1. Epidemiological differences

A study by Brack et al. concluded that the disease onset in patients with C-GCA varies from 54-89 years old with a mean age of 72 years old. The range of age of presentation of LV-GCA is similar, 52-85 years old, despite the mean age of disease onset being earlier at 66 years of age. The range of time to diagnosis in C-GCA is 0.5-11 months, averaging 2.6 months to diagnosis. Meanwhile, for LV-GCA the average time to diagnosis increases to 8.1 months, ranging from 0.1-48 months. This occurs possibly due to the non-specific signs and symptoms presented in the latter (Table 3). In addition, patients with LV-GCA do not always present a positive temporal artery biopsy which also can contribute to this delay in diagnosis [13].

Table 3: Patients' characteristics. Modified from Brack et al., 1999 [13].

	C-GCA	LV-GCA
Range of age at disease onset, years	54-89	52-85
Mean of age at disease onset, years	72	66
Range of time to diagnosis, months	0.5-11.0	0.1-48.0
Mean of time to diagnosis, months	2.6	8.1

Both subtypes of CGA usually present with the elevation of inflammatory markers such as erythrocyte sedimentation rate (ESR) and C reactive protein

(CRP), although normal values of these inflammatory markers do not exclude the diagnosis [14].

Most epidemiological studies have been carried out on patients with the classic cranial phenotype. All of them have shown a higher incidence in countries of Northern Europe and North America, around 10 cases per 100,000 inhabitants over 50 years of age and a predominance of women. To date, only one study has focused on analyzing the possible epidemiological differences between patients with the cranial and extracranial phenotypes. The authors have observed how the incidence of both phenotypes is similar in the age range between 50 and 70 years, while after 70 years the incidence of C-GCA is practically double compared to LV-GCA [15].

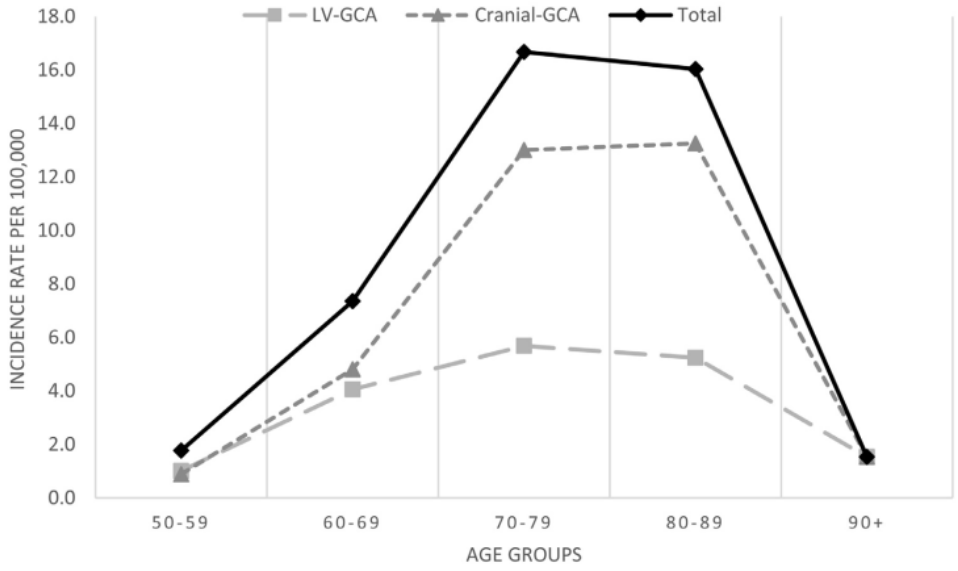

Figure 1: Incidence rates of GCA per 100,000 inhabitants/year by age and disease phenotype. Study made by Muratore F et al. in the Reggio Emilia area (Italy). Patients overlapping the two phenotypes were included in both groups, modified from Muratore F. et al. (2021) [15].

3.2. Genetic Association

To our knowledge, GCA is a polygenic disease in which the human leukocyte antigen (HLA) genes appear to play a crucial role. Large-scale genetic studies in patients with biopsy-proven cranial GCA, including a GWAS study, have revealed that GCA is primarily associated with HLA class II genes, primarily HLA-DRB1*04:01. In view of the clinical and epidemiological differences that exist between GCA patients with a classic cranial phenotype and those with a predominantly extracranial phenotype, several studies suggested that there could be a different genetic susceptibility that could explain these phenotypic differences. However, a study including 100 patients with extracranial GCA, 178

patients with cranial GCA, and 486 controls found a similar association with the HLA-DRB1*04:01 allele in patients with cranial and extracranial phenotypes [6].

Subsequently, another study was carried out analyzing the involvement of HLA class I genes, which revealed that patients with classic cranial GCA and extracranial GCA present a similar association with HLA-B*15, mainly with HLA-B*15:01. The presence of the HLA-DRB1*04:01 and HLA-B*15:01 alleles have an additive effect when it comes to increasing the risk of GCA, regardless of the clinical phenotype [16]. Another later study analyzing the role of VEGF found that the functional polymorphisms of VEGF (rs833061 T/C, rs2010963 G/C and rs3025039 C/T) have no influence on the development of the cranial or extracranial phenotype of GCA. VEGF haplotypes (CGC and CGT) are associated with the development of severe ischemic manifestations, regardless of the clinical phenotype of GCA [17].

4. Pathophysiology of GCA

The exact pathophysiology of GCA is not well understood. However, it is known for starting with immune activation, followed by arterial infiltration. The initial inflammation occurs in the adventitia layer with a subsequent affectation of the inner layer [8,11]. A temporal artery biopsy of the damaged artery wall shows transmural inflammation containing CD4+ T-lymphocytes (LTCD4+), macrophages, degeneration of myofibroblasts, vascular neoformation, multinucleated giant cells, granuloma formation, hyperplasia, vessel wall thickening, and luminal occlusion (Figure 2), CD8+ T-lymphocytes (LTCD8+) is present in a very small quantity [11,18]. Similar findings have been observed in the vessel wall of the aorta of patients with LV-GCA that required surgery due to aortic aneurysms or dissection (Figure 3, Figure 4) [19].

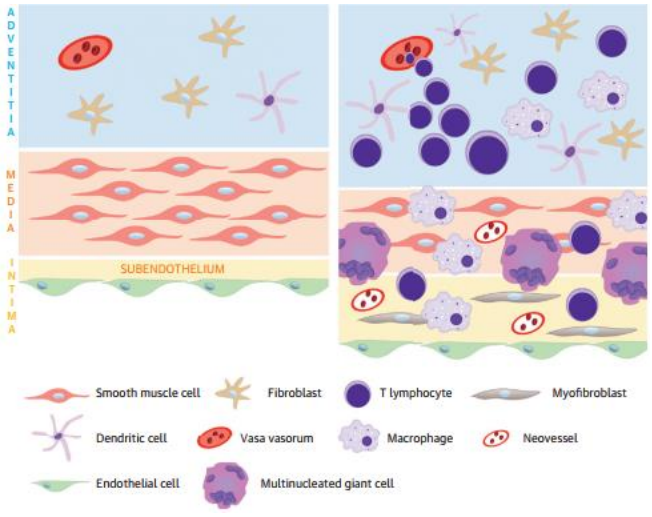

Figure 2: A normal vessel wall representation on the left, compared to GCA affectation on the right. Ironi G. et al. (2018) [18].

