Review paper

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Cardiovascular lesions in giant cell arteritis

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Abstract

Introduction: Giant cell arteritis (GCA) is a systemic vasculitis that affects large vessels. Cardiovascular complications that develop with GCA have high morbidity and can be fatal. The aim of this work was to discuss epidemiology, clinical picture, etiopathology and risk of development of cardiovascular complications in GCA.

Material and methods: A literature review was performed for 2002 to 2021 using PubMed and Medline scientific search databases. The following keywords were used to search academic journal databases: "giant cell arteritis", "heart attack", "cardiovascular system", "aortic aneurysm", "coronary heart disease", "aortic dissection", "myocardium" and "stroke". Articles written in languages, other than English, were excluded.

Results: The analysis of studies showed an increased risk of an aneurysm, aortic dissection, coronary heart disease, cerebrovascular events, and peripheral artery disease in patients with GCA. This was not surprising as it has been shown that, cardiovascular complications worsens the prognosis in GCA. According to the results of observations and cited studies the most significant risk of cardiovascular complications was observed in the first year following the diagnosis of GCA.

Conclusions: Patients with GCA have an increased risk of cardiovascular disease, but research data/findings are somewhat conflicting, and there is limited information/knowledge on how to treat the patients. Awareness of the risk of cardiovascular disease in GCA is essential, and monitoring these potentially fatal consequences is mandatory in patients with GCA. It is critical to be aware of the danger of cardiovascular illness in GCA patients and to keep track of these potentially deadly outcomes.

Key words: giant cell arteritis, cardiovascular disease, aortic aneurysm, aortic dissection, coronary heart disease, myocardial infarction.

Introduction

According to the International Chapel Hill Consensus Conference Nomenclature of Vasculitides (2012), giant cell arteritis (GCA, temporal angiitis, Horton's disease, Horton's syndrome) is a rare form of systemic vasculitis (SV) that affects large vessels. Giant cell arteritis, often granulomatous, usually affects the aorta and/or its main branches, including the branches of the vertebral and carotid arteries. It also often affects the temporal artery. The onset of the disease is usually at the age of over 50 years, and GCA is frequently combined with rheumatic polymyalgia [1].

The risk of death from cardiovascular disease (CVD) in patients with GCA is higher than in the general population [2, 3]. The incidence of CVD, such as stroke, aneurysm, thoracic aortic dissection, coronary heart disease (CHD), including myocardial infarction (MI), and peripheral vascular disease, is also higher in GCA patients [4].

Since GCA is associated with an increased CVD risk, monitoring potentially fatal effects and modified risk factors is mandatory [5]. Rheumatologists and primary

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care physicians should be aware of the increased CVD risk in patients with GCA for the timely appointment of appropriate treatment with high doses of glucocorticosteroids (GCs) [4].

Studies on CV pathology in GCA are limited and produce different results. This review is devoted to analyzing CVD risk and structure in patients with GCA, their prognostic value, and treatment recommendations.

Epidemiology

The population of Northern Europe and America suffers more often from GCA than Southern Europe. The incidence of GCA is 1.1–43.6 cases per 100,000 people ≥ 50 years [6]. The peak incidence of GCA is observed at 70 to 80 years, with women being more likely to get sick [7].

Etiology and pathogenesis

Despite numerous studies, the etiology and pathogenesis of GCA are not fully elucidated. The triggering role of environmental factors [8], particularly infection (associated with chickenpox virus), is considered.

The role of hereditary factors confirms family and ethnic predisposition to GCA. The disease has been linked to the HLA-DRB1*04 allele (usually DRB1*0401 and DRB1*0404).

Smoking is the most frequent risk factor for GCA, but the relationship with other cardiovascular risk factors has not been established [7]. It has been established that GCA is an immune-mediated inflammation that affects large arteries [9].

Histopathology

According to artery biopsy, the following signs were usually found [10]: disruption of the internal elastic lamina, luminal narrowing and intimal proliferation, necrosis and panarteritis, granulomatous giant cell formation, monocytes infiltration.

