Editorial

Giant cell arteritis and atherosclerosis: coexistence or causality?

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Giant cell arteritis (GCA), a type of large vessel vasculitis (LVV) (1) formerly known as temporal arteritis (2), is the most common vasculitis affecting elderly individuals in Western countries. Atherosclerosis is also considered an age-related disease, with increasing age being an independent risk factor for its development (3).

Although GCA and atherosclerosis are different conditions, there is some overlap between them. In this regard, both conditions are more common in individuals older than 50 years. Endothelial dysfunction, an early step in the process of atherogenesis (4), is also observed in patients with GCA (5, 6). GCA and atherosclerosis involve inflammation, although it is more immune-mediated in vasculitis and more related to lipid accumulation in atherosclerosis. Moreover, elderly patients can present with symptoms that might be attributed to either condition. In this regard, clinical features such as headache, limb claudication, and vision changes in GCA can be confused with symptoms of atherosclerotic vascular disease. In addition, elevated inflammatory markers can be seen in both conditions and emerging therapies targeting IL-6 and other cytokines may play roles in both diseases. Moreover, it is likely that chronic inflammation and prolonged glucocorticoid use may contribute to atherosclerotic risk.

Potential histopathological differences between GCA and atherosclerosis are shown in Table I.

Considering all of these points, the main question we have to address is whether patients with GCA have an increased atherosclerotic burden and higher cardiovascular mortality. However, when exploring this issue, we disclose several contradictory findings, which we discuss in this editorial.

The first issue to examine is whether atherosclerosis is more prevalent in individuals with GCA. With respect to this, Besutti *et al*. compared arterial wall calcifications on CT scans between patients with LVV and age- and sex-matched lymphoma patients who served as controls. Calcifications in the coronaries, thoracic aorta, and abdominal arteries were quantified using Agatston and volume scores from PET-CT images. Among 266 patients, abdominal artery calcification levels were similar between groups. After adjustment for age and year of diagnosis, LVV patients were more likely to have thoracic artery calcifications and higher thoracic calcification volume scores. In contrast, coronary calcifications were more extensive in lymphoma controls (7). These authors concluded that patients with LVV show greater calcification in thoracic arteries compared with controls, but no increase in coronary or abdominal artery calcifications (7). Another study evaluated vascular calcification in patients with LVV, including GCA and Takayasu's arteritis compared to patients with hyperlipidaemia. Using non-contrast CT, calcification was quantified across 14 arterial territories with cumulative Agatston scores. Among 88 participants (GCA = 29, Takayasu's arteritis = 22, hyperlipidaemia = 37), coronary artery calcification was more prevalent in hyperlipidaemia (67%) than in GCA (35%) or Takayasu's arteritis (9%). However, total vascular calcification across large arteries was higher in GCA than in hyperlipidaemia, and similar between GCA and Takayasu's arteritis. Multivariable analysis identified age, type of vasculitis, and prednisone use as factors associated with vascular calcification in LVV (8). The study suggested that patients with LVV have less coronary artery calcification than patients with hyperlipidaemia. However, overall cal-

Table I. Histopathological differences between giant cell arteritis (GCA) and atherosclerosis.

	GCA	Atherosclerosis
Inflammatory cells	T cells, macrophages, giant cells	Foam cells, macrophages
Location	Media and adventitia	Intima
Elastic lamina	Fragmentation common	Often intact or thickened
Lipid involvement	Rare	Prominent
Cell infiltration	T-cell mediated (Th1, Th17), macrophages	Macrophages, oxidised LDL, foam cells