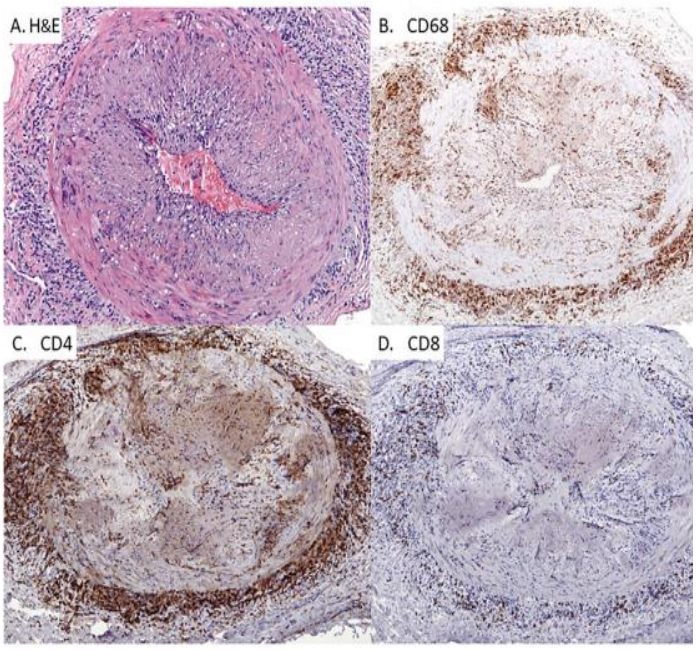

Figure 3: Biopsy of Temporal artery. (A) Transmural arterial inflammation showing luminal narrowing due to intimal proliferation. Multinucleated giant cells in the medial layer (H&E x125). (B) CD68-positive histiocytes accumulating within the medial and adventitial layers and scattered histiocytes in the intimal layer (x100). (C): LTCD4+ cells with a similar pattern of distribution as the CD68+ macrophages (x100). (D) Infrequent LTCD8+ cells within the T cell infiltrates (x100). Akiyama et. Al. (2021) [19].

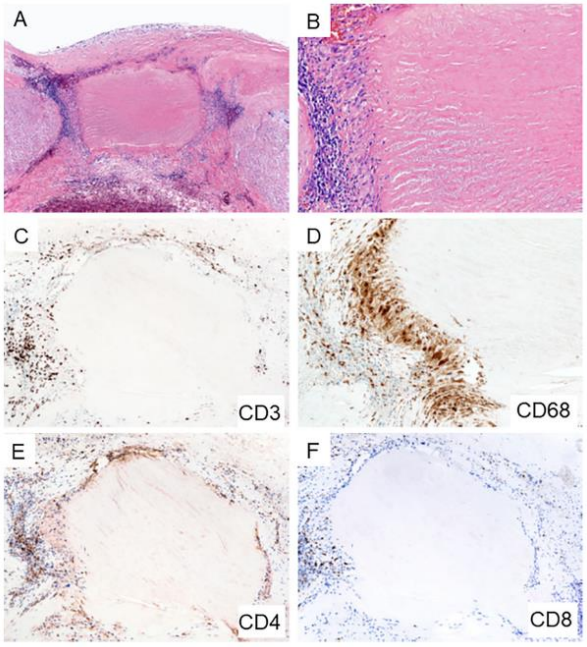

Figure 4: Biopsy sample the aortic wall of a patient undergoing emergency aortic repair. (A, B) Granulomatous inflammation with rings of predominantly lymphocytes and macrophages around necrotic medial tissue (A H&E x60; B H&E x200). (C) LTCD3+ cells form a collarette of inflammation enclosing the necrotic aortic wall (x100). (D) CD68+ histiocytes palisade at the edge of the damaged tissue (x200). (E) LTCD4+ cells are the dominant T cell subset within the granulomatous infiltrates (x100). (F) Infrequent LCD8+ cells in the aortic wall (x100). Akiyama et. Al. (2021) [19].

The adventitia layer usually contains macrophages and dendritic cells. In the presence of vasculitis, the Toll-like receptors expressed by these cells are abnormally activated. As a result, there is an overproduction of pro-inflammatory mediators such as, IL-1, IL-6, and T cells activation. In addition to this, The MHC-II expressed in the dendritic cells also activates LTCD4+, which are then polarized towards Th1 (in the presence of IL-12 and IL-18) and Th17 (in the presence of IL-6, IL-1β, and IL-23), producing IFN-γ and IL-17, respectively [11].

Interleukin-6 (IL-6) promotes the inhibition of LTreg, and in the liver, IL-6 is responsible for the production of acute-phase reactants such as CRP and fibrinogen, also resulting in an elevation of ESR. IL-6 is responsible for GCA symptoms and seems to be higher in patients who have more relapses, increasing its levels when relapse occurs. Interestingly, patients with a higher IL-6 serum level have fewer ischemic complications regardless of the presence of a relapse. Thus, it is evident the existence of a negative association between systemic inflammation and cranial symptoms [8].

Smooth vascular muscle, in the presence of the IFN-γ, produce several types of chemokines including, CCL2, CXCL9, CXCL10, and CXCL11. The release of CCL2 promotes the recruitment of monocytes, which merge to form multinucleated giant cells, hence the name GCA. The remaining chemokines are responsible for further recruitment of more Th1 and LTCD8+, amplifying the inflammatory process [11].

Macrophages, multinucleated giant cells, and vascular smooth muscle cells, all together contribute to intimal hyperplasia, luminal occlusion, and vessel wall remodeling. This occurs because these cells produce growth factors, including platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF) [11].

5. Complications of C-GCA

Patients with C-GCA are at a greater risk of suffering ischemic complications such as vision loss and cerebrovascular events, among others. These complications can affect the patient's quality of life producing important morbidity and mortality.

5.1. Vision loss

The main severe complication of C-GCA is permanent vision loss, which occurs in between 14-20% of patients. This complication is due to the affectation of the posterior ciliary artery, resulting in an anterior ischemic optic neuropathy (AION) (Figure 5). Less commonly, visual loss in C-GCA is due to occlusion of the retinal artery.

Patients with C-GCA are at risk of visual complications from the onset of the disease. It can manifest with diplopia, amaurosis fugax, and can progress to permanent vision loss. Thus, early clinical management of suspected CGA is crucial, requiring the instauration of glucocorticoid therapy to prevent the possibility of permanent visual loss [20].

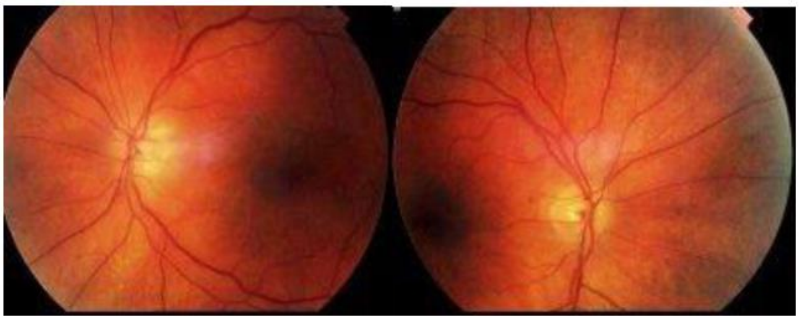

Figure 5: Acute anterior ischemic optic neuropathy (AION) of the left eye (early appearance with papillary edema), compared to the right eye (unaffected). Liozon et al. (2013) [20].

5.2. Cerebrovascular events (CVE)

Another severe complication of C-GCA is cerebrovascular events (CVE), such as transient ischemic attack (TIA) and stroke. This complication is more common in older patients, and the stroke etiology is often misdiagnosed as an atherosclerotic cause. A CVE is considered GCA-related when it occurs up to 4 weeks following the diagnosis or relapse of GCA. Moreover, 50-75% of the CVEs in GCA patients occur in the posterior circulation, such as a vertebra-basilar arteries (Figure 6). This CVE location is uncommon compared to typical stroke etiologies, which more frequently are observed in the cerebral carotid territory [21,22].

