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Lower Extremity Vasculitis in Polymyalgia Rheumatica and Giant Cell Arteritis

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Abstract

Purpose of review—Recent studies suggest that extracranial involvement by giant cell arteritis (GCA) may be more extensive than previously appreciated and clinicians should be aware of this complication.

Recent findings—Imaging studies in GCA and polymyalgia rheumatica (PMR) suggest that vasculitis can affect multiple vascular territories including the lower extremities (LE). The findings of imaging studies, clinical features and outcomes of patients with LE vasculitis are explored in this review. Possible mechanisms for the observed distribution of vessel involvement are discussed.

Summary—LE involvement in GCA and PMR may be associated with significant morbidity and is likely under-recognized clinically. Imaging studies can be useful in identifying this uncommon complication.

Keywords

polymyalgia rheumatica; giant cell arteritis; lower extremity vasculitis

INTRODUCTION

Polymyalgia rheumatica (PMR) is an inflammatory disorder of unknown etiology characterized by symptoms of stiffness and aching in the neck, shoulders, hips and proximal extremities. PMR typically occurs in individuals over the age of 50 years, with a mean age at diagnosis of 72.8 years (1). In a population-based study from Olmsted County, MN, the estimated annual incidence of PMR was 58.7 (95% CI 52.8–64.7) per 100,000 people aged 50 years and above (1). Approximately 16–21% of patients with PMR develop giant cell arteritis (GCA), a systemic vasculitis affecting the aorta and its primary and secondary branches. Conversely, 40–60% of patients diagnosed with GCA have clinical manifestations of PMR.

Like PMR, GCA almost exclusively affects individuals over the age of 50 years with mean age at diagnosis 74.7 years (2). Interestingly, the age at onset of GCA has risen in recent decades (3). The highest incidence rates of GCA occur in Scandinavian countries and in US populations of Northern European ancestry (4). Lower incidence rates have been reported

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for Southern European, Mediterranean and Asian populations(4). In Olmsted County, MN the estimated annual incidence is 18.9 (95% CI 12.4, 25.5) per 100,000 people aged 50 years and above (3).

Aortic aneurysm, dissection and large vessel stenoses are well-recognized complications of GCA and these occur in approximately one-third of patients (5). Until recently, few studies have evaluated the presence and distribution of large-vessel involvement in GCA. Use of ultrasonography and positron emission tomography (PET) in newly diagnosed GCA patients reveal a surprising frequency of large-vessel involvement (6, 7). In addition to aortic arch involvement, vasculitis affecting the LE vessels is often seen on imaging studies. Although clinically significant LE vasculitis appears to be rare in GCA, this can cause significant morbidity and requires prompt detection and treatment (8). Similarly, PET studies in PMR patients may also show subclinical vascular inflammation in patients even when temporal artery biopsy is negative (9) (10). In a recent study, a greater proportion of PMR patients (8%) developed LE claudication and were diagnosed with peripheral arterial disease (PAD) compared to age- and gender-matched subjects (5.3%) (11). Whether the excess PAD in PMR patients is due to accelerated atherosclerosis or subclinical vasculitis is presently unknown. Finally, the predilection of vasculitides like GCA for specific vessels is well recognized though the mechanisms remain unknown (12). A recent study explored toll-like receptor profiles in different vascular beds and found distinct profiles which may provide a plausible mechanism for the observed tissue tropism (13).

The focus of this update is to review radiographic, clinical and basic science studies that have furthered our understanding of LE arterial disease in GCA and PMR.

LARGE VESSEL DISEASE IN GCA

Although the vasculitic process in GCA preferentially involves the extra-cranial branches of the carotid artery, large vessel involvement of the aorta and its primary and secondary branches is a well-known manifestation of GCA (14). In a population-based study from Olmsted County, MN, 27% of GCA patients had incident large vessel involvement (aortic aneurysm/dissection or large artery stenosis) (5). Studies have found that presence of cranial symptoms at GCA diagnosis is negatively associated with large-artery stenosis while younger age and female gender are associated with large-artery disease (5, 15, 16). Overall mortality in patients with large vessel disease from GCA is not increased but patients with thoracic aortic dissection may have higher mortality (17). Several radiologic modalities including computed tomography angiography (CTA), PET, ultrasonography and magnetic resonance angiography (MRA) have been used to image large vessels in GCA but the optimal study remains controversial (18, 19).

