Influence of Cervical Crown Contour on Marginal Bone Loss Around Platform-Switched Bone-Level Implants

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Editorial

Aortic involvement in giant cell arteritis

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1. Introduction

Giant cell arteritis (GCA) is the most frequent form of large vessel (LV) vasculitis affecting people over 50 years of age [1]. GCA affects the aorta and its branches (mostly subclavian and axillary arteries, internal, external carotid arteries and its branches, and vertebral arteries). GCA pathophysiology is only partially understood. The current pathogenic model involves both innate immune cells (dendritic cells, monocytes and macrophages) as well as adaptive immune cells (interferon γ and IL-17 producing T cells) [2], and is largely based on studies in temporal artery biopsies. Availability of positron emission tomography coupled to computed tomography (PET-CT) has allowed extracranial forms of the disease to be investigated more precisely. The prevalence of extracranial GCA LV involvement in imaging studies of biopsy-proven GCA patients varies between 30 to 80%, where the latter percentage of 80% matches findings in autopsy studies. Among the extracranial vessels affected in GCA, aorta is the main site of inflammation, followed by the common carotid arteries, the subclavian arteries and the limb arteries [1,3]. GCA patients with extracranial involvement are younger, have a longer diagnostic delay, and more commonly present with overlapping polymyalgia rheumatica (PMR) than patients with isolated cranial GCA [4]. To prevent short- and long-term complications, it is important to investigate aortic involvement, in GCA patients. There is still much to learn about heterogeneity in immunopathology, especially of GCA aortitis, diagnostic strategies in order to reduce diagnostic delay especially in extracranial GCA, and monitoring strategies in order to prevent late-term complications.

2. Immunological and pathological analysis of aorta in GCA

The study of the inflammatory infiltrate in GCA has mainly focused on temporal arteries (TA), as TA biopsies often provide tissue for research (after diagnostic purposes). Besides, analysis of aortic tissue, obtained from GCA patients who underwent aortic aneurysm surgery, provides insight into the structural changes and inflammatory infiltrates in the aorta. However, data on GCA aortitis is still limited and the obtained aorta tissue may reflect a later stage of disease than TA biopsies.

Histologically, GCA aortas are characterized by granulomatous infiltrates in the media, dominated by macrophages that can form giant cells, and by an expansion of the vasa vasorum (Fig. 1) [5,6]. In the media, granulomas surround necrotic areas (the remains of smooth muscle cells and elastic lamina) and produce the tissue destructive protein matrix metallopeptidase 9 (MMP-9) [7], therewith damaging and weakening the vessel wall. The tissue-destructive phenotype of macrophages may be attributed to a specific $CD206^{+}$ subset [8]. The extensive medial and adventitial inflammatory infiltrates distinguish GCA aortas from aortas affected by atherosclerosis, whereby especially the intima and to a lesser extent the adventitia is affected.

The adventitial infiltrate in GCA aortas, which is more pronounced and organized than in atherosclerotic aortas, is dominated by lymphocytes. $CD4^{+}$ T cells in GCA aortas skew to a Th1 and Th17 phenotype after notch-1 and mTORC1 engagement [9]. Recent data imply that this pro-inflammatory response might be inhibited through IL-33 in GCA aortas, promoting a more tissue healing Th2 response to counteract the pro-inflammatory Th1 and Th17 response [10]. In contrast to GCA TA biopsies, B-cells outnumber T-cells in the adventitia of GCA aortas [6]. In the majority of patients, B- and T-cells organize into artery tertiary lymphoid organs (ATLO) with active germinal centers and associated plasma cells, indicating local B-cell activation and proliferation. Often, ATLO were observed opposite to medial granuloma. B-cells and ATLO formation has also been reported in TA biopsies from GCA patients, however to a lesser extent. The mere presence of these structures suggests involvement of humoral immunity, however, a disease-specific antibody has not yet been found in GCA. Nevertheless, B-cells could also contribute to disease pathology through antibody-independent mechanisms, like cytokine production. Differences between TA and aorta infiltration in GCA could be related to differences in expression of pattern recognition receptors and chemokines by tissue-resident cells, leading to a preferential migration of B-cells to the aorta. Alternatively, these differences could reflect different disease stages, with the aortic tissue reflecting late-stage, untreated or insufficiently treated chronic inflammation.