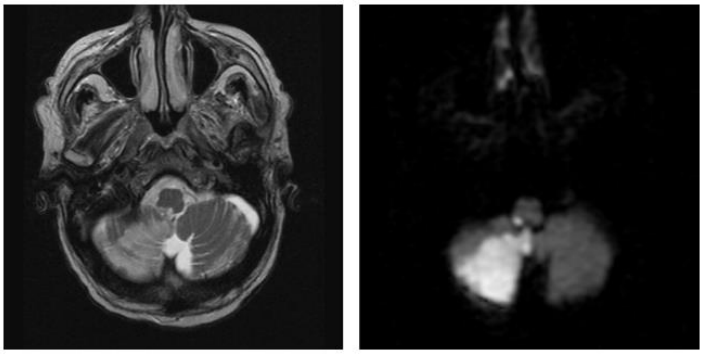

Figure 6: Right posterior-inferior cerebellar artery stroke. T2- and diffusion-weighted MRI sequences. Gonzalez-Gay et al (2009) [22].

Between 1.5-7% of GCA patients present a stroke episode at diagnosis or within the first 4 weeks of the onset of glucocorticoid treatment. CVE represents one of the main causes of mortality in GCA [21,22,23]. Gonzalez-Gay et al (2009) identified smoking within 10 years before the onset of GCA symptoms or at the time of diagnosis led to patients being at greater risk for suffering a basilar artery stroke [22].

5.3. Other complications

Less common complications of C-GCA include vestibulo-auditory complications, for instance, hearing loss, tinnitus, and vertigo (5-25%), together with tongue necrosis and scalp infarction (<5%) [1].

6. Complications of LV-GCA

Patients with LV-GCA have large vessel inflammation affecting the aorta and its main branches. This inflammatory process can then lead to life-threatening complications including, aortic aneurysms and dissections, and stenosis of the aortic branches.

Given the severity of the complications and the possibility that LV-GCA can be associated with C-GCA, patients with clinical signs and symptoms of large-

vessel affectation should be subjected to imaging tests to discard large-vessel implications, and to control the disease's evolution [24].

6.1. Aortic Aneurism and dissection

Aortic aneurism refers to the dilatation of the aortic structure. It is considered abnormal when its diameter is >4.5cm for the aortic root, >4cm for the aortic arch, or >3.5cm for the descending aorta [24]. Aneurysms are often at risk of rupture, which can lead to a hemorrhagic event and a hypovolemic shock. Aortic dissection, on the other hand, occurs due to a tear in the inner layer of the vessel. The blood flows through this tear splitting the inner and the middle layers of the aorta wall, thus originating in a fake lumen, a complication that is frequently deadly.

The prevalence of aortic aneurysms is unknown, it probably ranges between 0-27%. The diagnosis of aneurysmal disease usually occurs within 4 or 5 years after GCA is diagnosed. Risk factors include, younger males, polymyalgia rheumatica, symptomatic aortitis, smoking and arterial hypertension [25,26].

A study presented by Espitia et al. (2021), including 172 GCA patients with aortitis at the time of diagnosis, analyzed the occurrence of aortic complications. This study was composed of 117 asymptomatic patients (68%) and 55 symptomatic patients (32%). Symptomatic patients presented aortitis symptoms such as chest, abdominal, and back pain, or aortic insufficiency with dyspnea at the time of diagnosis. Control imaging was performed during follow-up time on 98 patients (54 asymptomatic and 44 symptomatic), 8 (14.8%) of the asymptomatic patients presented aortic complications, while amongst the symptomatic patients, 15 (34.1%) of them had an aortic complication. Complications included 19 (82%) aortic aneurysms and 4 (18%) aortic dissections. Symptomatic patients also had more cardiovascular risk factors, such as arterial hypertension, and were smokers, which could be related to a more severe aortic involvement. Patients who had asymptomatic aortitis at the time of diagnosis had higher survival-free aortic complications (Figure 7) [25].

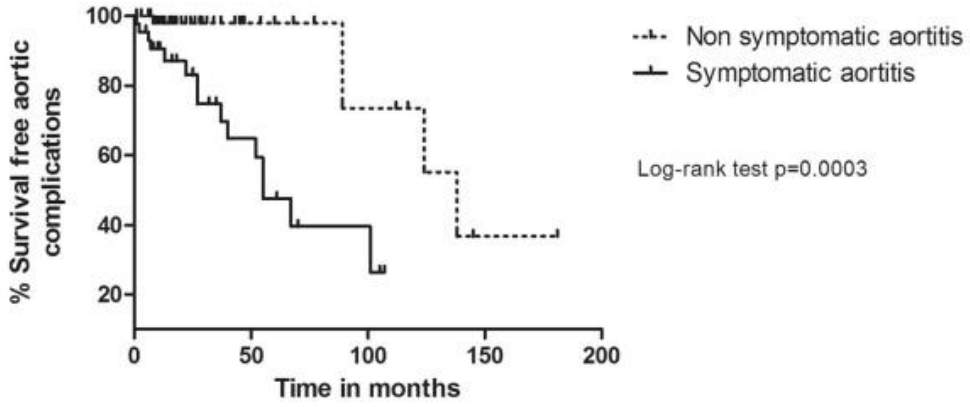

Figure 7: Survival without aortic complications on monitored patients with aortitis at diagnosis. Espitia et al. (2021) [25].

6.2. Stenosis of the aortic branches

In between 5-45% of LV-GCA patients present stenosis of arteries supplying the upper extremities. Vascular clinical manifestation occurs secondary to stenosis of >50% of supra-aortic vessels' lumen, resulting in lowering the blood supply. This can cause ischemic signs and symptoms such as limb claudication, Raynaud's phenomenon, vascular bruits, decrease or absence of carotid or radial pulses, and discordant blood pressures [24,26,8].

7. Prognosis

The earlier onset of LV-CGA, in addition to, time delay for a diagnosis, wide variation of presentations, and its potential life-threatening location adds up to a worse prognosis compared to C-CGA patients, including a higher risk of death [27,28].

A publication by Muratore et al. acquired data from patients diagnosed with C-GCA and LV-GCA from 1999-2008. A total of 332 patients were included in this study (212 with C-GCA and 120 with LV-GCA). The authors concluded that patients with a large vessel implication required a higher cumulative dose of corticosteroids and presented a greater relapse rate during the period of follow-up, appearing to relapse earlier than patients with GCA without large vessel affectation [29].

Overall, more than 60% of C-GCA patients were able to discontinue corticosteroid therapy for at least 6 months within 6 years period. Patients with LV-GCA, on the other hand, presented a lower percentage of corticosteroid discontinuation. Approximately 40% of them were able to discontinue the therapy for at least 6 months (Figure 8). In addition, nearly 80% of LV-GCA relapsed within three years. For C-GCA patients, the percentage of patients relapsing, given the same period, was close to 60% (Figure 9) [29].

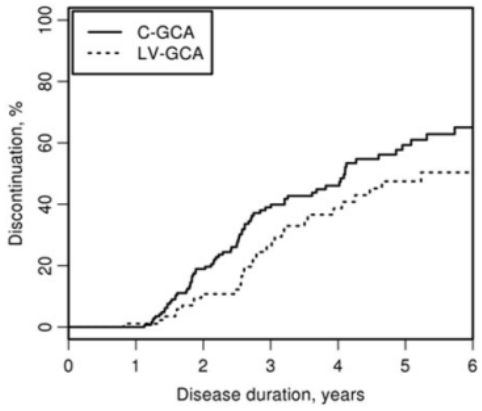

Figure 8: Percentage of GCA and LV-GCA patients that were able to discontinue corticosteroid therapy for at least 6 months by disease duration. Muratore et al. (2014) [29].

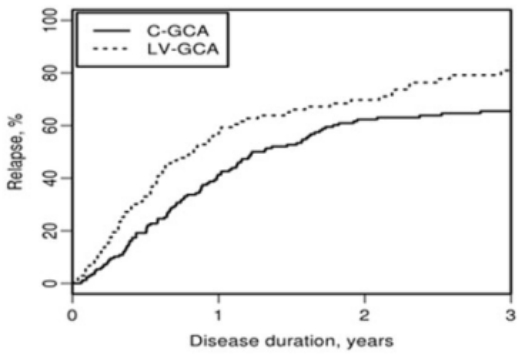

Figure 9: Percentage of GCA and LV-GCA patients that had at least one relapse by disease duration. Muratore et al. (2014) [29].

