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Review

Polymyalgia Rheumatica, an Age-Related Rheumatic Disease

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Abstract

Polymyalgia rheumatica (PMR) is an age-related chronic inflammatory disease with rheumatic features at the fore. In addition to the high-grade systemic inflammation, it is characterized by typical "polymyalgic" musculoskeletal symptoms, including diffuse and severe pain and prolonged morning stiffness of the shoulder girdle, pelvic girdle, and neck. PMR is a member of the so-called giant cell arteritis complex; however, in spite of the marked systemic inflammation in PMR, the local vasculitis process aborts. The pathological background is synovitis, with a predominant inflammation of the extra-articular synovial structures. Synovitis of PMR is mild, transient, and non-erosive. Distal musculoskeletal symptoms are also observed but are more variable and less recognizable than the predominant proximal polymyalgic syndrome. PMR often overlaps with elderly-onset seronegative arthritides, elderly-onset rheumatoid arthritis, late-onset seronegative spondylarthritis, and the RS3PE[1]

[1] remitting seronegative symmetrical synovitis with pitting edema.

syndrome. Although glucocorticoids are the cornerstone of PMR therapy, considerable hope is attached to tocilizumab, an IL-6 receptor inhibitor.

Keywords
Polymyalgia rheumatica; musculoskeletal symptoms; synovitis

1. Clinics

Polymyalgia rheumatica (PMR) is a common age-related inflammatory rheumatic disease characterized by typical musculoskeletal symptoms and marked systemic inflammation. Rapid response to glucocorticoid (GC) therapy is also a characteristic of PMR, which is close in nature to giant cell arteritis (GCA)—a systemic vasculitis that affects older adults [1-4]. Modern clinical research on inflammatory diseases has provided new impetus for rheumatologists [2].

One of the most famous artistic depictions of PMR and GCA is the painting of "Canon van der Paele," whose disease, pain, and stiffness in the arms and shoulders prevented him from fulfilling his morning duties. His enlarged temporal artery is a classic sign of the associated temporal arteritis (Figure 1).

Figure 1 Canon van der Paele, Jan van Eyck, 1436; Groeningemuseum, Bruges.

PMR is a disease that affects the older population. Although it primarily affects people aged 70–80 years, those aged 50 years and above are also prone to the disease. The key symptom of PMR is pronounced pain and stiffness of the proximal extremities, shoulder girdle, pelvic girdle, and neck. Shoulder pain has been reported in 70%–95% of patients with PMR. Hip involvement is rare and, if present, accompanies the shoulder symptoms. Pelvic girdle pain has been reported in only 5% of cases [3, 4]. The proximal symptoms are typical but are nonspecific to PMR. Bilateral shoulder pain may occur at presentation in older patients with several other rheumatic diseases, including inflammatory or noninflammatory rheumatic diseases, such as connective tissue diseases, various shoulder conditions (bilateral rotator cuff syndrome, tears or tendinitis, glenohumeral osteoarthritis, etc.), fibromyalgia, and generalized osteoarthritis. Polymyalgia presentation is common in elderly-onset rheumatoid arthritis (EORA), late-onset spondyloarthritis (LO-SpA), and remitting seronegative symmetrical synovitis with pitting edema (RS3PE) syndrome [5].

Proximal symptoms are generally more prominent than distal musculoskeletal symptoms that occur in 33%–50% of all PMR cases. However, the distal musculoskeletal symptoms are not characteristic, are less recognized, and are more variable than the proximal symptoms. In a study, 45% of 177 patients with PMR exhibited peripheral symptoms, with peripheral arthritis (25%) presenting as oligoarthritis or polyarthritis, affecting the knees and wrists being the most typical symptom. Carpal tunnel syndrome (14%) is also frequent in patients with rheumatoid arthritis (RA). RS3PE syndrome occurs in 12% and distal tenosynovitis in 3% of PMR cases [6, 7]. Therefore, peripheral symptoms of PMR should be differentiated from other types of chronic arthritis.

Patients with PMR who have new-onset localized headaches may have associated temporal arteritis and a protuberant and tender temporal artery with a decreased pulse on palpation. PMR is associated with temporal arteritis in 10%–30% of cases [2-4].

Elevated levels of inflammatory markers (erythrocyte sedimentation rate [ESR] and C-reactive protein [CRP]) are characteristic of PMR (frequency > 90%); however, less than half of the cases still commence with normal ESR or CRP. Constitutional symptoms are detected in one-third of the cases.

Prognostic signs of PMR are unknown, and the diagnosis is based on clinical presentation and differentiation from the polymyalgia mimics. Previous diagnostic criteria were introduced by leading PMR experts using their personal experience. However, new classification criteria were created in 2012 by an international PMR work group under the guidance of the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR). Herein, the scoring algorithm is based on clinical symptoms. Ultrasonography (US) was added to the criteria, and its contribution increased the specificity of the criteria [8].

GCs remain the cornerstone of PMR therapy and are generally required for 1–1.5 years. Nevertheless, one-third of patients with PMR are GC-resistant; moreover, they exhibit a chronic-relapsing course and require GCs for several years. The side effects of GCs, such as diabetes, hypertension, obesity, and osteoporosis, can cause considerable morbidity and economic burden on society [2, 3]. Interleukin-6 receptor (IL-6R) blockade is a successful therapeutic strategy for several inflammatory diseases, thereby providing considerable hope for PMR treatment in the future. Recommendations for PMR management were introduced in 2015 as a EULAR/ACR collaborative initiative [9].

2. Pathogenesis of PMR

Because PMR occurs almost exclusively in individuals over 50 years, age-related immune alterations in genetically predisposed individuals may be the contributing factor to PMR development. Although several infectious agents have been investigated as possible triggers of PMR, the results are inconclusive. Participation of the innate and adaptive immune systems has been proved in PMR; this is demonstrated by the activation of dendritic cells and monocytes or macrophages and the altered balance between Th17 and Treg cells. Moreover, disturbed B cell distribution and function have been demonstrated in patients with PMR, suggesting more complex pathogenesis than previously imagined [10].