Prevalence of LE arterial abnormalities in GCA

Studies using ultrasonography and PET in newly diagnosed GCA patients to assess extra-cranial vasculitis (including LE artery involvement) have been performed (6, 7, 20). Based on these studies, it appears that the prevalence of LE involvement in GCA may be clinically underestimated. In a study of 33 consecutive patients with newly diagnosed GCA, investigators performed systematic ultrasonographic examinations of the abdominal aorta and 15 peripheral arteries including the femoral, popliteal, posterior tibial and dorsal pedal arteries. The findings were compared to 33 age- and gender-matched controls. Ten GCA patients (30%) had characteristic ultrasound findings of inflammation (hypoechoic wall thickening or halo) in arteries other than temporal arteries compared to none of the patients in the control group. Four patients (12%) had abnormalities of arteries in the LE. While atherosclerotic changes were commonly seen in the femoral arteries of both cases and controls, 1 patient had inflammatory changes (halo sign) in the popliteal artery with stenosis.

Additionally, 3 patients with GCA had occlusive changes in the posterior tibial (2 cases) and dorsal pedal (1 patient) arteries while such occlusive changes were not seen in controls (20). In another study, duplex sonography of 11 arterial segments including common femoral, deep femoral, proximal and mid-superficial femoral and popliteal arteries, was performed in 72 subjects with suspected GCA (7). Thirty-eight patients were diagnosed with GCA, 12 (32%) of whom had extracranial involvement. Eight patients (21%) had changes of LE vasculitis including the common femoral artery (3 cases), deep femoral artery (6 cases), superficial femoral artery (6 cases) and popliteal artery (6 cases). Two of the 8 patients with LE vasculitis presented with claudication. Follow-up ultrasound examination at 6 months was available for 9 of the 12 patients and persistent changes of vasculitis were present in nearly all cases including 7 patients with LE involvement at baseline (7). Finally, a study using PET scans in 35 consecutive patients with GCA, found vascular fluorodeoxyglucose ((FDG) uptake in 83%. The most common site of FDG uptake was the subclavian arteries (26 patients, 74%) but LE uptake was noted in 37%. This included the iliac arteries (13 patients, 37%) and femoral arteries (13 patients respectively, 37%). Repeat PET scan performed at 3 months and 6 months showed persistent vascular FDG uptake in 14 and 8 patients respectively (6).

Although the above studies included small numbers of GCA patients, they clearly demonstrate changes of vasculitis in a significant proportion of patients with GCA (depending on imaging modality used). This includes subclinical, often asymptomatic LE vasculitis in 12–37% patients with newly diagnosed GCA. Additionally, based on the limited follow-up information, it appears that the vessel wall changes noted by ultrasonography or vascular uptake on PET may persist despite treatment with corticosteroids. Uncertainties continue to exist regarding the long-term significance of the findings.

Clinical features of LE vasculitis in GCA

Radiographic imaging studies suggest that GCA can involve the LE vessels and may not be as rare as previously thought. Histopathology has shown changes of GCA in LE arteries in some cases (21–23). In a series of 72 cases with histopathologic confirmation of aortic and extra-cranial large vessel disease from GCA, there were 13 cases (18%) with LE vasculitis (23). Femoral arteries were the most commonly involved (6 cases), followed by femoropopliteal arteries (4 cases) and popliteal arteries (3 cases). Extra-cranial large-vessel GCA had similar histopathologic features to that seen in the temporal arteries and showed a lymphocytic panarteritis with variable number of giant cells (23).

On the other hand, clinically significant, symptomatic LE arterial involvement in GCA appears to be rare. In a population-based study of 168 GCA patients there were 46 cases of large-artery complications; only one patient (0.6%) had LE stenotic disease attributed to GCA (5). Given its rarity, studies of symptomatic LE disease from GCA are confined to case reports and case series (8, 24, 25). However, this complication of GCA is very important to distinguish from the more common LE atherosclerotic disease given its morbidity and potential improvement with glucocorticoid therapy. We recently described 19 GCA patients (all women) with LE vasculitis seen over a 24.5 year period at a single institution (8). In 16 patients (84.2%), symptoms of LE claudication preceded the diagnosis of GCA by a median of 3 months. As has been noted in prior studies of patients with LE vasculitis from GCA (24, 25) approximately half the patients in this series did not have any cranial symptoms to suggest GCA (8). Thirteen subjects had a positive temporal artery biopsy and in 2 patients, there was evidence of arteritis on surgical pathology (8). Strikingly, 7 patients had no traditional cardiovascular risk factors. Imaging studies were available in 84% cases and showed smooth, long segments of tapered stenosis which is a more characteristic finding of vasculitis (Figure). The superficial femoral artery was the most

commonly involved (13 patients) followed by the popliteal artery (12 patients) and bilateral involvement was common. All patients were treated with corticosteroids but in spite of treatment, 2 patients required revascularization surgery, 2 patients underwent limb amputation and 1 patient underwent toe amputation. Additionally, five patients received other immunosuppressive agents (8).