An average of 4.9 out of 10 patients-year relapsed among those diagnosed with LV-GCA, meanwhile, patients with C-GCA presented a relapse rate of 3 per 10 patients-year. The cumulative corticosteroids dose was 11.4 g/year in patients with LV-GCA, and 9.1g/year for C-GCA (Table 4).

Table 4: treatment and outcomes among patients with GCA and LV-GCA. Modified from Muratore et al. (2014) [29].

Outcome	C-GCA (*n* = 167)	LV-GCA (*n* = 103)
Duration of follow-up, median (IQR), years	4.6 (2.5, 7.4)	3.6 (2.2, 6.4)
Relapses	252	215
Relapse rate per 10 person-years, median (95% CI)	3.0 (2.6, 3.4)	4.9 (4.2, 5.6)
Cumulative CS dose at 1 year, mean (S.D.), g	9.1 (3.7)	11.4 (5.9)
Additional immunosuppressive therapy, *n* (%)	27 (16)	54 (52)
Patients starting any immunosuppressive drug within 1 year of GCA diagnosis, KM method, median (95% CI), %	8 (4, 12)	32 (22, 42)
Within 2 years	14 (8, 20)	46 (36, 56)
Within 5 years	16 (10, 22)	57 (45, 69)
MTX, *n/N* (%)	23/167 (14)	42/101 (42)
AZA, *n/N* (%)	6/167 (4)	18/101 (18)
Anti-TNF, *n/N* (%)	1/167 (1)	6/101 (6)
MMF, *n/N* (%)	0/167 (0)	7/101 (7)
CYC, *n/N* (%)	0/167 (0)	5/101 (5)
Aortic aneurysm	9	14
Rate of development of aortic aneurysm after GCA diagnosis, KM method, median (95% CI), %		
1 year	2 (0, 4)	8 (2, 14)
2 year	2 (0, 4)	9 (3, 15)
5 year	3 (0,7)	15 (7, 23)

Furthermore, 31% of LV-GCA patients required additional immunosuppressive therapy within the first year of treatment, while only 4.8% of those with C-GCA need immunosuppressive supplementation. This difference is even higher 5 years after the start of the treatment, over 50% of the patients with LV-GCA required immunosuppressants, compared to 9.8% for patients with C-GCA. Immunosuppressants, from the most to the least used were; MTX, AZA, Anti-TNF, MMF, and CYC. Moreover, patients with LV-GCA presented an increased prevalence of aortic aneurysm compared to those with C-GCA, 31% and 4.2% respectively within the first 5 years after GCA was diagnosed [29].

Patients with large-vessel implication who present with an acute episode of aortitis as their first clinical manifestation of GCA have a high mortality rate (44-80%). In addition, mortality is considerably increased when aortic aneurysm or dissection develop. A retrospective study showed that patients with aortitis also died more often of vascular complications and presented more vascular events, such as stroke, than GCA patients without aortic involvement. Moreover, ischemic heart disease led to higher mortality rate in GCA patients than in patients with ischemic heart disease without GCA [26].

Another study by Macchioni et al. also reported that patients that presented LV manifestations at the time of the diagnosis were at a greater risk of dying. According to them, 28.1% of LV-CGA patients died during the follow-up compared to 6.2% of C-CGA patients. The main cause of death reported was due to vascular complications [30].

A prompt diagnosis of LV-GCA is fundamental for increasing survival rates. A good clinical understanding of the disease, and the advance in imaging techniques allow earlier identification of LV implications. Hence, it means a potential improvement for LV prognosis [31].

8. Image techniques for the diagnosis of C-GCA and LV-GCA

Following the recognition of signs and symptoms of C-GCA and LV-GCA, the diagnosis can still be challenging. Different images techniques can be used to confirm a suspected case of this disease, including; temporal artery biopsy (TAB), conventional angiography, ultrasounds (US), magnetic resonance imaging (MRI), 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT, and CT.

The European League Against Rheumatism (EULAR), published in 2018 recommendations for the diagnosis and monitoring of large-vessel-vasculitis. EULAR recommendations are based on new evidence for imaging tests used for assisting on C-GCA and LV-GCA diagnosis. They emphasized the importance of techniques such as, ultrasounds, MRI, PDG-PET/CT, and CT. These imaging techniques are especially interesting for being sensitive, faster, and less invasive than temporal artery biopsy and angiography [32].

Additionally, these imaging techniques enable the identification of extracranial vasculitis in GCA patients with refractory rheumatic polymyalgia and no cranial manifestations. By using ultrasound, MRI, PDG-PET/CT, and CT it is possible to spot inflammatory changes in the vessel wall of the aorta and other extracranial vessels. This is crucial for identifying patients that have LV-GCA without the classical cranial affectation seen in C-GCA [33].

Conventional angiography, which had been considered for a long time a gold standard, is a very invasive technique. Thus, it is no longer recommended by EULAR for the diagnosis of LVV. This technique may be reserved for therapeutical interventions such as percutaneous angioplasty or stenting, when required [32].

8.1. C-GCA imaging tests

Among the recommendations made by EULAR, the first one indicated that the diagnosis of GCA should not delay the start of treatment. Therefore, once the physician strongly suspects GCA, high doses of glucocorticoid should be

implemented immediately to avoid ischemic complications, such as blindness, that almost always occurs before the instauration of treatment [32].

A guideline published by the British Society for Rheumatology in 2020, also gives recommendations for GCA diagnosis. To obtain an accurate diagnosis, it is necessary to take into consideration; pretest probability, together with, sensitivity and specificity of imaging tests [34].

Patients with a positive temporal artery biopsy have a confirmatory diagnosis (specificity 100%). However, its sensibility is considerably below 100%, so that, a negative biopsy does not exclude diagnostic when the pretest probability is high [34].

Temporal artery ultrasound, on the other hand, is shown to have higher sensitivity than biopsy, although, its specificity is lower. According to several studies with moderate quality of evidence, ultrasound has 79% sensitivity and 94% specificity. Ultrasound is more cost-effective than temporal artery biopsy, it can be used when the pretest probability is low (<20%), to rule out GCA; and, when pretest probability is high (>50%), to confirm the diagnosis. In addition, ultrasound should also be performed on axillary arteries to add extra information to the diagnosis [34]. Figure 10 shows a recommended way of using ultrasound to assist in the diagnosis of C-GCA and to limit the number of patients that require a biopsy.

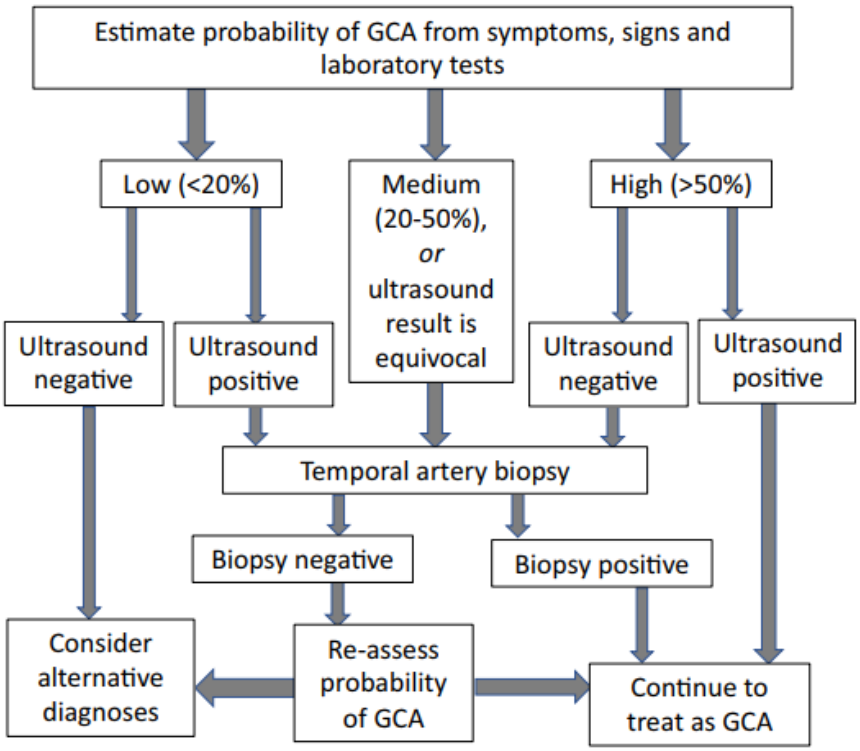

Figure 10: The use of ultrasound to rule out GCA in patients with a low pretest probability, and to confirm the diagnosis in patients with high pretest probability. In addition to when a temporal artery biopsy should be performed. Mackie S. et al. (2020) [34].