Clinical manifestations

Typical clinical manifestations

Typical clinical signs of GCA include headache, predominantly in the temporal region, different symptoms such as weight loss of more than 2 kg, low-grade fever, night sweats, fatigue, visual disturbances (amaurosis explosive, acute vision loss, diplopia), lameness of the jaw, and/or tongue, symptoms of rheumatic polymyalgia, systemic and other manifestations.

Physical examination reveals:

1. Sensitivity and/or thickening of the superficial temporal arteries with or without reduced pulsation.
2. The sensitivity of the scalp and bruits (particularly in the axilla).
3. Pulse weakening and lowering blood pressure in the upper extremities.
4. Pathological results of the ophthalmological examination, including anterior and optic neuropathy, paresis/paralysis of the oculomotor nerve, occlusion of the central retinal artery or its branches and/or choroidal ischemia oculomotor cranial nerve palsy, branch retinal artery occlusion and/or choroidal, and central retinal artery occlusion.

Cardiovascular damages

Although GCA is characterized by damage to the aorta and its branches [11], in particular, the brachiocephalic trunk, superficial temporal, carotid, subclavian, and femoral arteries, other arteries, including coronary arteries [12], can be affected less frequently, which can lead to CV pathology [5, 13, 14] and cerebrovascular events [15]. However, studies on the risk of cardiovascular events are limited [5, 13–15].

Heart damage in GCA occurs in less than 5% of cases and includes aortic insufficiency due to aortic aneurysm, epicardial coronary artery lesions (coronaritis), pericarditis, and myocarditis (Table I) [16].

A retrospective cohort study in Canada found an increased risk of CVD (stroke, coronary heart disease, peripheral artery disease, aneurysms, or aortic dissection).

Table I. Cardiovascular damages in giant cell arteritis

Localization	Type of damage
Aorta	Aortic aneurysm, aortic dissection [4, 14, 16]
Myocardium and coronary vessels	Myocarditis [16] Coronaritis, coronary heart disease, including myocardial infarction [5, 13, 14, 16]
Pericardium	Pericarditis [16]
Peripheral vessels	Peripheral vascular disease [4, 13, 14]
Cerebral vessels	Stroke [5, 13, 14]

The composite endpoint was more common with elderly patients who experienced GCA than in patients with osteoarthritis or the control group without either disease. The adjusted hazard ratio (HR) for CVD was 1.6 (95% confidence interval, CI: 1.1–2.2) in patients with GCA compared with patients with osteoarthritis and 2.1 (95% CI: 1.5–3.0) in patients with GCA compared with the control group [14].

Similar results were presented by Tomasson et al. [13], according to which, in patients with GCA, the incidence of MI, cerebrovascular events, and peripheral artery disease was 10.0, 8.0, and 4.2 events per 1,000 person-years, respectively, against 4.9, 6.3 and 2.0 events per 1,000 person-years, respectively, in the control group and a significantly increased risk of CVD was observed: combined events for the combined outcome HRs 1.70 (95% CI: 1.51–1.91), MI (adjusted HR 2.06, 95% CI: 1.72–2.46), cerebrovascular events (corrected HR 1.28, 95% CI: 1.06–1.54), peripheral vascular disease (HR 2.13, 95% CI: 1.61–2.81).

During the first month after diagnosis of GCA, these indicators were more pronounced: for HR the combined outcome was 4.92 (95% CI: 2.59–9.34), MI 11.89 (95% CI: 2.40–59.0), cerebrovascular events 3.93 (95% CI: 1.76–8.79) and peripheral artery disease 3.86 (95% CI: 0.78–19.17).

Evidence for higher risk of CVD in patients with GCA showed that more patients with GCA had a history of vascular disease and comorbidities other than MI, diabetes mellitus type 2, obesity, and cancer compared with patients without vasculitis.

Compared with the group without vasculitis, patients with GCA had an increased risk of such CVD as MI, stroke, peripheral vascular diseases, aortic aneurysm, and venous thromboembolism (Table II). Patients with GCA also had an increased risk of developing other comorbidities such as diabetes mellitus type 2, depression, etc., but not cancer [17].

