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Subclinical giant cell arteritis in polymyalgia rheumatica: Concurrent conditions or a common spectrum of inflammatory diseases?

Carlo Salvarani [a], Roberto Padoan [b,*], Luca Iorio [b], Alessandro Tomelleri [c], Benjamin Terrier [d], Francesco Muratore [a], Bhaskar Dasgupta [e]

[a] Rheumatology Unit, Azienda USL-IRCCS di Reggio Emilia and Università di Modena and Reggio Emilia, Reggio Emilia, Italy
[b] Rheumatology Unit, Department of Medicine DIMED, University of Padova, Padova, Italy
[c] Unit of Immunology, Rheumatology, Allergy and Rare diseases, IRCCS San Raffaele Hospital, Milan, Italy
[d] Department of Internal Medicine, Hôpital Cochin, AP-HP, Paris, France
[e] Anglia Ruskin University, Chelmsford, United Kingdom

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ABSTRACT

Giant cell arteritis (GCA) and polymyalgia rheumatica (PMR) are common conditions in older adults. Their clinical connection has been recognized over time, with many patients experiencing both conditions separately, simultaneously or in temporal sequence to each other. Early GCA detection is essential to prevent vascular damage, but identifying subclinical GCA in PMR patients remains a challenge and routine screening is not standard practice. Subclinical GCA prevalence in newly diagnosed PMR patients ranges from 23 to 29%, depending on the screening method. Vessel wall imaging and temporal artery biopsy can detect subclinical GCA. Epidemiology and trigger factors show similarities between the two conditions, but PMR is more common than GCA. Genetic and pathogenesis studies reveal shared inflammatory mechanisms involving dendritic cells, pro-inflammatory macrophages, and an IL-6 signature. However, the inflammatory infiltrates differ, with extensive T cell infiltrates seen in GCA while PMR shows an incomplete profile of T cell and macrophage-derived cytokines. Glucocorticoid treatment is effective for both conditions, but the steroid requirements vary. PMR overall mortality might be similar to the general population, while GCA patients with aortic inflammatory aneurysms face increased mortality risk. The GCA-PMR association warrants further research. Considering their kinship, recently the term GCA-PMR Spectrum Disease (GPSD) has been proposed.

1. Introduction

Giant cell arteritis (GCA) is the most common primary vasculitis, presenting with wide-ranging symptoms such as cranial manifestations, peripheral vascular claudication, constitutional symptoms, and muscle or joint pain. Polymyalgia rheumatica (PMR) is an inflammatory disorder that occurs more frequently than GCA, being the most common inflammatory rheumatic disease in people over the age of 50 years [1–3].

About half of GCA patients experience polymyalgia either at diagnosis or during relapse, while about a fifth may have a history of PMR before the onset of GCA [3]. Both conditions are quintessential conditions of older adults, characterized by elevated inflammatory markers, particularly C-reactive protein (CRP). These diseases were initially described separately, but their clinical and epidemiologic connection was slowly appreciated over the years. The failure to connect these syndromes at first was likely due to the differences in the typical manifestations of the two conditions. The "one disease" hypothesis of "polymyalgia arteritica" was postulated in 1964 by Hamrin and Colleagues, observing that, in phenotypical PMR, of the 21 biopsies of the temporal artery, 12 (57%) showed giant-cell arteritis and 4 (19%) non-specific inflammation of varying severity [4].

The relationship between PMR and GCA is complex, with a significant percentage of patients having both conditions. Some isolated PMR cases may show signs of subclinical GCA upon biopsy, but most do not. The prevalence of subclinical GCA in newly diagnosed PMR patients has emerged as 23–29%, primarily due to various imaging modalities [5,6].

Subclinical GCA can be detected through vessel wall imaging whereas temporal artery biopsy (TAB) has limited sensitivity [7]. Ultrasound and PET/CT scans offer better diagnostic accuracy, especially

* Corresponding author at: Rheumatology Unit, Department of Medicine DIMED, University of Padova, Via Giustiniani 2, 35128 Padova, Italy.
E-mail address: roberto.padoan@unipd.it (R. Padoan).

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for extra cranial large vessel GCA. However, routine screening for subclinical GCA in PMR patients is not considered standard of care in most clinical setting.

GCA and PMR share similarities and differences in terms of epidemiology, ethnicity, and trigger factors. Environmental and genetic factors likely play a role due to the decreasing incidence from north to south [8]. Pathogenesis studies revealed that both diseases involve dendritic cells and pro-inflammatory macrophages, and show an interleukin (IL)-6 signature [9].

