

Large-vessel involvement in giant cell arteritis and polymyalgia rheumatica

F. Muratore, G. Pazzola, N. Pipitone, L. Boiardi, C. Salvarani

Rheumatology Unit, Department of Internal Medicine, Azienda Ospedaliera ASMN, Istituto di Ricovero e Cura a Carattere Scientifico, Reggio Emilia, Italy.

Francesco Muratore, MD*
Giulia Pazzola, MD*
Nicolò Pipitone, MD, PhD
Luigi Boiardi, MD, PhD
Carlo Salvarani, MD

*These two authors made an equal contribution to this work

Please address correspondence to:
Carlo Salvarani,

Rheumatology Unit,
Department of Internal Medicine,
Azienda Ospedaliera ASMN,
Viale Risorgimento 80,
42100 Reggio Emilia, Italy.

E-mail: carlo.salvarani@asmn.re.it

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ABSTRACT

Giant cell arteritis (GCA) and polymyalgia rheumatica (PMR) are closely related disorders that affect people of middle age and older, and frequently occur together. With the widespread use of newer vascular imaging modalities, large-vessel involvement (LVI) has increasingly been recognised in patients with GCA and less often in those with PMR. LVI in GCA can result in complications such as aortic aneurysm and dissection, aortic arch syndrome, and limb arteries stenosis, while vascular complications in PMR are exceedingly rare. It is still controversial which patients should be investigated for LVI, and how LVI should be diagnosed, monitored and managed. In this review, we will try to address six important issues regarding LVI in GCA and PMR.

Introduction

Giant cell arteritis (GCA) and polymyalgia rheumatica (PMR) are closely related disorders that affect people of middle age and older, and frequently occur together. GCA is a systemic vasculitis that typically involves large- and medium-sized arteries (1). While the cranial arteries are commonly involved, giving rise to the classic cranial manifestations of GCA (headache, jaw claudication, scalp tenderness and visual impairment), the large vessels (the aorta and its major branches) can also be affected. In turn, large-vessel involvement (LVI) can result in complications such as aortic aneurysm and dissection, and aortic arch syndrome, while in the limb arteries stenosis is the most common complication (2, 3).

PMR is an inflammatory condition of unknown cause characterised by aching and morning stiffness in the cervical region as well as shoulder and pelvic girdles that swiftly responds to

low doses of glucocorticoids (4). The symptoms of PMR appear to be mainly related to inflammation of peri-articular structures (1). Subclinical vasculitis has been described in isolated PMR (i.e. in PMR without clinical features suggestive of GCA), but vascular complications are exceedingly rare (5-8).

Recently, with the widespread use of newer vascular imaging modalities, LVI has increasingly been recognised in patients with GCA and less often in those with PMR. However, it is still controversial which patients should be investigated for LVI, and how LVI should be monitored and managed.

In this review, we will try to address six important issues regarding LVI in GCA and PMR.

1. How common is large-vessel involvement in GCA and PMR?

Aortic involvement

The reported frequency of aortic involvement in GCA varies depending on the stage of the disease and the investigations used to demonstrate it. In early GCA, aortic involvement has been described in approximately one-half to two-thirds of patients using ¹⁸F-fluorodeoxyglucose positron emission tomography and computerised tomography (9, 10). Studies based on histological evaluations, which tend to include more severe cases with longstanding disease, have also shown aortitis in a significant proportion of patients with GCA. In 1972, a systematic study of the aorta and its branches performed by Ostberg (11) in necropsies from patients with GCA showed that the aorta was involved in 12 out of 13 cases (92.3%). However, such a figure is in all likelihood a gross overestimation of aortic involvement in GCA due to the necroptic design of this survey, which was skewed toward the inclu-

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sion of severe cases. In another, larger histopathologic study based on surgical or necropsy specimens from 72 GCA patients with LVI, Lie found involvement of the ascending aorta in 39% of patients (12). Retrospective population-based clinical studies performed over extended periods of time (20–50 years) have reported a prevalence of 9.5–18% of aortic aneurysmal disease after a median time of 3–6 years from the diagnosis of GCA (2, 13). The incidence of aortic aneurysm and/or dissection was 18.7–18.9 per 1000 person-years in subjects at risk (2, 13). Likewise, a cross-sectional imaging study of 54 patients with GCA (median disease duration 5.4 years) provided evidence of aortic aneurysm or dilatation in 12 patients (22.2%) (14). Taken together, these findings suggest that aortitis is common in GCA, although only a proportion of patients appear to develop clinically overt complications.

