

## Giant Cell Arteritis and Polymyalgia Rheumatica: Two Different but Often Overlapping Conditions

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**Objectives:** Giant cell arteritis (GCA) and polymyalgia rheumatica (PMR) are common and frequently overlapping diseases. In this manuscript similarities and differences between these conditions have been assessed.

**Methods:** A retrospective review of the literature was conducted. Reports emphasizing features in common and possible differences are reviewed.

**Results:** GCA and PMR are characterized by late age at disease onset, are more common in women, exhibit evidence of a systemic inflammatory response, and generally respond well to corticosteroids. In biopsy-proven GCA, PMR manifestations are observed in up to 50% of cases. PMR may be the presenting feature in patients who later develop typical cranial manifestations of GCA. However, PMR manifestations may be observed in diverse conditions other than GCA. Patients with isolated PMR are younger than those with PMR associated to biopsy-proven GCA and exhibit milder inflammatory disease as shown by significantly less abnormality in most laboratory findings. Recent observations have shown that the frequency of pathologic features of GCA in temporal artery biopsies of patients with clinically isolated PMR is less than that previously reported. Besides different steroid requirements, GCA is associated with more vascular complications. Genetic differences, in particular different HLA-DRB1 associations, also have been observed.

**Conclusions:** Polymyalgia manifestations may be observed in patients with biopsy-proven GCA, but isolated PMR may be the only clinical feature or the phenotypic expression of a number of conditions. Clinical features and immunogenetic studies show subtle differences between GCA and PMR.

*Semin Arthritis Rheum 33:289-293. © 2004 Elsevier Inc. All rights reserved.*

**INDEX WORDS:** Giant cell arteritis; isolated polymyalgia rheumatica; elderly; inflammatory response; immunogenetic studies

**P**OLYMYALGIA rheumatica (PMR) and giant cell (temporal) arteritis (GCA) are common conditions in Western countries (1). GCA is a vasculitis that involves large and middle-sized blood vessels with a predisposition for cranial arteries (2,3). The main manifestations of GCA are caused by vascular involvement, ischemic visual manifestations being the most feared (4,5). PMR, a disease more common than GCA, is characterized by severe bilateral pain and aching involving the neck, the shoulder and pelvic girdles, associated with morning stiffness (1,6,7).

Controversy remains as to whether PMR and GCA are the same disease or whether they are 2 different but often concurrent conditions. This lit-

erature review was focused on analyzing of epidemiologic studies that might provide help in establishing the limits between these overlapping conditions.

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0049-0172/04/3305-0001\$30.00/0

doi:10.1016/j.semarthrit.2003.09.007

## WHAT WE KNOW ABOUT SIMILARITIES AND DIFFERENCES BETWEEN GCA AND PMR

### *Are GCA and PMR Different Clinical Expressions of a Common Disease?*

Both conditions are characterized by late age at disease onset, are more common in women, exhibit evidence of systemic inflammatory response, and generally respond well to steroids (1). The frequency of GCA and PMR increases with aging and peaks in patients older than 70 years (1,2).

GCA patients often present clinical manifestations of PMR (3). In biopsy-proven GCA PMR manifestations are observed in up to 50% of cases (1,2,8,9). PMR may be the presenting feature in patients who later develop typical cranial manifestations of GCA (10,11). Different population-based studies have shown the presence of biopsy-proven GCA in 16% to 21% of the patients with PMR (12,13).

Previous reports pointed out that, in a variable proportion of cases, generally 15% to 20%, temporal artery biopsies taken from patients with isolated PMR, without any cranial manifestation related to vascular involvement in the setting of GCA, yielded inflammatory changes of GCA (7,14). Also, in some studies GCA and PMR exhibited similar HLA-DRB1 genotype associations (15,16). These observations have supported the concept, maintained by many authorities, that both conditions are the same disease.

In this issue of *Seminars in Arthritis and Rheumatism* Cantini et al (17) have sought to examine whether GCA and PMR are the same disease. These authors have assessed similarities between both conditions in terms of a possible common genetic background and the potential influence of infectious agents as trigger factors for the development of both diseases. However, after an ex-

haustive literature review, they could not draw definitive conclusions supporting that GCA and PMR are the same disease (17).