cification in large arteries was greater in LVV. Both traditional cardiovascular risk factors and disease-specific factors contributed to vascular calcification (8). With respect to this, a former study aimed to determine whether patients with biopsy-proven GCA had increased atherosclerosis and whether disease features or glucocorticoid treatment contributed to its development (9). For this purpose, 40 GCA patients who had completed glucocorticoid therapy and had at least three years of follow-up were compared with 40 age- and sex-matched controls. Atherosclerosis was assessed using carotid ultrasound to measure intima-media thickness (IMT) and detect plaques. In contrast to expectations, GCA patients had significantly lower carotid IMT than controls. Patients who had required glucocorticoid treatment for more than two years showed a trend toward higher IMT, but this was not statistically significant. As expected, age correlated strongly with IMT in GCA patients, but after adjusting for age, sex, traditional cardiovascular risk factors, inflammation markers at diagnosis, disease duration, and cumulative prednisone dose, no significant associations were found with IMT. Therefore, this study did not confirm evidence of increased macrovascular atherosclerosis in patients with biopsy-proven GCA. Factors such as cumulative glucocorticoid exposure or initial inflammatory markers did not appear to influence atherosclerosis development in this cohort of biopsy-proven GCA patients (9). Despite these findings, classic epidemiological studies have confirmed an increased frequency of aortic aneurysm and/or dissection in patients with GCA during the extended follow-up of these patients (10, 11). Hypertension as well as a severe inflammatory response at the time of diagnosis of GCA may predispose to the development of aortic aneurismal disease (10). With respect to this, it is possible that a persistent of silent "subclinical" inflammation along with traditional cardiovascular risk factors such as hypertension could favour the development of aortic aneurismal disease in the follow-up of these patients.

Another important finding in patients with GCA was an increased incidence of acute myocardial infarction during the first 30 days following GCA diagnosis (12). The same applied to the risk of cerebrovascular accidents, particularly strokes in the vertebrobasilar territory, whose frequency is increased shortly after GCA diagnosis compared with that of age-matched individuals in the general population (13). Interestingly, a French study showed that patients with GCA most commonly experienced myocardial infarction, without angiographic evidence of acute atherothrombotic plaque disruption (14). With respect to this, coronary plaque erosion represents a distinct mechanism of acute coronary syndrome that is driven by immune-mediated endothelial injury rather than fibrous cap rupture. As reviewed by Meteva *et al*., this process involves local recruitment and activation of neutrophils and T lymphocytes. Endothelial dysfunction and prothrombotic immune signalling also play central roles in triggering coronary thrombosis (15). These mechanisms provide a plausible pathophysiological link to the observation that myocardial infarction frequently occurs soon after the diagnosis of GCA, a disease characterised at onset by intense systemic inflammation with activation of innate and adaptive immune responses. In GCA, widespread endothelial dysfunction and circulating activated immune cells may target pre-existing coronary plaques, promoting endothelial denudation, neutrophil extracellular trap formation, and increased thrombogenicity without the need for plaque rupture. This inflammatory process is most pronounced around the time of diagnosis, when disease activity is highest and before complete suppression by glucocorticoid therapy. This supports the idea that an acute coronary event in this context might reflect immune-mediated plaque erosion, rather than progressive atherosclerotic instability.

A relevant point to address is whether mortality in GCA is actually increased compared with the general population. In this context, Jud *et al*. examined cardiovascular disease, lipid abnormalities, and endothelial dysfunction in patients with GCA relative to healthy controls. They found that GCA patients had significantly higher rates of carotid and vertebral artery disease. These patients also displayed a poorer lipid profile, more frequent endothelial dysfunction, more cardiovascular events during follow-up and overall worse long-term cardiovascular outcomes than controls (16). However, these findings contrast with those from population-based studies. In 1999, we analysed data from 109 biopsy-confirmed GCA patients from the Lugo region in northwest Spain (17). Apart from severe underlying comorbid conditions unrelated to GCA, neither sex nor clinical features of the disease were associated with increased mortality. Similar to the age-matched population in Lugo, most deaths were due to cardiovascular and cerebrovascular complications. The standardised mortality ratio was 0.80 (95% CI 0.47–1.13). The one-, two-, five-, and ten-year survival rates were 95%, 91%, 81% and 62%, respectively. The hazard ratio was 1.8% at day 30 after diagnosis and remained low through the first year of treatment, with only a slight increase thereafter. Because this rate was relatively constant, an exponential model was applied, estimating an annual mortality risk of 5.3% (17). In keeping with that,

a recent Scandinavian study supports these earlier observations. Tengesdal *et al*. evaluated 274 patients with isolated polymyalgia rheumatica (PMR) and 63 with GCA. Among patients with isolated PMR, the standardised mortality rate did not differ from that of matched population controls (18). Likewise, in the smaller GCA subgroup, no significant increase in all-cause mortality was observed compared with population comparators (18). Taken together, the notion of an increased cardiovascular mortality risk in GCA is not consistently supported. Epidemiologic studies include unselected patient populations, reducing the bias associated with recruiting patients based on disease severity, which we believe may partly explain the discrepancies observed in other study designs. Since cardiovascular events generally occur early after the disease diagnosis, as indicated by other authors, we support the claim that cardiovascular events in GCA may be more likely the result of direct vascular inflammation as opposed to accelerated atherosclerosis (19).