Large-vessel involvement

In GCA, the branches of the proximal aorta are commonly involved, in particular the subclavian, axillary and proximal brachial arteries (15, 16), while the branches of the abdominal aorta and the arteries of the lower extremities are less frequently affected (16, 17). The prevalence of LVI is not well defined. In early GCA, the vessels above the aorta appear to be involved in circa one-half to two-third of patients with GCA using PET and CT (9, 10), while at least one-third of patients have evidence of LVI at Colour Doppler sonography (18–21). The variability in the reported frequencies across different studies depend on the technique used, but also on the vascular segments examined and on the criteria chosen to define active disease. In the histological-based studies quoted above, the subclavian or brachial arteries were involved in all 13 cases (100%) of a necroptic series (11), while in the larger study by Lie, histologic evidence of subclavian and axillary arterial involvement was reported in 26% and femoropopliteal arterial involvement in 18% of 72 patients with GCA and LVI (12).

There are more limited data on LVI in patients with isolated PMR.

In a study based on PET, 2 of 35 patients (6%) with PMR had FDG vascular uptake consistent with vasculitis, but uptake intensity was less intense than that observed in GCA (7). Similarly, in another study only 2 of 14 (14%) untreated patients with PMR that underwent PET had increased FDG vascular uptake consistent with vasculitis (8). The clinical significance of these findings is unclear, since overt vasculitic complications in isolated PMR are exceptional.

2. When should large-vessel involvement be suspected in GCA and PMR patients?

Patients with LVI due to GCA can present early on both with the classical cranial manifestations (when the cranial arteries are affected) and with nonspecific constitutional features such as fever and weight loss. In this regard, it has been estimated that up to one-quarter of elderly (>65 yrs) patients presenting with fever of unknown origin (FUO) have an underlying GCA as cause of their complaint, often with LVI (22). Inflammatory markers are virtually always raised. Later on (usually a few years after the onset of the clinical manifestations), symptoms and signs of vascular insufficiency (most commonly in the upper limbs) may become apparent. These include arm claudication, Raynaud's phenomenon, decreased radial pulses, arterial bruits, and discrepancies in blood pressure readings in the arms.

Retrospective and prospective studies that compared GCA patients with LVI to those without have identified a number of characteristics that identify patients with LVI, including a younger age at onset (16, 18), a longer duration of symptoms prior to diagnosis (10, 16, 18), a higher frequency of female gender (16, 18, 19), less frequent cranial symptoms (16, 18, 19) and visual changes (10, 16, 18), and more frequent extremity vascular insufficiency (16, 18). Furthermore, patients with LVI due to GCA have less commonly temporal artery biopsies consistent with vasculitis (58%) (16). In contrast, no differences in the frequencies of constitutional or PMR symptoms and in serum inflammatory markers have been reported.

As a general guide, physicians should think about GCA with LVI in patients older than 50 years presenting with constitutional symptoms not explained by common causes such as tumours and infections, even when cranial symptoms are absent. A careful physical examination looking for signs of vascular insufficiency may also help to recognise this particular subset of GCA, although these signs are not precocious.

Patients with isolated PMR need usually not been monitored for LVI. However, in selected cases of PMR that incur repeated relapses and appear relatively resistant to glucocorticoids, a screen for LVI may be indicated, because a recent study showed evidence of vasculitis at PET scan in 3 of 8 (37.5%) patients with glucocorticoid-resistant PMR (23).

3. How should the diagnosis of large-vessel involvement in GCA and PMR be confirmed?

The diagnosis of LVI requires confirmation by vascular imaging studies, since biopsy is not feasible in the vast majority of cases. Early vascular changes are thought to be represented by inflammatory cell infiltration and thickening of the arterial wall, while luminal changes (stenoses, occlusions, dilations and aneurysms) develop only later on. FDG-PET is able to demonstrate the presence of metabolically active inflammatory cells in the arteries, while Colour Doppler sonography (CDS), computerised tomography (CT) and magnetic resonance imaging (MRI) are all able to demonstrate transmural vessel oedema in early LVI (24). Vessel wall oedema appears as a dark, hypoechoic signal on CDS ("halo sign") and as enhancement of the vessel wall on CT and MRI (24). CDS is best suited to study the arteries above the aorta because of its exquisite power of resolution for superficial vessels (10x higher than that of CT or MRI) (25). On the other hand, enhanced CT and MRI are the procedures of choice to study deep, large vessels (such as the aorta) that are hardly or not accessible to CDS. T2-weighted MRI sequences are less sensitive than enhanced T1-weighted images in detecting vascular inflammation (26), but may be used in patients in whom gadolinium is con-

traindicated. Finally, FDG-PET has the advantage of visualising virtually all arteries potentially involved in GCA (with the exception of the temporal and renal arteries), although it is more expensive and not widely available (27). False positive results can be due to atherosclerotic changes, while false-negative findings may occur in patients on glucocorticoid treatment (24, 28, 29). Smooth and symmetrical vessel alterations point to vasculitis, while spotty, asymmetrical changes would favour an atherosclerotic cause (30).