### *Are GCA and PMR Independent but Often Concurrent Diseases?*

To address this question, several epidemiologic studies on GCA and PMR performed at the Rheumatology Division of the Hospital Xeral-Calde in Lugo, Spain, were reviewed.

This hospital is the single referral center for a mixed rural and urban Caucasoid population of almost a quarter of a million people. This center provides medical care to a very specific area of the inner of Galicia in Northwest Spain, which has been geographically isolated from the rest of Galicia and the rest of Spain for many centuries. This population is relatively static, and no important migration has occurred during the past decades (18,19). One hundred eighty-five patients (117 women) were diagnosed with PMR between 1987 and 1996 (20). The patients were distributed in the following 2 groups: isolated PMR (n = 134) and PMR associated with GCA (n = 51). Forty-two of 185 patients with PMR (23%) were diagnosed with GCA by a positive temporal artery biopsy. This observation may provide further support to the association between both conditions. However, a careful analysis may yield subtle differences between both conditions:

1) PMR is a syndrome that may be observed in the setting a wide diversity of conditions (21).

In Lugo, during the same period (1987-1986), 23 patients presenting with PMR symptoms were finally diagnosed as having diseases different from PMR and GCA. Malignancies and rheumatic diseases, especially seronegative symmetrical polyarthritis, were the most common diseases that mimicked PMR (22). Five patients who initially had fulfilled classification criteria for PMR developed episodes of symmetrical polyarthritis, particularly in both hands, satisfying the American College of Rheumatology 1987 criteria for rheumatoid arthritis (23). These observations suggest that polymyalgia may be the presenting feature of diverse conditions unrelated to GCA.

2) Clinical differences between isolated PMR and PMR associated with GCA.

In examining the series of PMR and GCA patients from Lugo in Northwest Spain, our group sought to investigate whether there were some

Abbreviations	
GCA	giant cell arteritis
HLA	human leukocyte antigen
IL-6	interleukin 6
PMR	polymyalgia rheumatica
TNF	tumor necrosis factor

clinical differences between isolated (“pure”) PMR and that associated to biopsy-proven GCA. Based on patients with isolated PMR, on whom GCA was excluded by a negative temporal biopsy or by absence of GCA features during their follow-up, we observed that patients with isolated PMR were significantly younger than those with PMR associated to biopsy-proven GCA. Isolated PMR patients had lower frequency of asthenia, anorexia, and weight loss, and seemed to have a milder inflammatory disease as shown by significantly less abnormality in the majority of laboratory findings (24). In this regard, patients with PMR associated with biopsy-proven GCA exhibited higher elevation of erythrocyte sedimentation rate and platelet counts, and lower values of hemoglobin than those with isolated PMR (24).

3) Recent observations indicate that the frequency of pathologic findings of GCA in temporal artery biopsies of patients with isolated “pure” PMR is less than that previously reported.

In their review, Cantini et al (17) reported that, during the period from 1996 to 2000, 12 of 76 (16%) PMR patients from Prato, Italy, had histologic evidence of GCA. However, only 1 (1.3%) of these 76 PMR patients had a positive temporal artery biopsy without any clinical feature of GCA. In the remaining 11 PMR patients, cranial manifestations of GCA were present at the time of the biopsy. Because of this, these authors do not routinely perform temporal artery biopsies to patients with isolated PMR (17).

Our experience supports some of those conclusions. In Lugo, temporal artery biopsies are usually considered in isolated PMR patients, without any clinical manifestation of GCA, if they have constitutional symptoms (asthenia, anorexia, and weight loss) and/or if the erythrocyte sedimentation rate is greater than 80 mm/hour (20,24). After this protocol, temporal artery biopsies were taken in 89 patients with PMR without any clinical manifestation of GCA; only 8 (9%) had positive biopsy GCA (19).

In our experience, the cranial manifestations of GCA in those patients initially diagnosed as having isolated PMR generally occur within the first 2 years after the onset of PMR symptoms. In Lugo, only 2% of patients diagnosed as having isolated PMR and who did not exhibit symptoms of GCA within the first 2 years, developed features of GCA during their extended follow-up. Thus, our obser-

vations are in accord with those reported by Cantini et al (17) and support differences between isolated PMR and GCA.

4) GCA and PMR have different steroid requirements.