In fact, according to the most recent EULAR recommendations, ultrasound is considered the imaging technique of choice for the diagnosis of patients who mainly C-GCA is suspected. The diagnosis can be made, without the necessity of temporal artery biopsy, if the patient has a high pretest probability and a positive ultrasound imaging. In addition, the diagnosis can be considered unlikely if the pretest probability is low, and ultrasound imaging is negative, with no necessity of temporal artery biopsy in this case [32].

Furthermore, the ultrasound should be done as soon as glucocorticoid therapy is started, best if performed within one week of the instauration of treatment. This is because glucocorticoid therapy diminishes the size of the halo seen on the ultrasound, hence its sensitivity [32,34].

Ultrasound imaging should be assessed bilaterally, in both temporal and axillary arteries, and longitudinal and transverse planes. It is necessary to use a high-resolution color Doppler ultrasound to visualize the vessel wall vasculitis. A minimum of 15-18 MHz frequency is recommended for the temporal artery, and 12-15MHz for the axillary artery [33]. The ultrasound is suggestive of GCA when a non-compressible “halo sign” is visualized [32]. The “halo sign” is determined by intima-media thickness (IMT), presenting as a homogenous, and hypoechoic line towards the vessel lumen (Figure 11). The compression, on the other hand, is considered positive, when upon pressure and occlusion of the vessel the halo is still visible. Even though there are no specific cut-off values for the width of the “halo sign”, an acceptable value is 0.42 mm for the common temporal artery, and 1.0 mm for the axillary artery [33].

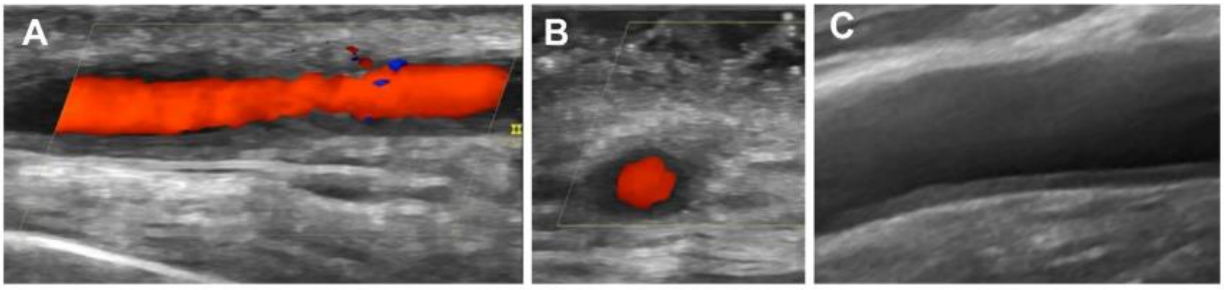

Figure 11: color Doppler ultrasound with a "halo sign". A: longitudinal plane of the temporal parietal artery; B: transverse plane of the temporal artery branch; C: longitudinal plane of the axillary artery. Prieto-Peña et al. (2021) [33].

Among other imaging techniques, MRI is also a potential diagnosis method to rule out C-GCA, however, even though its sensibility is high (75-94%), it has low specificity (79-89%). MRI has many false-positive cases [34]. The EULAR only recommends the use of high-resolution MRI for assessing mural inflammation if ultrasounds are not available, or if its results are inconclusive [32]. The guideline

published by EULAR does not recommend the use of either CT or PET for assessing inflammation of the cranial arteries [32]. The table below summarizes the diagnosis methods for C-GCA patients (Table 5).

Table 5: comparison and recommendations among different techniques for the diagnosis of C-GCA based on EULAR recommendations published in 2018 and the guideline published by the British Society for Rheumatology in 2020.

	Temporal biopsy artery (TAB)	Ultrasound	MRI
Recommendations for C-GCA	Patients with low pretest probability and positive ultrasound, patients with medium pretest probability, or patients with high pretest probability and negative ultrasound	Patients with predominantly C-GCA suspected	Only if ultrasound is not available or if its results are inconclusive
Anatomical region	Temporal arteries	Temporal ± axillary arteries	Cranial arteries
Technique	Biopsy of temporal artery	Color Doppler ultrasound: Temporal artery: 15-18 MHz Axillary arteries: 12-15MHz	MRI scanner and gadolinium contrast-enhanced
Positive inflammatory marker	Anatomopathological presence of multinucleated giant cells, inflammation, and artery thickness	Non-compressible "halo sign" Temporal artery: > 0.42mm Axillary arteries: > 1.0mm	Contrast enhancement, mural inflammation, luminal changes
Benefits	Gold Standard, no false positives	Low-cost, no radiation	Good resolution of cranial arteries, no radiation
Drawbacks	Invasive technique	Operator dependent, limited to superficial arteries	False-positives, restricted availability, high costs, and adverse effects of contrast agents
Sensitivity	Lower than 100%	79%	75-94%
Specificity	100%	94%	79-89%

8.2. LV-CGA imaging tests

For the diagnosis of extracranial manifestations, EULAR mentioned that imaging techniques such as ultrasound, PET, MRI, and CT may be used. [32]. Ultrasound could help identify homogeneous hypoechoic swelling of the arterial wall on the affected arteries. In addition, Doppler ultrasound could help identify stenosis. Nevertheless, due to the anatomic location bellow bone and air, the thoracic aorta is more difficult to access [26].

FDG-PET/CT is a promising imaging technique available to evaluate LVV implication of the aorta and proximal branches. The inflammatory cells of the vessel wall uptake high levels of glucose, which is detected in this technique [33]. It has 67% sensitivity, and 100% specificity when compared to clinical diagnosis. FDG-PET/CT is also an excellent imaging tool for excluding malignancies and infections that can mimic LV-GCA. [34].

Glucocorticoid therapy reduces the glucose uptake by the vessel wall, which underestimates the results. Thus, it is recommended to perform FDG-PET/CT no longer than 10 days after the instauration of the treatment, or temporary suspension of the treatment is advised, if possible [33].

For interpretation of FDG-PET/CT images, a visual FDG uptake scale from 0-3 is applied. A vascular score of 0 means no vascular glucose uptake, referring that the glucose uptake was lower or equal to the mediastinum glucose uptake. A score of 1 means low glucose uptake, in other words, the vascular glucose

uptake is lower than the liver's glucose uptake. A score of 2 means a moderate vascular glucose uptake, when the glucose uptake of the vessel wall and the liver are the same. Finally, a score of 3 corresponds to a high glucose uptake, which occurs when the vascular glucose uptake is higher than the one observed in the liver. A total PET vascular activity score (PETVAS) is then obtained by adding up the vascular scores from different areas [33,35].

PETVAS uses a scale ranging from 0-27, representing a qualitative summary score of Global arteries FDG uptake. The calculation is done by adding up the FDG uptake scale (0-3) in 9 arterial territories; ascending aorta, aortic arch, descending thoracic aorta, abdominal aorta, innominate artery, right carotid, left carotid, right subclavian, and left subclavian [36].