PMR pathogenesis is initiated by exposure to environmental factors, possibly viruses, and the key role is played by the genetic predisposition of the innate immune system. The immune system senescence is demonstrated by the loss of the CD28 surface antigen on senescent CD4+ T cells, possibly responsible for aberrant immune responses in PMR [11]. Adaptive immune alterations in PMR are characterized by the activation of Th17 cells, mainly driven by an increase in IL 6 levels. However, in spite of the altered B cell repertoire, a clear autoimmune response is absent in PMR. Moreover, the local activation of endothelial cells has been demonstrated in the noninflamed arteries and inflamed synovial tissues of patients with PMR. Interferon-gamma (IFN-γ) production can only be detected in temporal artery biopsies of patients with PMR with overt vasculitis [12].

Whether the seasonal distribution of PMR onset is connected to infectious etiology remains controversial to this day. The genetic predisposition of PMR, represented by immunogenetics, may be based on regional–ethnical diversity [13]. Human leukocyte antigen (HLA) class II associations of PMR are much weaker, though similar to those of RA (HLA DRB1 × 01, 04, and 10). Significantly decreased frequency of the HLA DRB1 × 0401 subtypes was detected in Hungarian patients[14, 15].

2.1 PMR, an Autoinflammatory Disorder?

Recently, several authors have suggested considering PMR as an autoinflammatory disease (AID). In 2006, a scientist, D. McGonagle, proposed the “immunological continuum model” that considers all immune-related diseases to be autoinflammatory, autoimmune (AD), or mixed forms. AIDs are characterized by the activation of the innate immune system, whereas ADs are characterized by adaptive immune reactions, autoantibodies, and autoreactive T lymphocytes [16]. However, according to A. Floris et al., PMR does not fit into the spectrum of the AID–AD disorders but rather into the middle group, with a greater affinity for AIDs [17].

The predominantly autoinflammatory nature of PMR is supported by numerous facts. Acute onset of the symptoms and complete response to GCs within four days are the characteristics of PMR. One of the most consistent features is the remarkable increase in inflammatory markers; therefore, ESR and CRP are included in the diagnostic and monitoring criteria of PMR. An increase of other acute phase reactants also occurs. Genetic background in initiating and regulating the immune response and the generated cytokine profile are also typical of an AID. Polymorphisms of non-HLA genes are recognized, and increased allele #2 frequency of the IFNγ-gene was detected in the Hungarian PMR series. Activation of the IL cascade and evidence of IL 6 playing a central role in PMR pathophysiology have been confirmed. Higher serum IL 6 levels have been reported in PMR and GCA cases, and the administration of IL-6R antagonists in patients with PMR has produced

encouraging results. Increased expression of toll-like receptors and the emerging involvement of Th17 cells support the bridging theory, i.e., PMR falls in between the AID and AD disorders.

2.2 GCA Complex

Although PMR and GCA overlap with each other, it is still unclear whether GCA represents a separate condition from PMR or whether it is a potential expression of the same disease. The concept of a GCA complex is gradually evolving [18, 19].

GCA is an immune-mediated disease of the large vessels, including cranial arteries (the most frequent target) and the aorta and its major branches. Inflammation commences in the adventitia and eventually spreads to the inner layers of the vessel wall. Systemic inflammatory syndrome with shoulder, hip, or spine bursitis and synovitis are typical in patients with isolated PMR (without signs and symptoms of overt vasculitis). PMR, as a conceptualization of the GCA complex, may be regarded as an early or aborted form of vasculitis, wherein the vascular inflammation stops at the adventitia of the vessel wall. The acute phase of GCA is mainly inflammatory, and chronic stages are characterized by inflammation, degradation, and repair mechanisms jointly resulting in structural changes of the vessel wall, ischemic complications, and aneurysm development [18, 19].

Clinicians have generally considered GCA as a disease with headache as the major symptom; however, reports by Horton and Hamrin in 1932 and 1972, respectively, have suggested the systemic nature of GCA. It was perhaps the 1990 ACR classification criteria of GCA that encouraged the clinicians' perception. The ACR criteria are predominantly used for classification, though they are frequently used for diagnostic purposes as well. The main focus of the criteria is the cranial symptoms of GCA, such as headache and swelling or tenderness of the temporal artery. Modern vascular imaging techniques have suggested a more frequent involvement of large vessels in GCA than previously thought. This has led to a deeper understanding of GCA as a vasculitic syndrome that is categorized as cranial GCA, large-vessel GCA, and PMR (Figure 2).

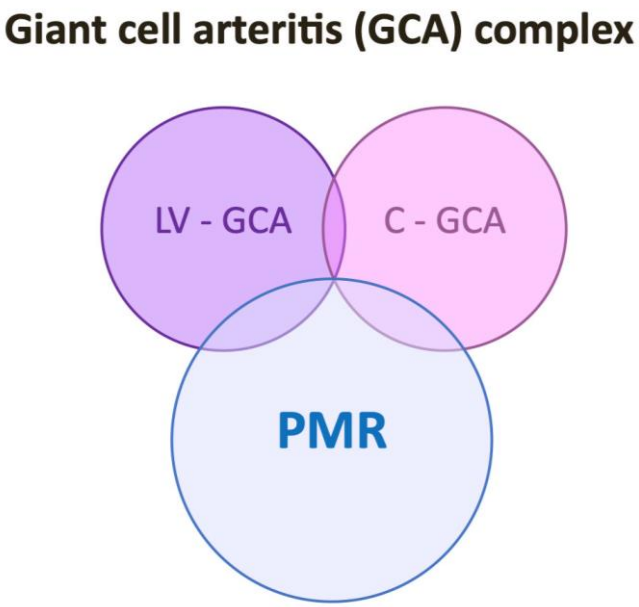


Figure 2 The GCA complex, including PMR. C-GCA: cranial GCA, including temporal arteritis, LV-GCA: large-vessel GCA, PMR: polymyalgia rheumatica (extravascular GCA).