In general, patients with isolated PMR respond rapid and dramatically to a dose of 10 to 20 mg/prednisone/day (7,13,20). In GCA, regardless of the presence of PMR manifestations, a dose of 40 to 60 mg of prednisone per day is required initially to prevent the development of blindness (4). 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 (25,26).

5) GCA is associated with more vascular complications.

Although most epidemiologic studies have shown that mortality in GCA and PMR is similar to that of the control population, an increased mortality due to cardiovascular disease in GCA recently has been reported in Northern Sweden (27). Additionally, stroke caused by occlusion of arteries, in particular in the vertebrobasilar territory (4), and aneurysm formation with rupture of the thoracic aorta due to arteritic involvement in GCA (but not in PMR) have been observed (28).

6) Genetic differences between GCA and PMR.

Recent immunogenetic studies indicate a polygenic basis for these conditions. Studies in different populations also suggest immunogenetic differences between GCA and PMR. It is possible that some genes that determine PMR manifestations may be common to isolated PMR and PMR associated with biopsy-proven GCA. Alternatively, other genes may contribute specifically to the development of GCA (29).

In Cantini et al's (17) report, immunogenetic differences in terms of Human Leukocyte Antigen (HLA) associations and interleukin (IL)-6 polymorphism have been addressed.

*Differences in HLA-DRB1 associations.* Most immunogenetic studies have shown an association between HLA-DRB1\*04 alleles and GCA (16,30-34). The HLA-DRB1 association with isolated PMR is more variable than with GCA (16,32,34,35). These variations may be explained by clinical heterogeneity and, perhaps in some cases, by difficulty in classifying patients presenting with PMR manifestations. In Northwest Spain, HLA-DRB1\*04 alleles were associated with GCA

regardless of PMR comorbidity (34). This finding supports the subtle clinical difference between isolated PMR and PMR associated with biopsy-proven GCA.

*May other HLA genes provide clues for differences between GCA and PMR?* Tumor necrosis factor (TNF)  $\alpha$ , which is released by macrophages and activated T cells, plays an important role in the inflammatory response. Although in some studies circulating TNF $\alpha$  concentrations were similar in GCA and PMR to those of controls (36,37), detectable plasma TNF $\beta$  does not necessarily represent the concentration of this cytokine produced at the inflammatory site. Thus, TNF $\alpha$  might also be implicated in the phenotype expression on these conditions. The TNF locus is highly polymorphic and different TNF genetic markers have proved to be associated with different variation in the amount of plasma TNF $\alpha$  expression.

Our group examined TNF microsatellite associations in isolated PMR and biopsy-proven GCA patients (with and without associated PMR) from Lugo (38). Biopsy-proven GCA without PMR manifestations was associated with TNF  $\alpha$ 2 microsatellite marker. This association was independent of the previously reported association of GCA with HLA-DRB1\*04 alleles (38). In contrast, isolated PMR was associated with TNF $\beta$ 3, independently of the association with HLA-DRB1\*13 (38). To our surprise, unlike GCA without polymyalgia manifestations, biopsy-proven GCA associated with PMR also exhibited association with TNF $\beta$ 3

(38). This finding suggests that the polymorphism of some cytokines may modulate the expression of PMR in susceptible individuals, whether or not GCA is present.

*Role of IL-6 polymorphism.* Increased production of IL-6 in serum and in temporal artery biopsies has been observed in both GCA and PMR (36,39,40). The observation of different TNF microsatellite polymorphism association in biopsy-proven GCA patients according to the presence of PMR manifestations moved our group to assess the potential role of the promoter polymorphism of IL-6 at position -174 (G->C) in the phenotypic expression of both conditions (41). In Lugo, an association with C allele was only observed in biopsy-proven GCA associated with PMR. This association was even stronger in HLA-DRB1\*04-negative patients (41). These immunogenetic results along with those of TNF may suggest a potential role of TNF $\alpha$  and IL-6 in the clinical expression of PMR.

## CONCLUSIONS

Both GCA are common and often concurrent diseases in the elderly. Although in some cases polymyalgia manifestations may be observed in patients with biopsy-proven GCA, PMR may be the only clinical feature or the phenotypic expression of a great variety of conditions. Clinical features and immunogenetic studies show subtle differences between GCA and PMR.

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