Digital subtraction angiography showing long segments of smooth arterial stenosis or smooth tapered occlusion has been considered in the past the gold standard for the diagnosis of GCA-related LVI (31). However, while angiography clearly depicts vessel luminal changes, it is unable to demonstrate early vasculitic lesions such as vessel wall oedema and thickening, and is thus not useful to clinch an early diagnosis (24). There is no validated algorithm to dictate the choice of imaging tests in suspected large-vessel arteritis. CDS has been shown to detect LVI of the epiaortic arteries in approximately one-third of patients with GCA (18-21). Because LVI without involvement of the epiaortic vessels is uncommon [15% of cases of GCA-LVI in the study by Prieto-Gonzalez (10)] [N.B. M. Cid personal additional communication], CDS could represent a valuable screening procedure for suspected large-vessel arteritis. However, if CDS is negative or inconclusive and there is a strong clinical suspicion, a second-tier investigation is required. PET is probably the most sensitive technique, not least because of its capacity to delineate inflammatory areas in nearly all large vessels (27). In this regard, a study by Blockman *et al.*, FDG-PET showed increased vascular FDG uptake in 83% of patients with GCA (9). MRI and CT are also a reasonable alternative, provided that most arteries potentially affected by GCA are examined. In a recent study, CT was able to pick up vascular changes judged consistent with arteritis (arterial thickening with or without enhancement) in 68% of 40 untreated (or treated for <3 days) patients with new onset of GCA (10).

4. How to monitor for large-vessel involvement in GCA and PMR during follow-up

Long-term surveillance in patients with GCA is important to monitor for vascular complications. Such monitoring is particularly warranted in patients with evidence of large-vessel arteritis at onset, but even patients without initial large-vessel arteritis may still develop LVI at follow-up (32). CDS, MR combined with angiography (MRA), and CT also combined with angiography (CTA) allow to demonstrate both arterial wall and lumen changes, and are thus theoretically well-suited for following up patients with LVI over time (24). However, resolution of imaging vascular signs considered inflammatory in nature (such as arterial wall oedema and thickening) may lag behind clinical improvement and remission. This holds especially true for arterial wall thickening, which may actually persist indefinitely in some patients with longstanding GCA that have otherwise no evidence of active disease (33). In contrast, in early GCA vessel wall thickening has been shown to improve rapidly following the institution of glucocorticoid treatment (10). It can be speculated that early vessel wall thickening may be due to active inflammation (and thus be responsive to glucocorticoids), while thickening in longstanding arteritis may reflect fibrotic and regenerative changes unaffected by glucocorticoids, but histological proof is lacking to confirm this hypothesis. PET may be more specific than morphological imaging in determining the activity of large-vessel arteritis, but low-grade vascular FDG uptake has also been observed in patients in remission (34). It is unclear at the present whether such low-grade uptake represents smoldering inflammation, tissue remodeling of the vessel wall, or both. DSA is an accurate procedure in defining lumen changes, but no more sensitive than MRA or CTA in the setting of GCA-related LVI (24). Therefore, given that DSA is fraught with more risks than CTA and especially MRA, it should not be routinely used, although it may still have a role in guiding vascular interventional procedures (24).

A basic *caveat* with all imaging studies is that the correlation between vascular inflammation and the subsequent development of anatomical changes in the same vascular segment is quite loose. A PET study mapped increased FDG uptake in the thoracic aorta to the development of aneurysms (35), while in another study MRI vascular inflammatory changes had only a moderate predictive value for the development of anatomical changes in the same arteries (36). In addition, evidence of active vasculitis at PET has not been shown to predict clinical relapses (9). Finally, there is a rather limited correlation between imaging signs, on the one hand, and clinical indices and laboratory parameters, on the other (24, 37).

It has been suggested that patients with GCA may be monitored by annual CDS of the superficial arteries and chest x-rays (to exclude aneurysms of the thoracic aorta) (3). However, MR(A) and/or CT(A) of the aorta should be performed if there is a strong clinical suspicion of aortitis (3). When available, PET may provide information about vascular metabolism that is often used as surrogate for inflammation. However, due to lack of proper imaging-based longitudinal studies, at the present the optimal imaging at follow-up remains a matter of debate.