Recent literature demonstrates that aortas, just like TA, are not sterile, but rather contain an extensive microbiome [11]. The aortic microbiome of GCA patients differs from both non-inflamed aortas and GCA TA. Moreover, the expression profile of the autoantigen 14-3-3 was significantly upregulated in GCA aortas compared to

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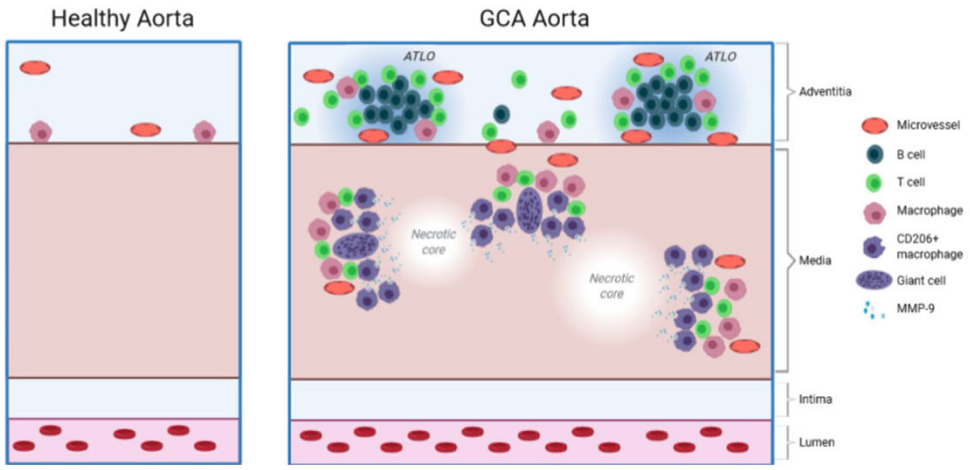

Fig. 1. Immunopathology of GCA in the aorta, based on studies of GCA-related aorta aneurysm. An illustration of the aortic wall, as observed in GCA affected tissues, with the lumen on the bottom. GCA affected arteries rarely show intimal proliferation or inflammation. Rather, accumulations of immune cells are found in the media and adventitia, where they can form granulomas and ATLOs, respectively.

uninflamed aortas [12]. However, like the changes in the microbiome, it is yet uncertain if this autoantigen expression precedes or follows aortic inflammation.

3. Imaging studies of aorta involvement in GCA

In the EULAR recommendations on imaging in LV vasculitis [13], computed tomo-angiography (CTA), magnetic resonance imaging (MRI) and PET-CT (using ^{18}F-fluorodeoxyglucose as a tracer) are the choice procedures to explore LV such as aorta (Table 1). The diagnostic value of these three imaging techniques in GCA has not yet been compared with each other in a prospective study and their use might depend on the local accessibility and expertise.

PET-CT (usually low dose CT) is of great interest in the diagnostic work-up in case of prominent constitutional symptoms, fever or high acute phase reactants of unknown origin for differential diagnosis with infections and malignancies (Table 1). It enables global assessment of the extracranial vessels, and branches from the external carotid artery can also be analyzed. However, its accessibility differs depending on countries and regions, and it remains expensive. To avoid falsely negative scans, initiation of glucocorticoid treatment should be avoided, or at least kept shorter than 3 days, before the PET-CT examination [14]. A standardized grading system is recommended [13,15]. More research is necessary to assess whether adding quantitative scoring, by experienced nuclear physicians and with good reproducibility, aids in monitoring and prognosis of GCA patients.

Aortic CTA imaging may be considered due to its repeatability, excellent spatial resolution and accessibility. Precise conditions are necessary to ensure a good quality (Table 1). Specific protocols for image acquisition are mandatory to ensure proper analysis of the aorta wall. On aortic CT scans, the main definition for aortitis is based on circumferential thickening of the arterial wall, at a distance from atheroma. But the cut-off for this thickening

Table 1
Clinical and biological manifestations suggestive of aortic of large vessel involvement and recommended imaging.