It is important to consider LE vasculitis in elderly patients with rapidly progressive LE claudication who have few traditional risk factors for atherosclerotic disease. Since this is a rare clinical manifestation of GCA, it is possible that cases of LE vasculitis are misclassified as atherosclerotic PAD which is more common in this age group. Imaging studies can be very useful in making the diagnosis especially when typical findings of vasculitis are observed. Prompt diagnosis and treatment is important but morbidity remains high. Clinicians should be aware of this rare complication of GCA. GCA patients should be questioned about symptoms of LE claudication with appropriate evaluation pursued when indicated.

VASCULITIS IN PMR

PMR and GCA are closely related conditions. Approximately one-fifth of patients with PMR have large-vessel vasculitis (GCA) which can involve the LE. Furthermore, PMR patients without clinically overt GCA may frequently have subclinical vasculitis. Indeed, Weyand *et al*. demonstrated the presence of macrophage- and T-cell-derived cytokines in temporal artery biopsy specimens from patients with PMR but without arteritis (26).

LE vasculitis in PMR

Recent studies using PET scans in newly diagnosed PMR patients show vascular uptake of FDG suggesting vasculitis even in cases without clinical suspicion for GCA. In an early study of PET in 5 patients with PMR (temporal artery biopsy negative), Blockmans *et al*. found increased uptake in PMR including 2 patients with uptake in the arteries of the LE (27). Moosig and colleagues evaluated vascular FDG uptake in 13 patients with untreated PMR. All subjects underwent duplex ultrasound of the temporal arteries with biopsy being pursued only in the presence of abnormalities. Three patients had a positive temporal artery biopsy. The study also included 6 control patients with other inflammatory conditions. Compared to controls, PMR patients had increased vascular uptake of the aorta or its major branches suggesting vasculitis (9). The findings were consistent with earlier observations made by Blockmans *et al*. Recently, a larger study was performed using PET in 35 patients with newly diagnosed PMR. Thirty of the patients had a temporal artery biopsy performed which was negative. Vascular uptake was present in 31% patients with subclavian arteries being most frequent (11 patients). Iliac artery uptake was present in 2 patients and 1 patient had FDG uptake in the femoral vessels (10). In summary, PET scan may reveal subclinical changes of vasculitis in patients with PMR and no symptoms or biopsy findings of GCA.

Clinically, patients with PMR have a higher risk of developing LE claudication. The incidence of PAD in PMR patients has been evaluated using a population-based cohort of 353 PMR patients from Olmsted County. The study included a comparison cohort of age- and gender-matched subjects from the same geographic region. Even after adjusting for hypertension, dyslipidemia and diabetes mellitus, PMR patients were at increased risk of developing PAD compared to the referent cohort (HR 2.50; 95% CI 1.53–4.08). There was no association between concurrent GCA and PAD. Survival in PMR patients with PAD was similar to PMR patients without PAD (11). The underlying mechanisms of the observed increased risk in PMR patients remain unknown. One possibility is subclinical vasculitis of the LE arteries. Alternatively, PMR patients may have a higher risk of accelerated atherosclerotic disease due to chronic inflammation, a key factor in the pathogenesis of

atherosclerosis (28). Patients with other chronic inflammatory diseases such as rheumatoid arthritis are known to have a higher risk of coronary artery disease as well as noncardiac vascular disease (29).

In summary, PMR patients may have increased LE claudication symptoms and a higher incidence of clinical PAD. Whether this is from accelerated atherosclerosis due to inflammation or subclinical vasculitis is unknown. Diffuse vascular uptake including FDG uptake in LE arteries on PET imaging of newly diagnosed PMR patients has been well-described even in the setting of a negative temporal artery biopsy. While this suggests subclinical vasculitis in a subset of PMR patients, the significance of the findings, its consequences or the implications for long-term outcomes in these patients remain unknown. Additionally, the presence of atherosclerosis may confound the interpretation of PET scans (19). Inflammatory infiltrates in atherosclerotic vessels may exhibit low grade FDG uptake which may be difficult to distinguish from subclinical vasculitis. However, the distribution of FDG uptake (subclavian arteries) and decrease in FDG uptake after treatment suggest that the findings from reported studies are likely due to subclinical vasculitis. In general, the role of PET scan in the evaluation of patients with PMR remains investigational.

