Editorial

Polymyalgia rheumatica: when should we suspect an underlying large-vessel vasculitis?

M.A. González-Gay[1,2,3], E.F. Vicente-Rabaneda[4], E. Heras-Recuero[1], S. Castañeda[4,5]

[1]RheumatologyDivision, IIS-Fundación Jiménez Díaz, Madrid, Spain;
[2]University of Cantabria, Santander, Spain;
[3]Cardiovascular Pathophysiology and Genomics Research Unit, School of Physiology, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa;
[4]Rheumatology Division, Hospital de La Princesa, IIS-Princesa, Universidad Autónoma de Madrid (UAM), Madrid, Spain;
[5]Catedra UAM-Roche, EPID-Future, Department of Medicine, Universidad Autónoma de Madrid (UAM), Madrid, Spain.

Miguel Ángel González-Gay, MD, PhD
Esther F. Vicente-Rabaneda, MD, PhD
Elena Heras-Recuero, MD
Santos Castañeda, MD, PhD

Please address correspondence to:
Miguel Ángel González-Gay
Rheumatology Division,
IIS-Fundación Jiménez Díaz,
Av. de los Reyes Católicos 2,
28040, Madrid, Spain.
E-mail: miguelaggay@hotmail.com

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Polymyalgia rheumatica (PMR) is an entity characterised by the presence of intense pain and stiffness that involves the shoulder and hip girdles, the neck, and the proximal arms bilaterally (1, 2). The pain is usually of recent onset and the clinical spectrum of manifestations generally develops acutely in a few days (1, 2). Therefore, the clinical suspicion of PMR is not difficult when the typical spectrum of manifestations is present (3).

PMR can present as an isolated condition. However, it is frequently seen in association with giant cell arteritis (GCA), a vasculitis involving middle and large vessels (4). In fact, although PMR is 2 to 3 times more common than GCA (5, 6), these conditions are often superimposed entities that occur in people 50 years of age or older, predominantly those of European origin (5, 6). About 40-50% of patients who have been diagnosed with GCA also have manifestations of PMR (4, 5). However, PMR can precede clinically evident GCA, being in this case the first manifestation of the disease (4). In this sense, ischaemic manifestations of GCA may appear during the follow-up of some patients diagnosed with isolated PMR, especially when the dose of glucocorticoids has been reduced or discontinued (4, 5, 7). In addition, the use of imaging techniques has revealed that up to a third of patients with isolated PMR may have subclinical inflammation of the large vessels (LV) (1, 8). In this sense, imaging techniques such as ultrasonography (US) and positron emission tomography/computed tomography with Flourine-18 fluorodeoxyglucose (18F-FDG PET/CT) have allowed us to broaden the clinical idea of the spectrum of GCA. Thus, GCA is not just a cranial "temporal" LV vasculitis limited to branches of the carotid artery (9, 10), but is often an extracranial LV vasculitis that in some cases is not associated with cranial ischaemic manifestations (11, 12). Therefore, although cranial and extracranial LV vasculitis involvement often coincides in the same patient, we can now define two well-differentiated phenotypes based on the predominance of cranial arteritis manifestations or the absence of these characteristics in patients with extracranial LV vasculitis involvement confirmed by imaging techniques (11, 12). Indeed, as noted by experts in the field, patients with the predominant pattern of extracranial LV vasculitis tend to be younger, often had a longer duration of symptoms before GCA diagnosis, have more disease relapses and generally need a longer duration of treatment, and, of particular relevance, they exhibit PMR manifestations more frequently than those with the predominantly cranial GCA phenotype (13). Therefore, PMR may constitute an alarm sign for the potential presence of an underlying LV vasculitis.

At this point, it is worth asking whether we are currently capable of identifying or predicting the presence of LV vasculitis in patients with isolated "pure" PMR and how to do it. Supporting a pessimistic view is an interesting study reported by Camellino *et al*. (14). They evaluated 84 patients with PMR, without clinical signs of GCA. Patients underwent a standardised clinical examination and FDG-PET/CT. They also assessed FDG-PET/CT data from 84 people aged 50 years or older who underwent FDG-PET/CT for suspected malignancy that was not confirmed by examination (14). Interestingly, PMR patients showed greater vascular uptake than controls in all vessels except the carotid arteries, when assessed by visual scoring. More importantly, PET/

CT demonstrated the presence of LV vasculitis in 42 of the 84 patients with PMR. However, Camellino *et al*. did not find a significant correlation between clinical findings and FDG vascular uptake. According to them, neither clinical nor laboratory findings can predict the presence of LV vasculitis in patients with isolated PMR (14).