Clinical and biological manifestations	
Clinical	Unexplained fever Asthenia Weight loss Limb claudication or ischemia Mesenteric ischemia Polymyalgia rheumatica Acute aortic syndrome Aortic involvement can be asymptomatic in some cases
Biological	High acute phase reactants
Imaging (should be performed before the start of glucocorticoids or within three days after)	
	^{18}F-fluorodeoxyglucose positron emission tomography coupled to computed tomography: Should include the top of the head and go below the knees Arms should be alongside the body Fasting should be strictly respected with blood glucose < 7 mmol/L
	Aortic computed tomoangiography: multislice CT scanner slice thickness between 0.5 and 1 mm for reconstruction high dosage of iodinated contrast agent (60-120 ml) with a power injector
	Magnetic resonance imaging: T1-wheigted, gadolinium-enhanced sequence with fat suppression (e.g. T1 Turbo Spin Echo with gadolinium injection) With magnetic resonance angiography of aorta 3 Tesla is preferred to 1.5 T MRI scan (low signal and long sequences lead to poor analysis of the vessel wall with 1.5 T MRI scans)

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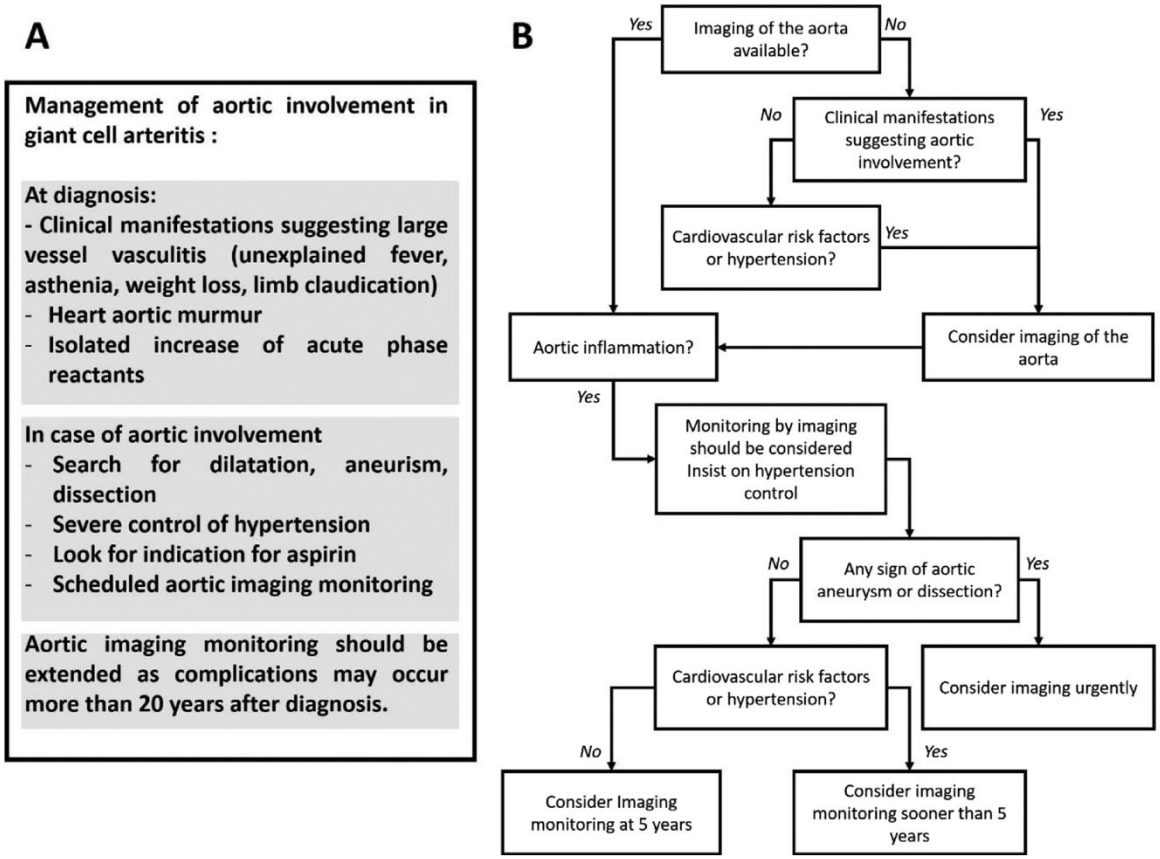

Fig. 2. Aortic involvement management in giant cell arteritis. A. Suggested "to do list" for physicians. B. Imaging should imply suitable computed-tomoangiography, magnetic resonance imaging or ^{18}F-fluorodeoxyglucose-positron emission tomography coupled with computed tomography. Clinical manifestations of aortic involvement include unexplained fever, asthenia, weight loss, limb claudication, high acute phase reactants.

(≥ to 2 or ≥ 3 mm) has been debated in publications. A recent study compared different cut-offs (from 1.5 to 4.2) in GCA patients, PMR patients and healthy controls. According to the authors, the best sensitivity and specificity combination was obtained with a 2.2 mm cut-off with values of 67.19% and 98.18% respectively [16].