5. How to treat GCA-related large-vessel arteritis

GCA with LVI should be treated as a rule just as classical GCA, *i.e.* with initial prednisone doses of 45–60 mg per day and subsequent gradual tapering (15). In fact, the Mayo Clinic experience has provided evidence of efficacy for glucocorticoids in GCA-related LVI in most patients, although the data have been collected and reviewed only retrospectively. Arterial bruits and claudication improved in the vast majority of patients (15). No studies have specifically investigated the efficacy of the steroid-sparing agents most commonly used in GCA (azathioprine and methotrexate) in the subset of patients with large-vessel arteritis (38, 39). An exception is a small case series of 5 patients with GCA-LVI, in whom methotrexate at 10-15 mg/week reduced prednisone

requirement from 13 to 8 mg/day, while FDG vascular uptake at PET decreased in all patients (40).

With regard to biological agents, TNF- α inhibitors have not proved efficacious in patients with new onset of GCA (41), while some efficacy has been noted in patients with relapsing disease (42, 43). However, it is unclear how many of these patients had LVI. Recent data (reported in case reports and small series) suggest efficacy of IL-6 blockade with tocilizumab in GCA-LVI (44-46). Altogether, a clinical response was noted in 13 out of 14 patients treated with tocilizumab, while improvement in imaging signs was observed in all 12 patients in whom imaging was performed before and after treatment (47). Therefore, while the limited published data do not allow to make formal recommendations, we suggest that in patients with GCA-LVI that suffer repeated relapses methotrexate or tocilizumab may be given a fair trial.

6. Do patients with GCA and large-vessel arteritis have a different prognosis from those without?

A number of studies have addressed the issue of whether patients with GCA-related LVI differ from those without in terms of morbidity and mortality (2, 13, 48, 49). The leading cause of GCA-related morbidity remains ischaemic complications, especially visual loss. Various reports have demonstrated that patients with LVI have, in fact, a reduced (although by no means abolished) risk of incurring visual loss compared to those without (10, 16, 18). Drug-related adverse events (particularly side effects due to glucocorticoids) also rank high as cause of morbidity in GCA patients with and without LVI (50, 51).

Mortality rates are, broadly speaking, not increased in patients with GCA compared to unaffected individuals (48, 49, 52, 53). However, mortality appears to be significantly increased in the subset of patients who have aortitis (48, 49, 53). Specifically, in a population-based retrospective study Evans *et al.* (53) showed that patients with GCA were 17.3 times more likely to develop thoracic aortic aneurysms and 2.4 times more likely to develop abdominal aneu-

rysm compared to the general population. The risk of aortic dissection was also increased, and occurred both in association with, and independently from the presence of aortic aneurysms. Mortality was significantly greater only in patients with aortic aneurysms or aortic dissection.

Prognostic factors linked to aortic aneurysm or dissection include an aortic insufficiency murmur at the time of GCA diagnosis, hyperlipidaemia, coronary artery disease and a very high ESR in combination with PMR symptoms (2, 3, 13, 49). Hypertension has been identified as risk factor in one (13) but not in other two population-based studies (2, 49). However, it is important to emphasise that even patients without the above mentioned risk factors have still an increased risk of aortic complications. Since aortic aneurysms/dissection are associated with decreased survival, and their incidence continually increases from 3–5 years after GCA diagnosis onward, an annual screening for aortic aneurysm in all patients with GCA has been recommended (see §4). Furthermore, a recent retrospective study has suggested that patients with inflammatory aortic involvement present at onset of GCA could predict a more chronic/relapsing course of GCA, with higher steroid requirement and an increased risk for vascular events in the long term (54).

The survival of patients with GCA-related large artery stenotic complications has been reported to be no different from that of patients with GCA without large artery stenosis (48, 49). The prognosis of LV-GCA was excellent in one retrospective study by Schmidt *et al.*, in which none of the patients with GCA and LVI developed ischaemic complications. All patients with symptoms at baseline improved after therapy, and no patients developed upper extremity ischaemic complications during follow-up. None of the patients required adjunctive immunosuppressive therapy (55). In contrast, a more severe prognosis was reported in the study by Assie *et al.*, in which signs and symptoms of upper/lower extremity vasculitis improved or resolved with medical therapy in 88.8% of patients with GCA and

LVI, and worsened in 11.2%. Upper/lower extremity revascularization procedures was required in 33% of patients (56). On the other hand, published data support the notion that patients with large-artery stenotic complications rarely incur aortic complications (57).

There is no evidence to suggest that patients with isolated PMR and subclinical vasculitis have a higher risk of vascular complications than that expected in the general population.

Conclusions

The availability of increasingly sophisticated imaging techniques has greatly helped to identify patients with GCA and LVI. Although never formally proved in a prospective study, it is likely that early recognition and prompt treatment of LVI may reduce the subsequent development of complications. Because aortic aneurysms and dissection are associated with significant mortality, care should be taken to screen for these rare, but potentially fatal, complications.

Large-vessel vasculitis in isolated PMR is rare and does not seem to be linked to a higher risk of vascular complications.

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