PMR is clinically characterized by aching and stiffness in the cervical region, shoulder and/or pelvic girdles. Large arteries, particularly the aorta and its supra-aortic branches, are mainly affected in large vessel GCA (LV-GCA). This was first discovered using vascular imaging studies performed on difficult-to-treat patients with polymyalgia and patients with constitutional symptoms, such as weight loss, night sweats, and fever of unknown origin. Upper limb claudication may be a result of LV-GCA-related arterial stenosis. Aneurysm formation is caused by aorta inflammation which may lead to dissection or rupture. These developments result in frequent abdominal, thoracic, and back pain in GCA with constitutional symptoms. However, the most dreaded complication of GCA is irreversible, permanent sight loss. Cerebrovascular strokes, infarction of the tongue, and scalp necrosis are less common. Permanent loss of vision due to anterior ischemic optic neuropathy occurs in 15%–20% of patients. Better disease recognition, prompt diagnosis, and prompt initiation of therapy in recent years have led to a reduction in visual and other ischemic complications. Moreover, the introduction of "fast track clinics" in the West has led to significantly reduced morbidity and mortality [18, 20, 21].

3. Epidemiology

PMR is the most common inflammatory rheumatic disease in older adults, with GCA being the most frequent primary vasculitis. Because of the clinical and subclinical overlap of PMR and GCA, determining their epidemiology remains challenging. Moreover, a lack of large-scale epidemiologic studies on GCA and PMR has been noted in certain parts of the world (Latin America, South Asia, and Africa). GCA and PMR have the highest incidence among Northern European populations, particularly among Scandinavians (Viking) [22]. The annual incidence of GCA and PMR among these populations range from 18 to 29 cases per 100,000 people aged >50 years and 41 to 113 cases per 100,000 people aged >50 years, respectively.

In addition, the occurrence of GCA increases as the population ages. The projected worldwide disease burden of GCA by 2050 is more than 3 million [18].

In GCA, 40%–60% of patients also have features of PMR at diagnosis. However, histologically proven GCA is associated with PMR in 16%–21% of patients only. Subclinical GCA in patients with PMR may be detected using vascular imaging (contributing to another 10%–35%), though this is not typically performed in patients with isolated PMR features. Moreover, no clear prognostic test exists for PMR, and even the gold standard temporal artery biopsy (TAB) for diagnosing GCA is positive in only 39%–87% of cases [18, 19].

4. Diagnosis – Imaging

4.1 Benign Synovitis in PMR

PMR is a synovial disease; however, despite the marked clinical discomfort and high systemic inflammation, polymyalgic synovitis is mild, transient, and non-erosive. Therefore, on physical examination, little evidence of proximal joint swelling and tenderness is observable. Mild hypervascularization in the synovial membrane on power Doppler US and mild contrast enhancement on MRI are detected. Arthroscopic biopsy samples from the shoulders of patients with PMR reveal mild synovitis with predominant macrophage and CD4+ T lymphocyte infiltration.

High HLA-DR expression but the absence of B cells—in contrast to RA—is also observed. X-rays of the joints reveal no pathologic signs of destructive progressive joint disease [3, 4, 23].

A much weaker RA-associated epitope (SE) and no production of anticyclic citrullinated antibody (ACPA) are characteristics of the destructive synovial process; however, these have also been discovered in PMR. In contrast, 65% of patients with EORA are ACPA positive. In a Hungarian immunogenetic study, the decreased HLA DRB1 × 0401 allele frequency, together with ACPA deficiency, partly explained the benign synovitis of PMR [14, 15].

4.2 Shoulder Bursitis in PMR

Despite the fact that an X-ray of polymyalgic joints reveals no pathology, the evidence of synovitis in PMR has been proven by different modern imaging techniques. Axial synovitis (increased radioactive isotope uptake) was revealed using scintigraphy as early as the 1970s at the Mayo Clinic. In a Finland-based study by J. Koski, shoulder and hip synovitis were detected in approximately 2/3 (68%) of patients using US [24]. However, the observed mild synovitis was not sufficient to explain the diffuse and severe shoulder discomfort of patients with PMR.

An Italy-based study by C. Salvarani et al. in 1997 suggested that bursitis is a characteristic feature of PMR. MRI and US detected bilateral subacromial-subdeltoid (SAD) bursitis with high specificity in PMR; therefore, it was proposed as a diagnostic criterion of PMR in 2001 by the Italian workgroup; the frequency of bursitis in PMR was 96% (Figure 3) [25, 26].