Early detection and treatment of GCA are crucial due to associated acute and chronic vascular and ischemic complications [5], however diagnosing subclinical GCA in PMR without imaging can be challenging. In PMR patients with undetected subclinical GCA, standard glucocorticoid PMR treatment may not be sufficient to prevent these complications. This remains a major problem since most PMR is managed in primary care.

There is a need to determine the true prevalence of subclinical GCA at the onset of PMR with proactive disease stratification to better understand if they represent different expressions of the same disease or independent conditions.

In the present review we will discuss converse perspectives on this unsolved problem: "co-occurrence of different disease" supported by Carlo Salvarani, or "common spectrum of inflammatory disease" supported by Bhaskar Dasgupta.

2. Co-occurrence of different diseases

2.1. Relationship between PMR and GCA

There is a strong relationship between PMR and GCA. Population-based studies showed that 16% to 21% of patients with PMR have GCA and PMR is present in 40% to 60% of patients with GCA. Furthermore, PMR might begin before, appear simultaneously with, or develop after the clinical manifestations of GCA [10–13].

On the other hand, isolated/pure PMR exists. In 15%–20% of patients with isolated PMR, TAB showed inflammatory lesions of GCA [12,13]. In the Lugo region, only 8/89 (9%) of patients with isolated PMR with constitutional symptoms and/or ESR > 80 mm/h had inflammatory changes resembling GCA at TABLE [1]. Cantini et al. reported that, during the period from 1996 to 2000, 12 of 76 (16%) PMR patients from Prato, Italy, had histologic evidence of GCA [14]. However, only one (1.3%) of these 76 PMR patients had a positive TAB without any clinical features of GCA. In the remaining 11 PMR patients, cranial manifestations of GCA were present at the time of the biopsy. Therefore, most patients with isolated/pure PMR have no evidence of GCA at TAB. These findings may be correct since the incidence of cranial GCA (the type detected by TAB) may be low in isolated PMR. A systematic literature review and metanalysis was performed to determine the prevalence of subclinical GCA in steroid-naïve, newly diagnosed PMR patients without cranial or ischemic symptoms [15]. Thirteen studies, including 566 PMR patients, were examined. Subclinical GCA was diagnosed by TAB in 3 studies, by ultrasonography (US) in 3, and by 18-fluorodeoxy-glucose positron emission tomography (^{18}F-FDG PET) in 7. The pooled prevalence of subclinical GCA across all studies was 23% for any screening method and 29% in the studies using ^{18}F-FDG PET.

This metanalysis confirmed that, independent of the screening method used, three quarters of patients with isolated/pure PMR don't have subclinical GCA. Also using PET, probably the most sensitive imaging technique to detect large vessel involvement, only 29% of patients with isolated PMR had large vessel vasculitis (LVV).

2.2. Epidemiology, ethnicity and trigger factors

Regarding epidemiology, there are similarities but also differences between GCA and PMR. The similarities are the following: 1) the incidence of both diseases increases after the age of 50 and peaks between 70 and 80 years of age; 2) the reported rates for both diseases are highest in northern European countries and in people with a strong Scandinavian ethnic background and lowest in Arabian and Asian countries; 3) women are affected 2 to 3 times more commonly than are men [10–12,16,17]. The decreasing incidence of GCA and PMR with a north–south gradient supports the role for both environmental and genetic risk factors.

The apparent differences are the following: 1) PMR is 2 to 3 times more common than GCA; 2) a cyclic pattern of yearly incidence rates, suggesting an environmental-infectious aetiology, was reported by some studies in GCA but not in PMR [10–12].

Several infectious agents, particularly viruses (parvovirus, human parainfluenza virus type 1, varicella-zoster virus), have been investigated as possible triggers of PMR and GCA with inconclusive results [12,18–21].

2.3. Genetic factors

The distribution of HLA-DRB1 alleles in PMR resembles that found in GCA. Weyand et al. showed that PMR and GCA share the associated sequence polymorphism encoded by the second hypervariable region (HVR) of the HLA-DRB1 gene [22]. Differently, rheumatoid arthritis is linked to a sequence motif in the third HVR of DRB1 alleles. However, studies in different populations suggested that the HLA-DRB1 alleles associated with susceptibility for developing PMR and GCA are different [23,24]. Lack of association between any DRB1 alleles and isolated PMR was found in some studies [25,26]. Furthermore, GCA and PMR were associated with different TNF microsatellite polymorphisms [27]. The differences between these studies might reflect not only the different genetic background of the two conditions, but also differences in the populations that have been studied, study design or in patient selection criteria.