Cardiovascular events were more common during the first month [13] and year after diagnosis [5], confirming the role of direct or systemic effects of inflammation [5, 13], potential mechanisms of which include oxidative stress, endothelial dysfunction, damaging inflammatory cytokines, and the proatherogenic effect of GCs [8, 18, 19].

According to a population study of 809 patients with GCA (mean age 75.9 years, women 75.8%), the incidence of MI and stroke was 38.1 and 26.4 per 1,000 person-years, respectively, compared with persons without GCA (15.2 and 13.8 events per 1,000 people). Compared with non-GCA cases, the age-, sex-, and entry time-matched HRs were 2.21 (95% CI: 1.68–2.91) for stroke and 2.75 (95% CI: 2.16–3.50) for MI.

Table II. Cardiovascular disease risk in patients with giant cell arteritis compared with the group without vasculitis [17]

CVD risk	Adjusted hazard ratio
Myocardial infarction	1.57 (95% CI: 1.36–1.82)
Stroke	1.41 (95% CI: 1.29–1.55)
Peripheral vascular diseases	1.75 (95% CI: 1.49–2.06)
Aortic aneurysm	1.98 (95% CI: 1.50–2.62)
Venous thromboembolism	2.03 (95% CI: 1.77–2.33)

CVD – cardiovascular disease.

After adjusting for other covariates, the corresponding HRs were 2.04 (95% CI: 1.43–2.93) and 1.77 (95% CI: 1.29–2.43), which were the highest during the 1st year after GCA diagnosis: for stroke (HR 3.20, 95% CI: 2.11–4.87) and MI (HR 4.76, 95% CI: 3.29–6.88).

As it can be seen from the data, patients with GCA have a significantly increased risk of MI and stroke compared to the general population. Additionally, the highest risk of CVD is observed during the first year following diagnosis, although the risk remains significant even after five years of follow-up [5].

In contrast, a cohort study in the United Kingdom found no increased risk of CVD in patients with GCA and/or rheumatic polymyalgia [20].

Cardiovascular events in patients with GCA are associated with the following risk factors: male [21], hypertension [22], smoking [23] and low socioeconomic status [21].

Results

Aortic pathology

Giant cell arteritis is often associated with aortic damage, which can cause life-threatening complications [24] while affecting the thoracic aorta and its branches [25] and can be complicated by the development of aneurysms, and dilatation, aortic dissection, or rupture of large arteries [25, 26].

The results showed that the incidence of large vascular lesions (aortic aneurysm and/or dissection, significant artery stenosis) was high during the first year after diagnosis of GCA, and the incidence of aortic aneurysm/dissection increased after 5 years and continued to increase throughout the observation period (average duration of the observation was 8.8 years) [26].

Large vessel pathology was observed in 9–22% of patients during the first years of the disease [27–29]. These results are consistent with the study by García-Martínez et al. [28], according to which 22.2% of patients were diagnosed with structural changes of the aorta (aneu-

Table III. The use of imaging research methods in clinical practice in systemic vasculitis (EULAR 2018) [45]

1. Ultrasound
2. Magnetic resonance imaging
3. Computed tomography
4. Positron emission tomography with 18F-fluorodeoxyglucose

rysm or dilatation), which were more common in men (50%) than in women (12.5%) (relative risk HR 3.5, 95% CI: 1.53–8.01, $p = 0.007$).

However, according to another study, pathology of large arteries was more common in women ($p = 0.01$); these patients have less cephalgia ($p < 0.0001$) and rheumatic polymyalgia ($p = 0.001$), but more often – symptoms associated with extracranial vascular lesions ($p = 0.05$) compared with patients without large vascular lesions [27].

According to another study, 27% of patients with GCA were diagnosed with complications of large artery disease, which was 30.5 per 1,000 person-years. Aneurysm and/or aortic dissection were diagnosed in 18% of patients, of which thoracic aortic lesions were observed in 11% of cases and aortic dissection in 5% of patients. Thirteen percent of patients had stenosis of the large arteries, the frequency of which was 13.5 per 1,000 person-years. In addition, the association of coronary heart disease and hyperlipidemia with aortic aneurysm and/or dissection ($p < 0.05$ for both) has been established [25].