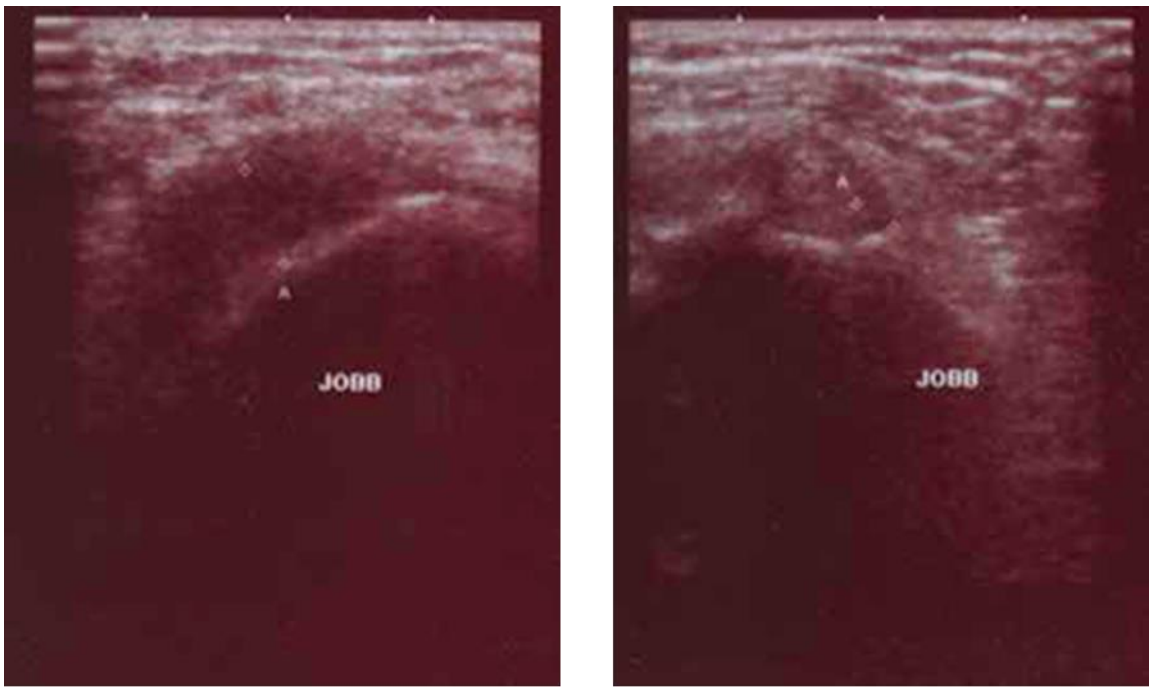


Figure 3 Ultrasonography of the shoulder in PMR. Subacromiodeltoid bursitis (hypoechoic area), coronal oblique image (A), long head biceps tenosynovitis, axial image (B) (courtesy A.R. Mester and Natl Inst Rheumatol Physiother, Budapest).

The optional US section of the EULAR/ACR Classification Study 2012 for PMR mentioned only a relative dominance of bursitis in PMR shoulder inflammation compared to RA; the frequency of

bursitis in PMR was 59% [8]. A recent systematic literature review and meta-analysis further supported the importance of extra-articular manifestations in PMR inflammation [27]. The increased metabolic activity caused by SAD bursitis, trochanter or iliopectineal bursitis, and interspinous bursitis along the spine can be detected on positron emission tomography (PET) and computed tomography (CT).

Although studies using MR and PET/CT revealed the potential characteristic features of PMR, only the US-based studies included enough control patients with the inflammatory disease for exact estimates of diagnostic accuracy. The most informative US feature so far appears to be bilateral SAD bursitis, with a specificity of 89% and sensitivity of 66% [27].

In line with the Italian data, in a Hungarian US-based study, SAD bursitis was detected in all patients, whereas long head biceps (LHB) tenosynovitis was detected in 86% of patients with active PMR. Glenohumeral synovitis could only be detected using MRI. Inflammation in all sites was of mild-to-moderate degree. Degenerative signs of the rotator cuff syndrome, muscle weakness, tendon ruptures, instability signs, and osteoarthritis of the acromioclavicular joint were more frequent with advancing age. Signs of enthesitis and bone and soft tissue edema adjacent to the joint capsule could not be observed even by using fat-suppressed techniques. Signs of shoulder inflammation detected using US at baseline proved to be a superior prognostic marker of GC response [23].

4.3 Subclinical Large Vessel Vasculitis in PMR

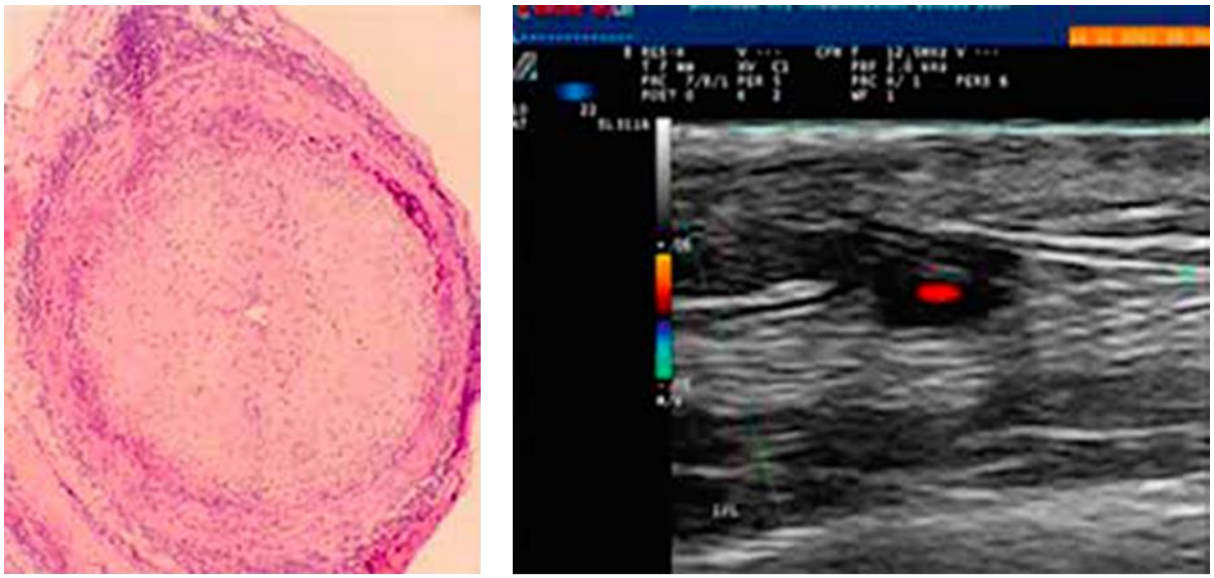
Subclinical large vessel vasculitis could be detected in isolated PMR (iPMR) by using 18F-FDG-PET (18F-fluorodeoxyglucose-positron emission tomography), the most modern imaging modality. In 2007, D. Blockmans et al. reported that approximately one-third (33%) of patients (n = 35) with iPMR exhibited an increased vascular uptake, predominantly in the subclavian arteries, in addition to FDG-uptake in the shoulders, hips, and cervical spine. Despite this, uptake intensity in iPMR was less than that in overt GCA with clear vasculitis symptoms. Several other authors also reported an increased FDG-uptake in the aorta and its major branches in untreated patients with iPMR [28].

Identification of subclinical GCA in iPMR is possible only through imaging studies. The possibility of coexistent GCA arises in patients with PMR who exhibit an incomplete GC response, constitutional symptoms, and markedly elevated acute phase reactants. A biopsy of larger arteries is not feasible; thus, diagnosing LV-GCA in PMR is based on imaging methods, such as 18F-FDG-PET, axillary US, CT angiography, and MRI, that assess mural inflammation and changes in the lumen [29, 30].