BASIC SCIENCES DISCOVERY

The predilection of vasculitis for certain vessels is known but the mechanisms for the pattern of involvement are poorly understood. GCA appears to preferentially involve the thoracic aorta and aortic arch branches. A recent study may shed some light on the above observations (13).

Dendritic cells (DC) are specialized antigen-presenting cells and function as immuno sensors of the local environment. In human macrovessels, DCs are present and are located in the media-adventitial border and are important antigen-presenting cells in GCA (30) (31). DC activation via specific toll-like receptor (TLR) types has been shown to induce distinct types of vasculitis (32). Through a series of experiments, Pryshchep and colleagues studied the TLR profiles from the following human arteries: temporal, carotid, subclavian, mesenteric, iliac and thoracic aorta. They found that while TLR2 and TLR4 were expressed in all 6 vessel types, TLR1, TLR3, TLR5, TLR6 and TLR8 expression varied by the vessel type and that the arteries have different TLR profiles. The greatest difference in TLR profile pattern and expression was between the subclavian and the iliac vessels (13). The findings are intriguing and suggest a possible explanation for the tropism observed in vasculitides like GCA.

CONCLUSION

While symptomatic LE vasculitis is rare, imaging findings suggesting vasculitis of the LE arteries have been observed at diagnosis in PMR and GCA. Symptoms of claudication, including LE claudication should be included in the routine evaluation and follow-up of PMR and GCA patients. Further longitudinal studies to determine the correlation of the imaging findings to potential long-term clinical consequences will be of great importance. Other questions that warrant further investigation are whether all GCA patients should be systematically screened for extra-cranial disease, and which would be the best and most cost-effective imaging modality to evaluate disease extent. Eventually, ‘disease staging’ according to extent and severity of vasculitis may allow for a more tailored approach to therapy.

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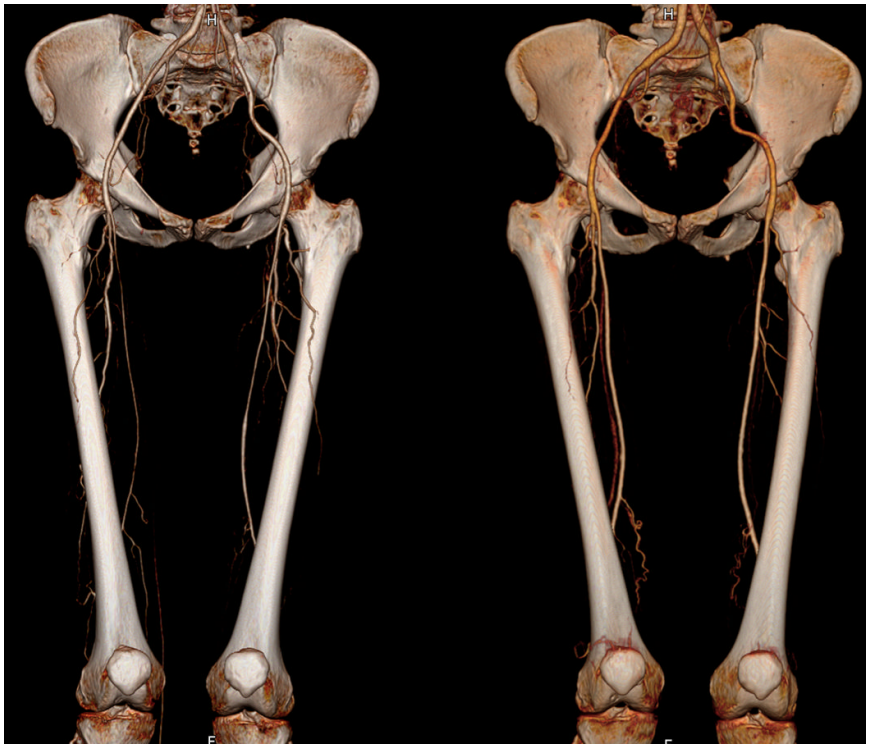

Figure 1.
Three dimensional CT-angiogram reconstruction images in a GCA patient with LE vasculitis shows smooth narrowed tapering of both superficial femoral arteries (A). After corticosteroid treatment there was marked improvement with minimal residual stenosis (B).