In other study, the authors found that out of 171 patients with aortitis and GCA, 32% had different signs of aortitis, such as dorsal or lumbar abdominal pain or aortic insufficiency at diagnosis. Aortic dissection or aneurysm was found in 23.4% of patients, and 5.8% of patients required surgery due to GCA [24].

Survival without aortic complications differed significantly between symptomatic and asymptomatic patients. Multivariate analysis shows that the presence of aortic symptoms at diagnosis is associated with the occurrence of aortic complications [24].

According to a retrospective study by Gonzalez-Gay et al. [29], 9.5% of patients with GCA (confirmed by biopsy) developed an aneurysm and/or aortic dissection (often thoracic aorta), the incidence of which was 18.9 per 1,000 person-years.

According to a retrospective examination of patients with GCA with/experiencing thoracic aortic pathology, emergency surgery was performed in 10% of patients. The mega-aortic syndrome was found in 10% of patients. It should be noted that 100% of patients had lesions of the ascending aorta.

In addition, 80% of patients underwent surgery on the aortic valve, among whom, in 50% of cases, a prosthetic aortic valve was implanted. The 5-year survival of patients after aortic surgery was 91%.

Based on the analysis, the authors concluded that thoracic aortic pathology could be suspected in less than 25% of patients before surgery. The lesion may be acute or chronic with local or diffuse aortic lesions, but the ascending aorta is always involved in the pathological process. Surgery shows good results, and further imaging is mandatory to assess the condition of the aorta [30].

Another investigation [21] showed that in patients with GCA, the adjusted sub-HR (95% CI) for aortic aneurysm was 1.92 (1.52–2.41). Predictors of aortic aneurysm were:

- history of smoking 2.64 (2.03–3.43) or current smoking 3.37 (2.61–4.37),
- previous history of antihypertensive drugs 1.57 (1.23–2.01),
- and history of diabetes mellitus 0.32 (0.19–0.56),
- or GCC 1.98 (1.50–2.63).

In the case of the sudden death of an older woman, autopsy results showed hemopericardium and cardiac tamponade. Granulomatous inflammatory skip lesions and giant cells, characteristic of GCA, were found in the aorta, coronary and pulmonary arteries [12].

Aortic insufficiency

Aortic insufficiency develops due to dilatation of the aortic root due to the development of its aneurysm. The findings of Nuenninghoff et al. [25] ($n = 168$) showed that among 18 patients with GCA diagnosed with an aneurysm and/or thoracic aortic dissection, 56% had mild and 39% had moderate aortic regurgitation. According to another study, aortic valve insufficiency was diagnosed in 35% of patients with aortitis [24].

Cerebrovascular events

Acute cerebrovascular ischemic events are severe complications of GCA. According to a retrospective analysis [31], 16% of patients had acute ischemic cerebrovascular events, age 83 (67–96) years compared with patients without stroke 76 (58–96, $p = 0.014$), and men accounted for 61% (against 30%, $p = 0.014$).

Overall survival was significantly lower in patients with GCA who experienced strokes (4.4 months) compared with patients without stroke. Three-year recurrence-free survival decreased in stroke patients (8.42 vs. 78.0 months, log-rank test = 0.0001), as well as the du-

ration of sustained remission (78 vs. 139 months, log-rank test = 0.0004) [31].

Patients with GCA compared with the control group had an increased relative risk of cerebrovascular disease and CVD. In the GCA cohort, predictors of cerebrovascular disease or CVD included: age > 80 years vs. < 65 years, male sex, and social-economic status.

These predictors were also present within the non-GCA cohort [21]. A systematic review and meta-analysis of cohort studies by Ungprasert et al. [15] reported a significantly increased risk of cerebrovascular (CV) events in patients with GCA compared with the group without GCA. The pooled risk ratio was 1.40 (95% CI: 1.27–1.56). The statistical heterogeneity was low, with an I^2 of 31%. Statistical inhomogeneity was low (I^2 was 31%).