A contrast-enhanced CT has 73% sensitivity and 78% specificity. It might also help to evaluate LVV when FDG-PET/CT is not available. Malignances, infections, and atherosclerosis also need to be excluded [34].

MRI does not use radiation, and it is supposed to detect active inflammation. However, there are no studies published performing MRIs specifically for LV-GCA patients [32, 33]. Gadolinium-enhanced, magnetic resonance angiography (MRA) can help to identify cases of aortitis, as it helps to identify arterial wall thickening, edema, and contrast enhancement. Nevertheless, it is also very sensitive to corticosteroid treatment. Therefore, it has a limited application for patients that are already in long-term glucocorticoid therapy [26,34]. The table below summarizes the diagnosis methods for LV-GCA patients (Table 6).

Table 6: comparison and recommendations among different techniques for the diagnosis of LV-GCA based on EULAR recommendations published in 2018 and the guideline published by the British Society for Rheumatology in 2020.

	Ultrasound	**MRI**	**CT**	**FDG-PET**
Recommendations for LV-GCA	Mainly based on expert opinion	It may be used to support the diagnosis	When FDG-PET/CT is not available	Diagnosis and when a relapse is suspected
Anatomical region	Large vessels	Large vessels	Large vessels	Large vessels
Technique	Color Doppler ultrasound	MRI scanner and gadolinium contrast-enhanced	Multislice CT scanner and 60–120mL of non-ionic iodinated contrast agent	Hybrid PET with low-dose CT, FDG uptake
Positive inflammatory marker	Homogeneous hypoechoic swelling of the arterial wall	Contrast enhancement, mural inflammation, luminal changes	Contrast enhancement, mural inflammation, luminal changes	Qualitative visual grading, compare it with the liver background (grading 0–3)
Benefits	Low-cost, no radiation	Good resolution, no radiation	Short procedure time, good resolution	Identify GCA along with other pathologies such as infections or tumors
Drawbacks	Limited value for assessment of aortitis (limited access to the thoracic aorta). Depends on local settings and expertise	False-positives, restricted availability, high costs, and adverse effects of contrast agents	Restricted availability, high costs, and radiation exposure	Restricted availability, high costs, and radiation exposure (combined with CT)
Sensitivity	79%	75-94%	73%	67%
Specificity	94%	79-89%	78%	100%

The accuracy of these imaging techniques for diagnosing LV-GCA is still under study. Despite that, they are valuable tools for the evaluation of aorta and proximal branches manifestations. LVV imaging evaluation depends on whether the GCA is active (Figure 12), smoldering (Figure 13), or inactive (Figure 14). FDG-PET/TC can identify LVV affectation in patients with an active GCA without corticosteroid therapy, and in patients ongoing treatment with a smoldering GCA. MRI, on the other hand, can identify LVV affectation in patients with an active LVV, however, it has a very limited application for patients ongoing treatment. Neither FDG-PET/CT nor MRI can identify LVV in patients with an inactive GCA [(18)].

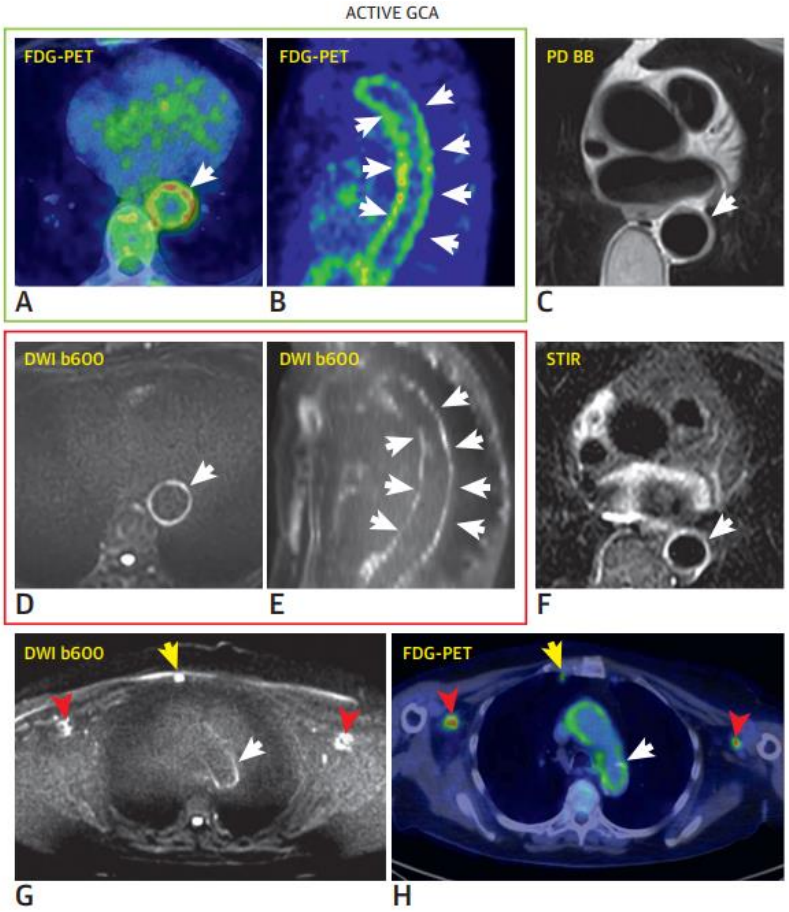

Figure 12: Patient with an active LVV of descending thoracic aorta, without ongoing glucocorticoid therapy. Pathological FDG-PET/CT study, A. Axial FDG-PET/CT, B. Sagittal FDG-PET/CT; Pathological MRI imaging; C. Arterial wall hyperintensity with mild wall thickening, D. Axial, E. Sagittal reconstruction, F. edema, G and H. Comparison of MRI and FDG-PET/CT, subclavian arteries (red arrowheads), right mammarian artery (yellow arrows), aorta (white arrows). Ironi G. et al. (2018) [(18)].

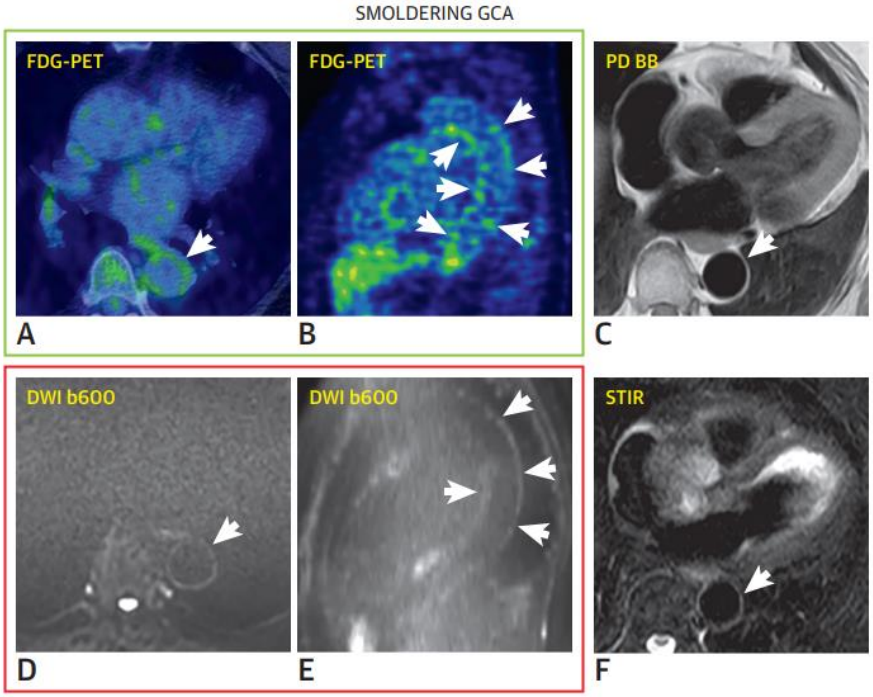

Figure 13: Patient in ongoing treatment without systemic signs and symptoms of GCA. Persistent slight pathological FDG-PET/CT, A. Axial FDG-PET/CT, B. Sagittal FDG-PET/CT; MRI imaging with very little affectation; C. Arterial wall thickness is not increased, D. Axial, E. Sagittal reconstruction, F. No significant vessel wall hyperintensity. Ironi G. et al. (2018) [(18)].