4.4 Temporal Arteritis

No CT and PET are applicable for cranial arteritis. The gold standard for GCA diagnosis in PMR is to perform a temporal artery biopsy. However, a long enough fragment and a well-trained pathologist are crucial for correct histology. Temporal arteritis is diagnosed if mononuclear cell infiltrates, giant cell granulomas (often, not always), and rupture of the internal elastic lamina are present. Intimal hyperplasia of the vessel wall with narrowed lumen is characteristic of temporal arteritis and responsible for the ischemic signs and symptoms. Immunostaining may be positive for CD3 and CD68 cells. TAB has high sensitivity (85%–90%) and the highest specificity of all modalities in demonstrating histologic inflammation (100%) [31].

Color duplex US (CDUS) and high-resolution MRI (HRMR) are alternative imaging techniques for detecting cranial arteritis. The "halo sign" on CDUS was depicted in 1995 by W. Schmidt, with similar sensitivity (69%–93%) and specificity (75%–93%). The halo sign is characteristic of GCA and implies concentric, homogeneous, and hypoechoic artery wall swelling; it maintains visibility upon mechanical compression. Changes to the intima-media thickness are an excellent measure of disease severity. CDUS has better diagnostic sensitivity when the temporal artery is not involved, but several other cranial arteries are involved. The interpretation of CDUS results requires highly qualified sonographers (Figure 4) [32, 33].



(A) (B)

Figure 4 Histologic and sonographic signs of GCA. Multiple enlarged inflamed intima on biopsy, HE staining (A), Halo sign on CDUS, transversal section (B) (courtesy M. Bély, DSc, Hospital of the Order the Brothers of Saint John of God, Budapest (A) and N.P. Kaposi, Natl Inst Rheumatol Physiother, Budapest).

5. Classification Criteria

As PMR is a common inflammatory rheumatic disease affecting the older population, long-term GC treatment is often required. A wide variety of clinical specialties in primary and secondary care deal with PMR because of the considerable uncertainty related to its diagnosis, course, and management. No diagnostic laboratory test exists, inflammatory markers are not specific, and clinicians often use good GC response as a diagnostic tool. Early diagnostic criteria of PMR stem from the empiric work of some highly experienced PMR experts [5, 34-36].

The lack of standardized classification criteria has been a major factor limiting the development of rational therapeutic approaches and challenging the evaluation of patients in clinical studies. In response to a EULAR/ACR initiative, a criteria development work group was convened in 2005. A systemic literature review, a 3-phase hybrid consensus process, and a wider survey were performed to identify the candidate criteria items. In the third phase, over 70% of respondents agreed on the importance of seven core criteria (with 100% support in the second phase): patients aged over 50 years, with a symptom duration of 2 weeks or more, with bilateral shoulder and/or pelvic girdle

aching, with a morning stiffness duration of over 45 min, with elevated ESR levels, with elevated CRP levels, and with a rapid GC response. Moreover, consensus on the requirement for a prospective cohort study that would evaluate the disease course from presentation in patients with proximal pain and stiffness was reached. The study was planned for 6 months to evaluate the predefined parameters of patients receiving a standardized GC treatment protocol. The group also agreed to include musculoskeletal ultrasound (MSUS) for PMR diagnosis [8].

As proposed by the international work group, the first international multicenter prospective study was established to examine consensus-based candidate classification criteria for PMR. According to the study classification protocol, patients aged 50 years or older presenting with new bilateral shoulder pain and elevated CRP and/or ESR levels can be provided a diagnosis of PMR in the presence of morning stiffness >45 min and new hip involvement (pain, tenderness, or limited movement). The likelihood of PMR is increased by the lack of peripheral synovitis and a positive RA serology. Rheumatic factor (RF) positivity is a rare finding in patients with PMR; thus, the absence of RF serology is useful to differentiate PMR from elderly RA. The specificity of the clinical classification criteria may be substantially improved by the ultrasound findings of bilateral shoulder abnormalities (SAD bursitis, LHB tenosynovitis, and GH effusion) or abnormalities in one shoulder and one hip (trochanteric bursitis and hip effusion). The EULAR/ACR classification criteria are not meant for diagnostic purposes, though sometimes they are a great help in everyday practice (Table 1).

Table 1 EULAR/ACR 2012 classification criteria.

	EULAR/ACR 2012
Age	≥50 years
Neck, shoulder, and hip bilateral aching	Shoulders +/−hips
Elevated CRP/ESR	Yes
Morning stiffness duration	>45 min
Symptom duration	--
Rapid GC response	--
Others	US-criterion (optional)
Exclusion of other diseases	Negative RA serology, no peripheral joint involvement
Diagnosis	**3 required criteria + 4/5 points**

Four clinical and laboratory criteria, along with the optional US criteria, can be applied to identify patients with PMR who are suitable for low-dose GC therapy. The scoring scale is 0–6 (without US) and 0–8 (with US). A score of 4 or greater (without US) or 5 or greater (with US) is indicative of PMR. Patients with a score of less than 4 cannot be provided a diagnosis of PMR. The scoring algorithm is shown in Table 2. US improves the specificity of PMR diagnosis and demonstrates particularly good performance in differentiating PMR from noninflammatory conditions.

Table 2 Scoring algorithm of the EULAR/ACR criteria.

Criterion	**US-**	**US+**

≥50 years		
New bilateral shoulder pain onset	required	required
Elevated CRP/ESR		
Morning stiffness > 45 min	2	2
Hip pain or restricted range of motion	1	1
Absence of RF/ACPA	2	2
Absence of peripheral synovitis	1	1
At least 1 shoulder BTS* + 1 hip BS on US		1
Both shoulders BTS on US		1
	4 (0–6)	**5 (0–8)**

*B bursitis, T tenosynovitis, S synovitis.

The 2012 classification criteria were originally considered provisional because they were not validated in another cohort. Since then, several studies have evaluated the provisional classification criteria, with high sensitivity (92.6%) and specificity (81.5%) [37]. However, studies with longer follow-ups exceeding the median time of GC treatment are still required. GC treatment may mask mimicking conditions, such as inflammatory joint diseases and GCA; these conditions may become apparent when the GC dose is lowered or discontinued. Reassessments of patients with PMR and non-PMR polymyalgia must be performed by experienced rheumatologists and well-trained sonographers.