Advantages of MRI include the absence of ionized radiation and its ability to identify many aspects of arterial lesions [13]. Recommended sequence to analyze LV inflammation is T1-wheigted, gadolinium-enhanced sequence with fat suppression (e.g. T1 Turbo Spin Echo with gadolinium injection). This method is more sensitive than a single T2-wheigthed non gadolinium-enhanced turbo spin echo sequence. Magnetic resonance angiography of aorta is also recommended for LV assessment. The accessibility of MRI is particularly heterogeneous and will define its usefulness for each particular center. The MRI has less spatial resolution than the CTA.

4. Complications of aortic involvement in GCA

Aortic involvement may lead to severe complications for GCA patients and justifies a close follow-up, especially imaging monitoring. The incidence of aortic aneurysm and aortic dissection is elevated in GCA patients five years after the diagnosis and remains elevated up to 20 years after diagnosis [17]. These complications might reflect the consequences of long-term vascular inflammation, leading to a reduced ability to resist the high pressure milieu of the aorta that eventually causes aortic aneurysm or dissection. More studies are mandatory to sustain this hypothesis. These late-complications are responsible for a significant increase of the standardized mortality ratio (2.63) of GCA patients compared to the general population [17]. Nevertheless, aortic dilatation might be seen at diagnosis but no study is available to evaluate systematically aortic involvement at diagnosis. As ultrasonography is easily available and without irradiation, it might be a powerful tool to screen early aortic complications, but no study evaluates this role so far.

Several patterns of aortic and extracranial involvement have been described, based on imaging: inflammation of the aorta, dilatation of the aorta or stenosis of the aortic branches [18]. The thoracic aorta is the most common site of aneurysms. Inflammation of the aorta and stenosis of the aortic branches were found predictive of cardiovascular events [18]. Classical cardiovascular risk factors (RF) and cardiovascular comorbidities have been associated with an increased risk of complications in GCA. These RF could add to the arterial damage caused by GCA. Hypertension was assigned to be the most important of these RF and a stringent control of the blood pressure in GCA patients, especially with aortic involvement, is recommended [19].

GCA patients with aortitis have more disease relapses, more cardiovascular complications and use a higher cumulative dose of glucocorticoids [4]. These observations may reflect a more difficult disease's control leading to more glucocorticoid use, which in turn favor cardiovascular complications. It may be thus difficult to separate cardiovascular complications caused by GCA from those caused by the side-effects on the glucocorticoid treatment. Moreover, GCA patients with extracranial involvement have a significantly lower aneurysm-free survival rate at 10 years and a lower relapse-free survival rate at 5 years compared to Takayasu's arteritis patients [20]. This might be related to a younger age and a low number of cardiovascular RF of Takayasu's arteritis patients. There are no recommendations available regarding the frequency of monitoring with imaging in GCA.

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5. Practical management of aortic involvement in GCA

Aortic involvement might be underdiagnosed in GCA patients, because this diagnosis does not imply currently imaging of the aorta and clinical manifestations of aortitis are often nonspecific or absent (Table 1). The immunopathology of GCA in the aorta appears to be similar compared to the TA, with macrophages and lymphocytes being the main suspected culprits (Fig. 1). However, other features of the disease (e.g. the dominance of B-cells over T cells in the adventitia) may be specific for the aorta. Currently no criteria are available to select patients that might benefit from aortic imaging. Apart from the patients with clinical manifestations suggesting aortic involvement (Table 1) and depending on the availability of imaging, patients with classical cardiovascular RF (especially hypertension) should be considered for assessment of aorta inflammation at diagnosis (Fig. 2). No recommendations are available for image monitoring in patients with aortic inflammation. In patients with extracranial involvement at diagnosis, apart from patients with clinical manifestations suggesting aneurysm or dissection, imaging control should be performed at least 5 years after diagnosis and findings at 5 years should determine the subsequent rhythm for monitoring. Patients with hypertension and cardiovascular risks factors should be considered for closer monitoring (Fig. 2).

Aortic involvement is an important feature of GCA. Immunopathology of GCA aortitis resembles that of the temporal artery, however some features may be specific for aorta. Monitoring of aorta involvement is currently based on expert opinion. Clearly, long term follow-up data are mandatory for evidence-based guidelines how to monitor aneurysm development in GCA patients at risk.

Disclosure of interest

The authors declare that they have no competing interest.

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