In patients with GCA, vertebrobasilar stroke was the main reason for mortality. The researchers noted that duplex US is a routine test in stroke patients, which can be a critical diagnostic method if the classical hypoechoic "halo sign" is recognized at the vertebral artery level [32].

Lesions of the coronary arteries

Studies have provided conflicting information on the risk of coronary heart disease in GCA, so this issue remains unclear, and therefore further research is needed [4]. Lesions of the coronary arteries were diagnosed in less than 1% of patients with GCA, and coronary angiography revealed their stenosis [33].

An observational cohort study conducted by Tomasson et al. [13] revealed an increased risk of MI, especially during the first month after diagnosis of GCA. According to a population-based, cross-sectional study, the proportion of coronary heart disease was higher in patients with GCA compared with the control group (27.5% vs. 12.5%, respectively, odds ratio of 2.65).

Diabetes, hypertension, hyperlipidemia, and smoking are more common in patients with GCA than in the general population. After stratification for these diseases/conditions by logistic regression, GCA remained independently associated with coronary heart disease [34].

Armellin et al. [12] described a 76-year-old woman with coronary angiography showing 90% stenosis of the proximal left anterior descending and large-caliber intermediate arteries, 70% of the mid-right coronary artery, and 30% stenosis of the left main artery. Primary percutaneous coronary intervention with drug-eluting stents was performed.

Temporal artery biopsy 13 days after the onset of symptoms showed the signs of GCA such as lumen sub-occlusion, disrupted internal elastic lamina, intimal fibroplasia, multinucleated giant cells, and cellular infiltrate mainly consisting of histocytes and lymphocytes.

Computed tomography (CT) angiography showed typical changes in vasculitis such as multifocal stenotic lesions in different vessels (left subclavian, right vertebral, bilateral superficial femoral, and popliteal arteries). The authors note that coronary artery disease is possible due to previous atherosclerosis in combination with vasculitis [12].

In a case of the sudden death of an 83-year-old woman with GCA, the autopsy revealed MI with rupture of the anterior wall and development of cardiac tamponade, thrombosis of the anterior descending branch of the left coronary artery, stenosis of up to 80% of other arteries (internal carotid, vertebral, basilar, ophthalmic and abdominal arteries), which had a segmental character (characteristic of GCA), generalized atherosclerosis and vasculitis of the coronary arteries [35].

Although no specific changes in coronary angiography in GCA indicate coronary artery arteritis, changes such as tapered, smooth narrowing have been described in cases of GCA with coronary involvement and skip lesions [33].

Unlike other studies, a systematic review and meta-analysis of 6 observational studies did not show any statistically significant increased risk of coronary heart disease in patients with GCA. The pooled risk ratio of coronary heart disease in patients with GCA was 1.51 and did not reach statistical significance (95% CI: 0.88–2.61), but the statistical heterogeneity was high at I^2 = 97% [36].

These results are consistent with data from another study, which showed no increased risk of developing acute coronary syndrome in patients with GCA compared to those without GCA (HR 0.74, 95% CI: 0.44–1.26).

In addition, revascularization was performed less frequently in patients with GCA (19% vs. 50%, p = 0.015). Cardiovascular risk factors for coronary heart disease, such as diabetes, were less common in patients with GCA, HDL cholesterol was higher, and triglycerides were lower in these patients [37].

Atherosclerosis

In general, there is no significant evidence of accelerated atherosclerosis in GCA. Although the number of CVD cases in patients with GCA is increased, the time of their development (usually at the beginning of the disease, during the 1st year after diagnosis) suggests that ischemia may occur directly as a result of vasculitis appropriate vascular basins or as a consequence of inflammation-induced endothelial dysfunction and/or plaque instability that stabilizes after inflammation suppression [18].

In patients with GCA, the thickness of the intima-media carotid artery complex was smaller compared to the control group ($p = 0.005$). The authors concluded that atherosclerotic macrovascular disease is not increased in patients with GCA [38]. However, there is evidence of increased arterial stiffness in patients with GCA [39]. Armellin et al. [12] noted that although atherosclerosis of the coronary arteries is found in patients with GCA, this may not indicate its accelerated development.