2.4. Pathogenesis

There are many similarities in the pathogenesis of PMR and GCA, but there are also differences. Dendritic cells play an important role in triggering the inflammatory response in the arterial wall in GCA and probably also in the synovium of PMR patients [28]. There is a predominance of pro-inflammatory macrophages in GCA inflamed arteries and PMR synovium [28,29]. Activated vascular dendritic cells were observed by Weyand's group in TABs of patients with isolated PMR, in the absence of vascular inflammation [28].

There is a predominant IL-6 signature in both conditions, and there is an expansion of circulating myeloid cells (monocytes and neutrophils) as well as IL-17 producing T cells (T helper 17 cells and T cytotoxic 17 cells) observed in peripheral blood of PMR and GCA patients [29–31].

However, there are also differences in the inflammatory infiltrates: inflamed arteries in GCA patients are characterized by extensive infiltrates of T helper 1 and T helper 17 cells, while T cell infiltrates in PMR synovium are limited, with most of these cells being T helper 1 cells [32–34]. Finally, Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF) expressing macrophages are seen both in PMR synovium and inflamed arteries in GCA [35].

2.5. Pathology

>10 years ago Meliconi et al. evaluated leukocyte infiltration in synovial tissue from the shoulder of patients with PMR [34]. The main lesion was a mild-to moderate synovitis. Differently from rheumatoid arthritis, relevant lining layer hyperplasia was absent. Infiltrating cells were predominantly macrophages and CD 4 T cells. There was intense expression of HLA class II antigens (predominantly DR) in macrophages and lymphocytes, indicating activation, and an absence of synovial vasculitis. More recent work using ultrasound driven bursal, synovial and tenosynovial biopsies added to our understanding of tissue

inflammation in PMR with contribution of pathogenic TH1 and TH17 cells to the inflammation and tissue expression of interleukin-6 [33,36].

GCA is a vasculitis characterized by transmural lympho-monuclear infiltrate and interruption of the internal elastic laminae. Giant cells are present in 50–60% of the inflamed biopsies [37].

2.6. Differences between isolated PMR and PMR associated with GCA

There are very few studies comparing clinical differences between isolated PMR and PMR associated with GCA [38–40]. In these studies, GCA was excluded by a negative temporal biopsy or ultrasound, or by absence of GCA features during the follow-up. Patients with isolated PMR were significantly younger, they had a lower frequency of asthenia, anorexia, and weight loss, a shorter duration of morning stiffness, and less frequently reported hip pain compared to those with PMR associating GCA. Furthermore, they seemed to have a milder inflammatory disease as shown by the lower values of ESR and CRP. In a recent ultrasound study, PMR with subclinical GCA showed a predominant extracranial large vessel pattern of vasculitic involvement, while patients with PMR associating classical GCA showed a pattern of vessel involvement similar to classical GCA without PMR [40]. This suggests studies are required to urgently understand the stratification of both PMR and GCA to understand the eventual outcomes in these diseases.

2.7. Treatment and outcomes

There are several similarities in the treatment and outcomes: glucocorticoid (GC) therapy response, response to IL-6 inhibitors but not to TNF-blockers, high rate of flares, particularly reducing too quickly GC therapy, and high rate of GC side effects [12,13,41]. However, there are also differences. Giant cell arteritis and PMR have different steroid requirements, a prednisone dose of 10 to 20 mg/day may improve polymyalgic manifestations but it does not decrease the risk of permanent visual loss in biopsy-proven GCA patients [12,13,42,43]. Overall polymyalgia rheumatica mortality is considered similar to that of control population, while there is an increased mortality in GCA patients developing aortic inflammatory aneurysms [12,13]. Specific mortality of more severe disease such as GCA with sight loss or PMR with LVV remains to be established.

3. A common spectrum of inflammatory diseases

The current literature evidence strongly indicates the presence of subclinical vasculitis in PMR. Lavado-Pérez et al. used ^{18}F-FDG PET/CT for the detection of LVV in patients with PMR [44] and Prieto-Peña et al. reported predictors of positive ^{18}F-FDG PET/CT-scan for LVV in persistent or relapsing polymyalgia rheumatic patients [6]. In the ultrasound study by De Miguel and Colleagues, in 346 patients with PMR the prevalence of subclinical GCA in PMR was 22.8% within which LVV subtype was most frequent although cranial arteritis was also seen in 10% of the cases [40].