6. Differential Diagnosis

Difficulties in diagnosing and classifying patients with PMR are inherent in its definition. The proximal pain and stiffness syndrome may occur at presentation in several other inflammatory and noninflammatory illnesses in older adults [38]. Approximately half of the patients with PMR may have distal manifestations, such as peripheral arthritis, tenosynovitis, hand swelling with pitting edema, and carpal tunnel syndrome. Benign synovitis in older adults and the overlap of different syndromes are presented in Figure 5 [3-5]. Polymyalgia presentation is common in late-onset rheumatoid arthritis, spondyloarthritis, and RS3PE syndrome; it is also associated with GCA in 10%–30% of cases. Heterogeneity in the disease course, uncertainty regarding disease assessment parameters, and the evolution of alternative diagnoses on follow-up complicate PMR management. Uniform responsiveness to low doses of GCs has been assumed to be a cardinal feature of PMR; however, further evidence is required to substantiate this assertion. A report revealed that a 3-week treatment of prednisolone 15 mg a day extracted a full response from only 55% of patients.

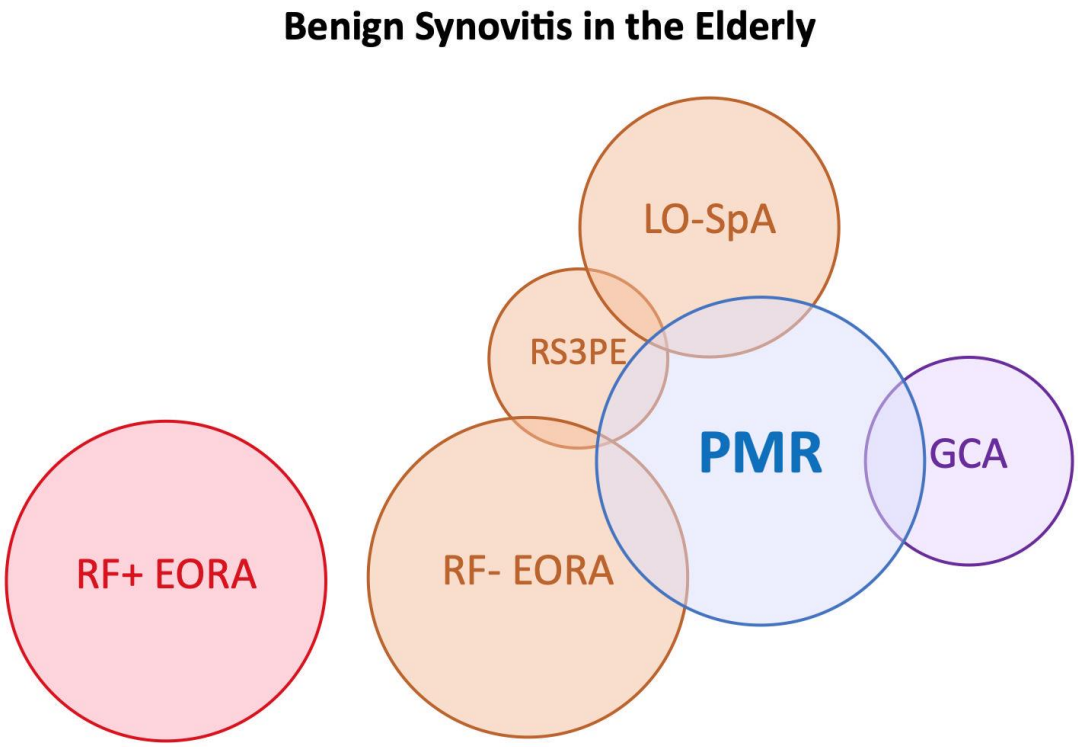


Figure 5 Benign synovitis in older adults and their overlap. EORA: elderly-onset RA, LO-SpA: late-onset SpA, RS3PE: remitting seronegative symmetrical synovitis with pitting edema, PMR: polymyalgia rheumatica, GCA: giant cell arteritis.

Clinicians should exclude infections and malignancies with predominant constitutional symptoms and investigate fever, weight loss, and other polymyalgia mimics. In general, a typical presentation does not require a detailed medical check-up, but clinicians should thoroughly assess whether another—potentially life-threatening—illness might be behind the symptom complex. Polymyalgia syndromes are listed in Table 3.

Table 3 Polymyalgic syndromes in the differential diagnosis.

Diagnosis	Clinical features
INFLAMMATORY DISORDERS	
Polyarthritides:	
Rheumatoid arthritis (RA)	Symmetrical and mainly distal joint symptoms, RF and ACPA positivity, erosive joint disease on radiography
Late-onset spondyloarthritis (LOSpA), including SPA and PsA.	Predominant low back pain and stiffness, large and distal joint symptoms may occur, spinal ankylosis on radiography, associated psoriasis
RS3PE* syndrome	symmetrical peripheral hand and/or foot edema
Autoimmune diseases:	

SLE, scleroderma, Sjögren-syndrome, vasculitides	Fatigue, stiffness, multisystem disease, presence of ANA and ANCA antibodies,
Dermatomyositis/polymyositis	proximal muscle weakness, rash, raised CK levels
NONINFLAMMATORY DISORDERS	
Degenerative joint and spine	
Osteoarthritis Spondylosis	Articular pain of shoulder, neck, and hip joints, gelling, spinal pain, degenerative changes on radiography
Shoulder problems	
Rotator cuff (ROK) disease Adhesive capsulitis (frozen shoulder)	Periarticular pain, restricted range of motion, US and MR may reveal characteristic bursal and synovial inflammation
Infections	
osteomyelitis, bacterial endocarditis, tuberculosis	Fever, weight loss, deep soft tissue and bone pain, heart murmur, microscopic hematuria
Malignancies	
lymphoma, leukemia, myeloma, amyloidosis, occult solid tumors	Weight loss, fatigue, investigations according to symptoms, sex and age,
M. Parkinson	stiffness, rigidity, shuffling gait, gradual onset
Generalized pain syndromes	
Chronic pain syndromes (CPS), Fibromyalgia generalisata (FM)	Fatigue, longstanding pain, tender points, sadness, loss of usual interest, depression
Endocrinopathies, metabolic bone diseases	Bone pain, fatigue, abnormal PTH, Ca, P, Vitamin-D, and TSH levels
TSH	
hyper/hypothyroidism	Hyper/hypometabolic state, tachycardia, diarrhea
PTH	
hyper/hypoparathyroidism	Altered bone metabolism, bone loss, fractures
Vitamin-D	
hypovitaminosis/osteomalacia	Bone demineralization, fractures, bone pain, proximal muscle weakness, pain and cramps, waddling gait
Crystal arthropathies	
pseudogout, calcium-pyrophosphate deposition disease (CPPD)	Acute and recurrent articular pain and swelling, peripheral joints, atypical for osteoarthritis

*Remitting seronegative symmetrical synovitis with pitting edema.