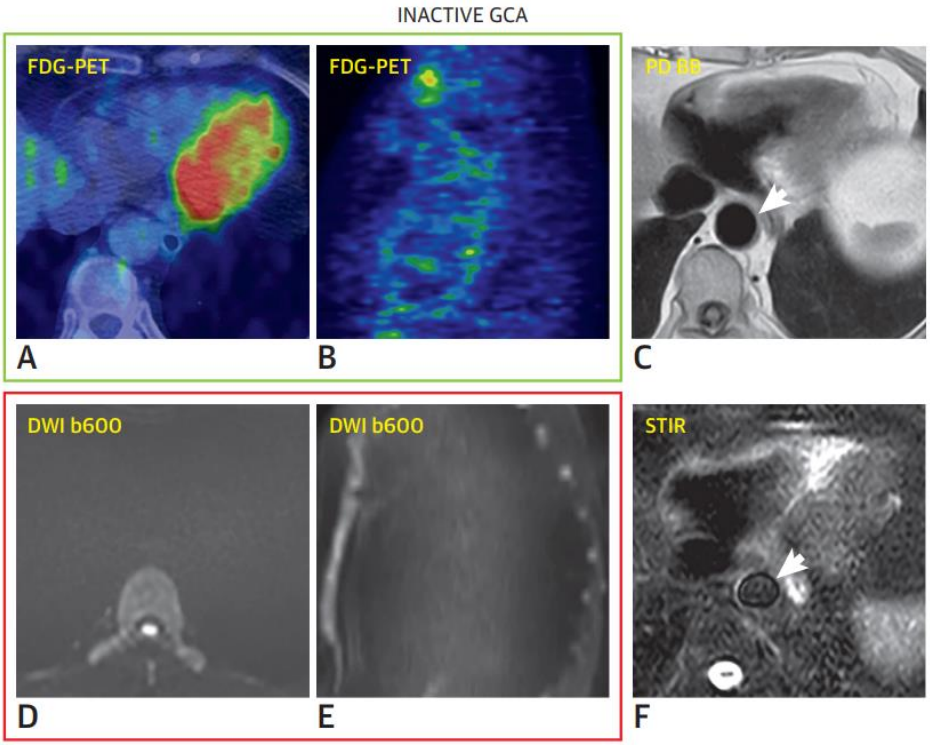

Figure 14: Patient in ongoing treatment, GCA clinically inactive. Negative FDG-PET/CT imaging test. A. Axial FDG-PET/CT, B. Sagittal FDG-PET/CT; MRI imaging with no affectation; C. Arterial wall thickness is not increased, D. Axial, E. Sagittal reconstruction aortic wall not detectable, F. No pathological changes. Ironi G. et al. (2018) [(18)].

Nevertheless, imaging techniques should be analyzed with prudence. It is important to consider that imaging displaying residual vascular inflammation may persist even after complete clinical remission of signs and symptoms [37].

FDG-PET/CT should not be performed routinely for patients in clinical remission. However, EULAR recommends using them when recurrence of active disease is suspected. In contrast, ultrasound, CT, and MRA should be used for long-term monitoring of complications such as, stenosis, occlusion, and aneurysms [32].

9. Treatment of C-GCA and LV-GCA

Currently, according to EULAR's 2018 recommendations, there is no difference in the treatment of C-GCA and LV-GCA. In general, the treatment for both is based on high-dose glucocorticoids for remission, with a possibility of adjuvant immunosuppressant agents for a selected group of patients [37].

EULAR recommends the use of high dose prednisone, or equivalent, for induction of remission. The treatment should be started immediately to avoid complications. The induction is done with 40-60 mg/day of oral glucocorticoid. Oral glucocorticoid is preferred over intravenous treatment. However, for patients with visual disturbances such as, visual loss or amaurosis fugax, 0.25-1 g of methylprednisolone could be given for up to 3 days intravenously, and then oral glucocorticoids management should be started as recommended [37].

Treatment guidance is divided into two phases (Figure 15). In phase I, once the patient is induced with 40-60 mg/day of glucocorticoid, within the following 2-3 months glucocorticoids therapy is gradually tapered to achieve a dose of 15-20 mg/day, and then to achieve ≤ 5 mg/day after 1 year. If there are no signs and symptoms of relapsing, glucocorticoids therapy is continued to be tapered until stopped, which usually takes 2 or more years to achieve. Nevertheless, if during glucocorticoids therapy the patient presents signs and symptoms of a minor or major relapse, phase II of the treatment is started [37].

A major relapse is defined by the recurrence of active disease presenting either ischemic events, such as jaw claudication, visual disturbances, scalp necrosis, and/or limb claudication; or aortitis with complications, such as large vessel dilatation/aneurysms, dissection, stenosis. A minor relapse is when there is a recurrence of active disease without meeting the aforementioned conditions criteria of the major relapse [37].

As a major relapse represents a risk of end of organ damage and progressive large vessel complications, it should be treated as a new onset of the disease. Therefore, a dose of 40-60 mg/day of glucocorticoids should be restored. In a case of a minor relapse, EULAR recommends increasing glucocorticoids dose to

the last effective dose administered or 5-15 mg/day above the last effective dose. In addition, patients with major or minor relapse should be started on tocilizumab or methotrexate. Posteriorly, glucocorticoid therapy should be tapered until stopped, within the following 6 months. If a sustained remission is achieved, tocilizumab or methotrexate is then tapered [37].

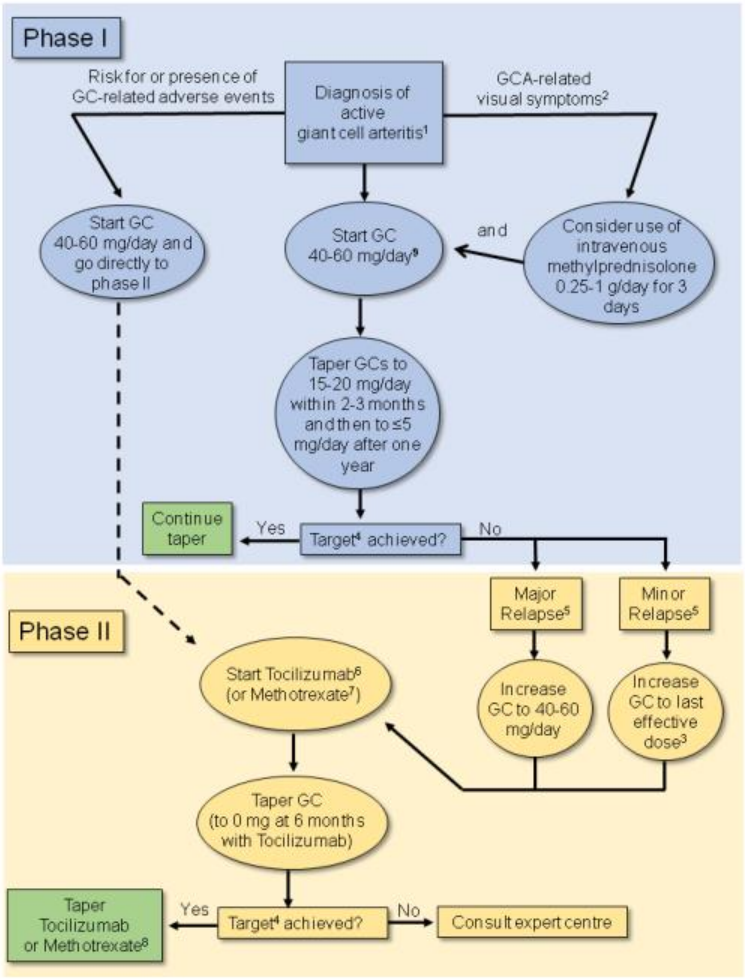

Figure 15: The 2018 EULAR algorithm for pharmacological treatment of GCA, Hellmich et al. (2018) [37].