Pericarditis

Studies on the development of pericarditis in GCA are few. According to Tiosano et al. [40], an independent association has been established between GCA and pericarditis, especially in patients < 70. Pericarditis was observed in 1.22% of patients with GCA and the control group in 0.33% of cases ($p < 0.001$). According to another study, pericardial effusion was found in 3.5% of patients. Often the course of pericardial effusion in GCA is asymptomatic [41].

Myocarditis

There are sporadic reports in the literature on the development of myocarditis in patients with GCA. There was reported a case of diffuse myocarditis with a decrease in the left ventricular ejection fraction and its recovery after treatment (methylprednisolone, prednisone) [42] and myocarditis with the development of atrial fibrillation [43].

Diagnosis

Untreated active GCA is an urgent condition, as such patients have a significant risk of vision loss and other ischemic complications. Therefore, it is recommended that patients ≥ 50 years with acute or subacute development of signs and symptoms indicating GCA and the presence of markers of inflammation in the absence of other reasons for their increase (e.g., infection), urgently refer to a specialist/center for other multidisciplinary diagnostic search and treatment [11].

Giant cell arteritis diagnosis is usually performed using symptom assessment, history, laboratory tests, vascular imaging data, and temporal artery biopsy [44–46]. To assess the activity of GCA, the British Society of Rheumatology (BSR) recommended the determination of laboratory markers of inflammation (C-reactive protein for all patients and erythrocyte sedimentation rate or plasma viscosity) and general blood tests (maybe increased platelet count in GCA) [46].

In 2018, the European Alliance of Associations for Rheumatology (EULAR) published recommendations on the use of imaging research methods in clinical practice in SV affecting large vessels (Table III) [45].

These methods assess both cranial and extracranial arteries and the aorta. They are more sensitive, less invasive, and more accessible than temporal artery biopsy and angiography, which have been the only diagnostic standards for GCA and nonspecific aortic arteritis for decades.

Patients with suspected GCA are recommended to conduct an early imaging study to supplement the clinical criteria for diagnosing GCA. Imaging should not delay the start of treatment (recommendation 1). If patients have a high clinical suspicion of GCA and a positive imaging study, the diagnosis of GCA can be made without further examination (biopsy or subsequent imaging).

In patients with low clinical probability and negative imaging results, the diagnosis of GCA can be considered unlikely. In all other situations, additional diagnostic tests are required (recommendation 2).

Ultrasound (US) examination of the axillary arteries is recommended as the first imaging method in patients with a suspected predominantly cranial form of GCA. The US finding is a non-compressible "halo" sign, the most suggestive of GCA (recommendation 3).

Magnetic resonance imaging (MRI) or magnetic resonance angiography with high resolution of cranial arteries to detect inflammation of the vascular wall can be used as an alternative for the diagnosis of GCA if US is not available or not informative (recommendation 4).

Computed tomography (CT) (also applies to CT angiography) and positron-emission tomography (PET) (usually combined with CT or CT angiography) are not recommended for the assessment of cranial artery inflammation (recommendation 5).

Ultrasound, PET, MRI, and/or CT can be used to detect inflammation of the vascular wall and/or changes in the lumen of the extracranial arteries to confirm the diagnosis of GCA. Ultrasound is of limited value in assessing the presence of aortitis (recommendation 6).

(Recommendations 7 and 8 do not concern GCA).

Angiography is not recommended for diagnosing GCA and nonspecific aortic arteritis, as it has been replaced by the above imaging techniques (recommendation 9).

Imaging may be helpful for confirmation or exclusion in patients with GCA or nonspecific aortic arteritis with suspected exacerbation (recommendation 10).

In patients with large-vessel vasculitis (GCA, etc.) with suspected flare, imaging is recommended to confirm or exclude it. In patients with remission, imaging is not recommended. In patients with GCA or nonspe-

cific aortic arteritis, magnetic resonance angiography, CT angiography, and/or US may be used for long-term monitoring of structural damage, especially for stenosis, occlusion, dilatation, and/or aneurysms (recommendation 11) [45].