7. Treat to Target (TTT)

The TTT approach aims to reach a prespecified treatment goal and has been successfully employed in the management of various rheumatic diseases. TTT for RA has considerable advantages over conventional treatment protocols in terms of abrogation of inflammation and structural damage progression. The development of TTT approaches for PMR should include the natural history of the disease and general principles of patient assessment and management.

Treatment of PMR should be a joint decision of patients and the rheumatologist. The primary goal is to maximize the long-term health-related quality of life through symptom control, vascular compromise prevention, and normalization of function and participation in social and work-related activities. Abrogation of inflammation is the most crucial method to achieve these goals. TTT based on disease activity measurement and therapy adjustment is essential to optimize outcomes. Although timely and accurate diagnosis is critical to minimizing treatment-related adverse events, it is vital to remember that patients may achieve treatment-free remission after a variable time period; however, neither PMR nor GCA should be thought of as "curable" diseases. Both require long-term and often life-long follow-ups [39].

TTT focuses on obtaining disease remission with minimal treatment-related side effects, some of which may be difficult to distinguish from disease activity and damage. Validated composite measures of disease activity are required to appropriately define disease remission and relapse.

The disease activity score for PMR (PMR-AS) was developed in 2004 by Leeb and Bird; PMR-AS was confirmed by others [40]. Five clinical and laboratory parameters make up the composite score to define disease activity (see Table 4), the scoring scale (0–17) of which determines high (>17), medium (7–17), and low (<7) disease activity. Patients with PMR-AS < 1.5 have achieved the treatment goal of disease remission. A clinical version of PMR-AS, introduced in 2016, does not contain CRP or a laboratory parameter; therefore, it is easier to calculate and apply to the patient at the bedside [41]. However, PMR-AS and its clinical version are awaiting their routine implementation in everyday practice.

Table 4 Calculation of PMR activity score. The easy-to-calculate PMR-AS is the result of the multiplication of five items (CRP [mg/dL] + VAS p [0–10] + VAS ph [0–10] + MST [min] 0.1 + EUL [3–0]). The ability to elevate the upper limbs (EUL) is assessed the other way round (3 = none, 2 = below shoulder girdle, 1 = up to shoulder girdle, and 0 = above shoulder girdle). For reasons, weighting morning stiffness (MST) is multiplied by 0.1.

parameter		numerical value
CRP (mg/dL)		+
Patient's global assessment of pain (VAS)	0–10	+
Physician's global assessment of patient's pain (VAS)	0–10	+
Morning stiffness (min)	× 0.1	+
Elevation of upper limbs	3–0	+
PMR-AS		∑

8. Treatment

GCs are the standard treatment for both GCA and PMR; however, GC-related adverse events (such as obesity, osteoporosis, diabetes, hypertension, and cataract) occur in up to 85% of cases. Several patients have pre-existing comorbidities that may pose relative or absolute contraindications to GC therapy. The prevalence of flares is high and is related to the dose and duration of GC therapy. Flares have been observed in 34%–62% of patients. With the rapid tapering of GCs, sustained remission is achieved in no more than 15%–20% of cases treated with GCs alone.

Multiple relapses and variable presentations (polymyalgia, oligoarthritis, and RS3PE) of a GC-resistant PMR were observed in a 72-year-old female patient during the first 2 years of her disease. Well-known side effects of long-term GC therapy (such as obesity, skin fragility, suffusion, osteoporosis, fracture, myopathy, cataract, and hypertension) were also observed [42].

To reduce GC-induced side effects and GC cumulative dose, GC-sparing agents should be included in the treatment of GCA and PMR. Currently, MTX is the only conventional disease-modifying antirheumatic drug (cDMARD) that exhibits a modest reduction in the cumulative dose or no effect at all. Current EULAR/ACR recommendations are conditionally in favor of using this drug in GCA and PMR. Other conventional DMARDs, such as azathioprine and cyclophosphamide, are ineffective or toxic. Some potential benefits of leflunomide have been demonstrated in patients with refractory GCA. A randomized controlled trial (RCT) on leflunomide in new-onset PMR, organized by the EULAR/ACR study group, is currently under recruitment [43].

Among biological agents (bDMARD), TNFα antagonists were the first agents to be studied in both GCA and PMR. Initial case reports and case series displayed promising results; however, the results of RCTs on infliximab, etanercept, and adalimumab were below expectations, and the unsatisfactory results could not be explained [4, 9].

The results from recent trials on tocilizumab (TCZ) for GCA have generated optimism for this approach. In the GIACTA study, TCZ resulted in sustained prednisone-free remission at 52 weeks in 53%–56% of TCZ-treated patients and only in 14%–18% of prednisone-treated patients. The cumulative GC dose was >40% lower in TCZ-treated patients than in GC-treated patients, and serious adverse events occurred in 14%–15% of TCZ-treated patients compared with 22%–26% of patients in the placebo groups. Extended follow-up of patients taking TCZ is now necessary to determine the durability of remission and safety of TCZ. On the basis of GIACTA and other trial results, TCZ has recently been approved by FDA for use in GCA.