Up until today, there are no clinical trials comparing tocilizumab and methotrexate in GCA patients. Meta-analysis on methotrexate's use, showed a large heterogenicity among the results on different studies. Tocilizumab, on the other hand, appeared to have a larger benefit reducing the risk of relapse and reducing the cumulative glucocorticoids exposure [37]. Currently, tocilizumab is the only approved biological agent for treating GCA, being approved by the European Medicine Agency (EMA) and the Food and Drug Administration (FDA) [38].

Adjunctive glucocorticoid sparing therapy should also be used for patients with diabetes, osteoporosis, glaucoma, or cardiovascular disease, or at risk of developing any of these glucocorticoid-related adverse events. After induction, with the standard high dose glucocorticoids, tocilizumab should be added for those patients as indicated in the phase II management. Tocilizumab helps to lower the cumulative glucocorticoid dose and the risk of relapse [37].

The minimal duration of GCA therapy lasts 2 years, and the final duration of treatment is highly variable, as some patients experience a chronic relapsing course. Therefore, osteoporosis prophylaxis and gastric protection should be considered [26].

A study published by Prieto et al. (2021), which included 30 patients with refractory LV-GCA, aimed to determine the clinical improvement correlated to the reduction of vascular activity on FDG-PET/CT imaging. Tocilizumab was administered in monotherapy in 16 patients and in addition to methotrexate in 14 patients. The dose used of tocilizumab was 8 mg/kg/4 weeks intravenous or 162 mg/week subcutaneous. Prieto et al. published that even though 83.3% of the patients achieved clinical remission, less than a third of them presented a normalization of FDG-PET/CT scans [38].

Grayson et al. (2018) studied the risk of relapse of patients with vascular inflammation upon a clinical remission. During the FDG-PET/CT follow-up, 58% of the patients treated with prednisone had persistent vascular inflammation even though they were in clinical remission. Furthermore, in a median period of 15 months follow-up, these patients experienced higher rates of clinical relapse compared to patients with a low total vascular score on clinical remission [35].

These findings suggest that both glucocorticoids and tocilizumab may not lead to total suppression of vascular inflammation in every patient. FDG-PET/CT might be used to identify patients at a higher risk of future clinical relapse [38, 35]. However, imaging findings must be interpreted with caution, as it remains unclear if the persistent vascular inflammation represents an active disease or vascular remodeling [37, 35]. Imaging cut-off values, which are currently under research, could help differentiate vascular inflammation from vascular remodeling. Patients with a PETVAS score ≥ 20 presents significantly higher rates of clinical relapses compared to those with a PETVAS < 20 [8,35].

The GiACTA one-year trial performed by Stone et al (2017) with 251 patients, aimed to compare the use of tocilizumab as adjunctive glucocorticoid sparing therapy, to glucocorticoid monotherapy. The patients were randomly divided into groups. Two groups were treated with tocilizumab weekly or every other week, plus 26 weeks of prednisone taper. Two more groups were treated with placebo plus 26 weeks or 52 weeks of prednisone taper. The trial concluded that tocilizumab glucocorticoid sparing therapy was superior to glucocorticoid monotherapy achieving sustained remission. Patients treated with tocilizumab weekly, or every other week presented 56 and 53% sustained remission at week 52, respectively. The placebo group, on the other hand, presented 14 and 18% remission, for 26 and 52 weeks of prednisone taper, respectively [39].

EULAR recommends the use of tocilizumab as an adjunctive glucocorticoid treatment, if not already started at the disease onset, for refractory and relapsing patients. They also recommend its use for patients in the presence of an increased risk of suffering adverse effects of glucocorticoids. Methotrexate can be used as an alternative treatment, especially after the first relapse. As published in a meta-analysis, patients on methotrexate showed to have a 50% lower risk of presenting a second clinical relapse [37]. Data for other immunosuppressant agents as adjunctive therapies are limited or have low quality; abatacept, ustekinumab, azathioprine, leflunomide, cyclophosphamide, dapsone, etanercept. A few others agents; adalimumab, infliximab, and cyclosporine, showed no efficacy in clinical relapse of GCA [37].

10. Conclusion

Although GCA is well known for this classical cranial artery affectation, it can present with clinical features of two phenotypes, C-GCA and LV-GCA. Both seem to have the same pathophysiology behind them. However, C-GCA due to its affectation of the temporal artery, presents mainly with temporal or occipital headache, jaw claudication, scalp and temporal artery tenderness, and visual disturbances. LV-GCA, on the other hand, due to its extracranial large-vessel affectation, usually presents with constitutional symptoms, including fever, weight loss, malaise, and very frequently with PMR. Thus, PMR refractories to the treatment can be an indicator of the presence of LV-GCA, it is important to keep it in mind to avoid delaying the diagnosis. Patients can present with either C-GCA or LV-GCA, or both can coexist simultaneously.

The mean age at disease onset for C-GCA is 72 years old, and for LV-GCA it is 66 years old. However, while to diagnose C-GCA it takes an average of 2.6 months, for patients with LV-GCA this time can extend to an average of 8.1 months. This delay and the life-threatening location of LV-GCA can contribute to complications and a worse prognosis.

The main complication of C-GCA is vision loss, a prompt instauration of glucocorticoid therapy is fundamental to prevent it. Another important complication is CVE, it affects preferably the posterior circulation, and it is one of the main causes of mortality. Patients who are or were smokers are at a greater risk of suffering CVE. Meanwhile, the main complication of LV-GCA is aneurysms and dissections. This complication occurs more often when patients have symptomatic aortitis at the time of diagnosis, being more frequently seen on patients that are smokers and have HTA.

LV-GCA patients require a higher cumulative dose of glucocorticoids and present greater relapse rates, they also have a greater risk of suffering vascular complications that lead to higher morbimortality rates. In addition, LV-GCA patients more often require adjunctive immunosuppressive therapy to control their symptoms and to achieve remission. Sustained remission is still lower

among LV-GCA patients than C-GCA patients, even when adjunctive therapy is applied.

Temporal artery biopsy had been used for almost every patient suspected to have C-GCA. However, ultrasound has been recently considered the imaging technique of choice for the diagnosis when mainly C-GCA is suspected. According to EULAR recommendations, the diagnosis can be made without TAB if there is a high pretest probability and a positive ultrasound imaging. In addition, the diagnosis can be excluded if there is a low pretest probability and ultrasound imaging is negative.

FDG-PET/CT is a promising imaging technique for an early diagnosis of LV-GCA. EULAR recommends its use to diagnose and when a relapse is suspected. It is important to consider that imaging displaying residual vascular inflammation may persist even after complete clinical remission. It remains unclear if the persistent vascular inflammation represents an active disease or vascular remodeling. Nevertheless, greater relapse rates are seen among patients with a high total vascular score than the ones with a low total vascular score upon clinical remission. Currently, there are studies investigating ways to differentiate vascular inflammation from vascular remodeling. However, further studies are necessary to refine the diagnosis.

There is no difference in the treatment guideline for C-GGA and LV-GCA, further studies are necessary to confirm if a different treatment approach for each of them would be more appropriate. Advancing treatment options is crucial to have greater control of the symptoms and to avoid clinical relapses. Tocilizumab is the only currently approved biological agent for treating GCA. Studies have proven that Tocilizumab helps lower cumulative glucocorticoids and achieve sustained remission, hence, it is recommended by EULAR for patients with refractory and relapsing disease. Methotrexate showed to lower risk of presenting a second clinical relapse, however, results from different studies are heterogeneous. Data for other adjunctive therapies such as, abatacept, ustekinumab, azathioprine, leflunomide, cyclophosphamide, dapsone, etanercept are limited or have low quality, further studies are necessary to better understand their applicability treating GCA.

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