More than 20 years ago, when the use of imaging techniques for the diagnosis of GCA was not widespread, we set out to establish possible differences between isolated PMR and PMR associated with GCA (15). To do this, we compared 117 patients with isolated PMR without any clinical characteristics to suspect GCA with 45 patients with biopsy-proven GCA associated with PMR. Patients with isolated PMR were younger (70.7 *vs*. 74.3 years) and had less commonly constitutional syndrome (45% *vs*. 71%). The differences were more evident when laboratory markers of inflammation were compared. In this sense, patients with isolated PMR had higher mean haemoglobin values (12.6 versus 11.6 g/dl), and lower mean platelet count and erythrocyte sedimentation rate (ESR) values (318,000 *vs*. 429,356 platelets/mm^3 and 65 versus 91 mm/1st hour, respectively) than those with biopsy-proven GCA associated with PMR (15). Therefore, it is possible that a more severe inflammatory response could be a clue to help us suspect underlying LV vasculitis in patients presenting as isolated PMR.

The EULAR working group recommends performing an early imaging test in patients with suspected LV vasculitis. They have positioned the US as the first imaging technique to be used in patients with suspected GCA, pointing out that CT or PET can be used as an alternative (16). These experts also indicate that in case the diagnosis is still uncertain after initial clinical examination and US, further investigations can be brought about, including temporal artery biopsy and/or additional imaging (16). In our experience, the yield of a temporal artery biopsy to identify subclinical GCA in PMR is low, since we only found 8 (9%) positive temporal artery biopsies for GCA in 89 patients with isolated PMR in whom temporal artery biopsy was indicated based on the presence of constitutional symptoms and/or an ESR higher than 80 mm/1st hour (4). In contrast, we support the use of alternative imaging techniques, particularly PET/CT in patients with isolated PMR and involvement of the pelvic girdle or with the presence of atypical symptoms, such as inflammatory low back pain or bilateral diffuse pain in the lower extremities (Table I), because these clinical findings were predictive of an underlying LV vasculitis in our patients at the time of PET/CT evaluation (17). However, in our study, 18F-FDG PET/CT yielded negative results for LV vasculitis when performed due to unexplained marked elevation of C-reactive protein or ESR that was not associated with manifestations of PMR (17).

Table I. Proposed potential red flags for suspicion of large-vessel vasculitis in patients presenting with isolated polymyalgia rheumatica*.

Clinical and/or laboratory features
Inflammatory low back pain
Marked pelvic girdle involvement
Bilateral diffuse pain in the lower extremities
Presence of a marked inflammatory response revealed by abnormalities in any of the following laboratory tests:
ESR greater than 80-90 mm/1st hour
Thrombocytosis
Marked anaemia (haemoglobin value lower than 11 g/dl)
Inadequate (incomplete) response to 20 mg/day of prednisone

*In these cases, consider performing imaging techniques, especially ultrasonography and positron emission tomography/computerised tomography (PET/TC).

Regarding the presence of pain in the lower extremities, it is important to highlight that it has been reported as a consequence of the involvement of the femoral and tibial arteries in the context of LV vasculitis (18). In this sense, we described the presence of LV vasculitis in the lower extremities in a 63-year-old woman, who initially had with typical PMR features, started to complain of diffuse lower limb pain and intermittent vascular claudication associated to persistent pelvic girdle pain when prednisone dose was tapered. Besides typical bursitis in the setting of PMR demonstrated by ^{18}F-FDG PET/CT in the shoulders and cervical and lumbar interspinous spaces, trochanteric and ischiatic regions of both hips, a PET/CT also showed the presence of LV vasculitis with increased ^{18}F-FDG uptake involving the femoral arteries (17).

A systematic review and meta-analysis on the prevalence of subclinical GCA in patients with new-onset PMR, which included studies in which different techniques had been used for the detection of GCA, revealed a higher prevalence of subclinical GCA with PET/CT (29%) than with temporal artery biopsy (20%) or ultrasound (15%) (19). However, efforts to create a predictive model of subclinical GCA using those variables that had shown an association in the univariate analysis (inflammatory low back pain, absence of lower limb pain, female sex, temperature >37ºC, weight loss, platelet count, and haemoglobin) yielded poor results as the diagnostic accuracy of this predictive model was modest (area under the curve 0.66) (19).

Certainly, we need more studies to establish the best predictors of GCA in patients presenting with isolated PMR. Meanwhile, we proposed potential red flags for suspected LV vasculitis in patients with isolated PMR (Table I). In patients with these characteristics, imaging techniques can be considered, especially US and PET/CT (20). Furthermore, since severe ischaemic manifestations of GCA can occur in patients who present as isolated PMR, we recommend periodic evaluation of patients with PMR for early identification of the onset of ischaemic manifestations of GCA.

Competing interests

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