Treatment

Giant cell arteritis treatment aims to achieve clinical remission and prevent complications, especially such severe ones as vision loss [4]. According to the EULAR recommendations, treatment of GCA should begin with the appointment of high doses of GC to induce remission, followed by a dose reduction while achieving control of inflammation.

Adjunctive therapy with tocilizumab may be used in some patients (refractory or recurrent course of the disease, the presence or increased risk of side effects or complications associated with GC). Methotrexate is recommended as an alternative drug.

Inhibitors of tumor necrosis factor α can be considered in case of recurrence or refractory course of GCA, despite using disease-modifying drugs. Antiplatelet or anticoagulant therapy should not be used regularly for treating SV affecting large vessels unless prescribed for other reasons such as coronary heart disease or cerebrovascular disease.

In some situations, for example, ischemic vascular complications or high risk of CVD, their use can be considered individually. In systemic vasculitis involving large vessels, planned endovascular interventions or reconstructive surgery should be performed during remission. However, such urgent conditions as artery dissection or critical ischemia require immediate referral to vascular surgeons [11].

In the literature, data on the use of acetylsalicylic acid as an adjunct in treating GCA are contradictory. A retrospective study showed that antiplatelet or anticoagulant therapy reduced ischemic events compared with patients who did not receive them ($p < 0.0005$) without increasing the risk of bleeding [47].

In contrast, a meta-analysis of 6 retrospective studies showed that antiplatelet/anticoagulant therapy before the diagnosis of GC was not associated with a reduction in severe ischemic complications, or bleeding [48]. These contradictory results require further research on the use of acetylsalicylic acid as an adjunct in GCA and for the prevention of cardiovascular pathology in patients with GCA [4].

The effect of statins on the risk of cardiovascular complications in GCA is also controversial [44]. The findings of three retrospective cohort studies did not show the advantage of statin use in terms of GC sparing effect [49]. However, exposure to statins for up to 20 months may favor a quicker corticosteroid tapering [50].

The commentary on the recommendations of the French group for the study of vasculitis of large vessels in 2016 states that when using low prophylactic doses of aspirin or statins, current guidelines should be followed to prevent complications of atherosclerosis [44].

Prognosis

Data on mortality of patients with GCA are contradictory. There is growing evidence that the overall mortality of patients with GCA is slightly higher than expected in the general population, especially due to aortic aneurysms or other cardiovascular causes [7].

According to another study, patients with GCA did not show an increase in all-cause mortality compared with the general population (standardized mortality ratio was 1.081, (95% CI: 0.963–1.214, $p = 0.184$) without significant differences in the region, gender; however, the risk of death from CVD was significantly increased [3].

These results are consistent with data from another study, which did not show differences in the overall survival of patients with GCA and the control group ($p = 0.413$), but revealed differences in the main causes of death. Patients with GCA showed an increased risk of death from circulatory diseases (HR 1.31, 95% CI: 1.13–1.51, $p < 0.001$) but a lower risk of death from cancer (HR 0.56, 95% CI: 0.42–0.73, $p < 0.001$) compared with the control group [2].

The GCA patient's survival was similar to that of the general population, but the presence of aortic aneurysm/dissection was associated with a decreased survival of patients with GCA, but not in patients with large-artery stenosis.

In patients with GCA, the presence of large vascular lesions was associated with an increase in mortality compared with patients with HCV without large vascular damage. Aortic aneurysm/dissection was associated with increased mortality in patients with GCA. The mortality of patients with GCA and large-artery stenosis was similar to that of GCA patients without this manifestation [26].

Conclusions

Patients with GCA have an increased risk of CVD development which can be fatal, especially in the cae of the pathology of an aorta with the development of its dissection.

There is a need for further research on short-term and long-term risks of cardiovascular events in GCA and

the development of recommendations for treating CV pathology in this condition.

The patients with GCA should be closely monitored and each patient's individual CVD risk factors should be assessed.

The authors declare no conflict of interest.

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