It therefore appears that LVV is seen in at least 22–25% of PMR. The burning question is which patients with PMR may have LVV? According to current evidence and our clinical view LVV should be suspected in relapsing PMR, PMR with systemic inflammation, prominent constitutional symptoms, low-back pain, incomplete response to safe doses of glucocorticoids, high steroid-dependency and in upper limb claudication which may be hard to distinguish from shoulder girdle pain. These sub-features on PMR were originally outlined in the 2009 British Society for Rheumatology (BSR) and British Health Professional in Rheumatology (BHPR) PMR guidelines for the management of polymyalgia rheumatica as indications for specialist referral and further imaging [45]. There is a special health economic benefit with early diagnosis of LVV in these cases to introduce targeted therapy with disease-modifying anti-rheumatic drugs (DMARDS) and biologic-DMARDS to prevent vascular damage (such as aortic aneurysms, arterial stenosis, and aortic dissection) and spare glucocorticoid toxicity.

It is therefore now time to embrace the concept that these are non-monolithic conditions [46] and consider these linked under a single term of GCA-PMR Spectrum disease (GPSD) [47]. The common features of GPSD include IL-6 signature, excellent initial response to glucocorticoids, tendency to a chronic and relapsing course and older age of the affected population. There is also shared pathophysiology including ageing, genetics, innate and adaptive immune responses to unknown triggers; increased auto-reactive immunosenescent cells; altered Toll like receptors, phagocyte dysfunction; peripheral blood showing altered CD8+ T and B cells, increased T helper 1 or T helper 17 cells and decreased regulatory T cells in PMR. Moreover, granulocyte-macrophage colony-stimulating factor (GM-CSF) producing macrophages seen in PMR synovium and inflamed arteries of GCA and T cells from engrafted GCA arterial lesions can migrate to TABs derived from PMR patients, but not to controls.

The first overarching principle of the T2T recommendations for GCA and PMR [48] states that 'Clinical management of GCA and PMR should be driven by the awareness that they are closely interrelated conditions in a common spectrum of inflammatory diseases and can occur separately, simultaneously or in temporal sequence to each other'. We should now embrace the concept that several conditions should be now seen as part of the GPSD spectrum. These include isolated PMR, polymyalgic arthritis, cranial GCA, large vessel GCA, remitting seronegative symmetrical synovitis with pitting edema (RS3PE) as well as other unclassified patterns proximal to features of GCA or PMR. All these conditions vary in the anatomical sites of inflammation (bursa, tenosynovium, synovium, cranial arteries, extra-cranial arteries, aorta). Like demyelination and multiple sclerosis, GPSD conditions may share common pathophysiology by their expression may relate to the sites of inflammatory lesions and damage.

This concept of GPSD is now being tested in a prospective, longitudinal, multi-centre, inception cohort stratification study over two years that will map the anatomical sites of disease using ultrasound and other imaging modalities, and their evolution to disease course, damage and critical outcomes.

4. Conclusions

Polymyalgia rheumatica and GCA are common and often concurrent diseases in the elderly. Nowadays, the kinship of PMR and GCA is well recognized, with strong clinical, epidemiologic and immunologic connections. Approximately half of GCA patients have PMR at the time of diagnosis or during relapse, while a fifth have a history of PMR before GCA onset. These shared features justify the concept of a spectrum disorder, referred as GCA-PMR spectrum disease (GPSD). Despite significant progress in GCA diagnosis, detecting subclinical vasculitis without specific vasculitic symptoms (subclinical GCA) can still be challenging in the clinical practice. In PMR patients with undetected subclinical GCA, standard PMR treatment may be inappropriate, with prednisone doses being too low to prevent vascular complications.

Subtle differences exist between these two conditions, and several unanswered questions remain. Retrospective/prospective international multicentre studies are needed, implementing artificial intelligence models to analyse data on clinical features, laboratory findings, histology, imaging at baseline and during the follow-up, as well as genomics, proteomics, and metabolomics. These efforts will help stratify PMR and GCA patients based on predicting of relapses and treatment resistance.

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None to be declared.

Declaration of Competing Interest

The authors declare that they have no known competing financial

interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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