A final issue is related to the use of anti-aggregation or statins to prevent cardiovascular events in patients with GCA. In our experience the use of anti-aggregation before the diagnosis of the disease did not lead to a reduction of cardiovascular events (20). With respect to this, a meta-analysis concluded that anti-aggregation may be useful after the disease diagnosis to prevent ischaemic complications (21). In this regard, the meta-analysis showed that antiplatelet or anticoagulant therapy before GCA diagnosis was not associated with a reduction in major ischaemic events. However, a marginal benefit was observed when these agents were combined with glucocorticoids in patients with established GCA without an increased risk of bleeding (21). With regard to the use of statins in the management of GCA, Jud *et al*. assessed the prevalence and incidence of cardiovascular disease, and their relationship with lipid profiles and endothelial dysfunction in patients with GCA compared with controls (16). According to this study patients with GCA have an elevated cardiovascular risk that appears to be linked more to abnormalities in lipid metabolism than to endothelial dysfunction. The authors of this study concluded that there is a need for improved preventive care that included more consistent lipid-lowering treatment in patients with GCA to reduce cardiovascular risk (16). In keeping with these observations, a retrospective observational study investigated whether statin therapy is associated with reduced vascular inflammation in patients at risk for LVV, using FDG-PET-CT imaging (22). The study included patients with PMR, GCA, and fever of unknown origin who underwent PET-CT scans to assess vascular FDG uptake as a marker of inflammation. Vascular inflammation was compared between patients who were receiving statins and those who were not at the time of imaging. The results showed that statin use was associated with significantly lower vascular FDG uptake, suggesting reduced arterial wall inflammation, particularly in large vessels. This association remained after adjusting for potential confounders such as age, cardiovascular risk factors, and inflammatory markers. The findings suggested that statins may exert an anti-inflammatory effect at the vascular level in conditions associated with or at risk for LVV. Therefore, this study supported the hypothesis that statins could have a role in modulating vascular inflammation (22). Given the known anti-inflammatory properties of statins, an observational study evaluated whether statin therapy improved outcomes in patients with GCA. The study retrospectively compared GCA patients who were receiving statins with those who were not, assessing relapse rates and glucocorticoid requirements. However, there were no significant differences between the two groups in terms of disease course, frequency of relapses, or cumulative glucocorticoid doses (23). The authors concluded that statins do not appear to provide clinical benefit as an adjunct treatment for GCA and should be used in these patients only for standard cardiovascular indications rather than for disease control (23). According to this study statin therapy did not appear to confer a therapeutic benefit in the treatment of GCA beyond standard care and the authors of this study did not support statin use as an adjunct treatment for GCA (23).

In conclusion, although GCA and atherosclerosis share age-related prevalence, inflammatory features, and overlapping clinical manifestations, available evidence does not consistently support a generalised increase in atherosclerotic burden or long-term cardiovascular mortality in patients with GCA. Imaging and epidemiologic studies suggest that vascular complications in GCA preferentially involve large vessels and tend to occur early after diagnosis, likely reflecting active vascular inflammation rather than accelerated atherosclerosis. While antiplatelet therapy initiated after diagnosis may reduce ischaemic complications, and statins appear to modulate vascular inflammation and address lipid abnormalities, their role as disease-modifying adjuncts in GCA remains unproven. Overall, cardiovascular risk in GCA seems to be driven more by inflammatory vascular injury than by classic atherosclerosis, highlighting the importance of optimal control of disease activity and individualised cardiovascular risk management rather than routine use of adjunctive therapies solely for GCA outcomes.

From a clinical perspective, these findings emphasize the need for individualised assessment and management of cardiovascular risk in patients with GCA. Rather than assuming uniform accelerated atherosclerosis, clinicians should focus on early recognition and intensive control of vascular inflammation, careful monitoring for acute ischemic complications, especially at the time of diagnosis, and systematic management of traditional cardiovascular risk factors, tailored to each patient's comorbidity profile and disease activity.

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