Two prospective open-label studies on TCZ for PMR reported low disease activity at 12 weeks in 100% of patients; the disease activity was measured according to a PMR-AS < 10 or GC-free remission at 6 months. However, data on PMR are still insufficient to recommend TCZ treatment for this condition outside trials or for exceptional cases with GC-resistant disease or contraindications to GCs. A placebo-controlled double-blind study in phase 3 to evaluate the efficacy of TCZ as a remission induction and GC sparing regimen in patients with new-onset PMR has been completed in the Department of Rheumatology, Medical University Vienna; 39 patients were included, and their assessment is in progress.

Registered clinical trials for other bDMARDS, including Janus kinase inhibitor baricitinib, IL-2, and abatacept, are being conducted.

Currently, treatment of patients with GCA or PMR and exhibiting a persistent high burden of inflammation remains challenging because of multiple relapses with an inability to taper GCs, failure

of MTX and other DMARDs, presence of comorbidities, the occurrence of GC-related adverse events, and resistance to GC therapy. Biological agents, particularly IL-6 inhibitors, should be administered first to these seriously afflicted subpopulations; however, clinical trials have focused on patients with new-onset or relapsing diseases. The application of biological agents early in patients at risk of disease complications and/or treatment-related adverse events should also be considered. Unfortunately, there is a lack of definite data on prognostic factors in PMR and GCA, complicating the definition and identification of the "at risk" population. A pronounced inflammatory response at disease onset is often associated with a higher probability of relapses in both GCA and PMR. Assuming that IL-6 blockade would be particularly effective in cases with high levels of systemic inflammation, these patients would possibly benefit most from treatment with IL-6 blockers [9, 18, 19].

For decades, the key tool for both GCA and PMR diagnosis has been a rapid response to GCs. To prevent blindness in GCA, both immediate GC treatment and rapid response are crucial. Recently, TCZ has yielded impressive results regarding the maintenance of remission in GCA trials; however, it cannot be assumed that TCZ therapy without GCs will prevent vascular complications, such as sight loss or aneurysm. These studies used outcome parameters other than the underlying vessel wall damage, which mostly reflects the inflammatory response. In PMR, no rapid improvement of symptoms was achieved by TCZ without GCs. Although 100% of patients with PMR achieved GC-free remission at 6 months, improvement was more gradual than that noted with GCs[44].

GCs remain the mainstay treatment for both PMR and GCA, but the basis for the use of different treatments is empiric. According to consensus-based recommendations, initial therapy for PMR is prednisone 12.5–25 mg/day, followed by individualized tapering regimens. The optimization of the benefit–risk ratio of GCs to minimize adverse events while achieving sustained remission is an ongoing challenge. The adoption of current treatment recommendations may lead to their optimal use, thereby reducing the burden of GCs. According to a recent EULAR task force study, the risk of GC-related harm is low if doses of <5 mg/day prednisone are prescribed but high if doses >10 mg/day are used, especially in patients taking GCs for a prolonged period (3–6 months or more).

The EULAR/ACR recommendations for the management of PMR 2015, especially for optimal GC therapy, are provided in Table 5 [9]. Minimum effective individualized dose of GCs, individualized tapering, and minimum effective individualized duration of GC therapy are strongly recommended. Regular monitoring of patients' disease activity, laboratory markers, and adverse events are highly suggested.

Table 5 EULAR/ACR 2015 recommendations for GC therapy in PMR management.

Intervention	Dose	Specification
Oral prednisone		
Initial dose	12.5–25 mg/day	Increase the dose for patients at risk of relapse or on long-term therapy (female, elevated ESR, and peripheral arthritis) Decrease the dose for patients at risk of side effects (female, comorbidity, and comedication)

4–8 weeks	targeted dose 10 mg/d	Superior GC response, if 70% improvement (VAS) in PMR symptoms
>4–8 weeks	−1 mg/d per 1 month to discontinuation	In case of 1 mg tablet 1, a decrease 1 mg/d is not feasible; however, a similar dose reduction should be performed
Relapse	back to prerelapse dose	In case of re-remission, dose reduction in 4–8 weeks to dose at relapse should be performed
Intramuscular prednisone		
Initial dose	120 mg/3 weeks	When low cumulative dose is recommended, possible alternative of oral therapy should be applied
12–48 hét	100 mg/month −20 mg/3 months	
>48 hét	40 mg/month −20 mg/4 months to discontinuation	

The second major approach to increasing the benefit–risk ratio of GCs is the development of innovative GC preparations and GC receptor ligands. A novel class of GCs, selective GC receptor modulators (SEGRAM), are dissociated agonists of the GC receptors. Liposomal GCs have been designed to deliver conventional GCs to inflamed tissues by using small nanometer-sized liposomes. This technology may provide strong therapeutic effects with minimum systemic adverse effects.

Modified-release prednisone (MR prednisone) was recently investigated in PMR treatment. This drug enables optimal chronotherapy with bedtime administration of the drug and release of prednisone at the optimal time for suppression of pro-inflammatory cytokines (at 2 am). MR prednisone yielded clinical superiority over conventional prednisone in RA; however, a multicenter randomized phase 3 study evaluating the effects of MR prednisone in patients with PMR was terminated early due to insufficient recruitment [4, 9].

9. Closing Remarks

The fields of PMR and the associated GCA have developed rapidly in recent years, resulting in a new comprehension of the disease concept. Knowledge of older patients' shoulder pain and stiffness, the marked systemic inflammation, and the good response to GCs has widely changed. The rapid development of molecular biology, immunology, and new imaging modalities contributed to a better understanding of disease epidemiology and pathogenesis. The establishment of the EULAR/ACR PMR work group and its consensus studies resulted in internationally unified classification and treatment proposals for PMR.

According to the new concept, PMR should be regarded predominantly as an autoinflammatory disease driven by the IL cascade complex. It belongs to the GCA arteritis complex, and polymyalgic manifestation may represent serious background large vessel vasculitis; PET/CT should be used to distinguish the diseases. The definition of disease activity and treatment to target therapy has been developed, leading to the improved treatment of PMR with high relapse rates and long-term GC

requirements. Ultrasound has been introduced into daily clinical routines, and fast-track clinics have been opened. Promising reports have been published on the efficacy of biological agents, in particular IL-6 antagonists.

In our review, recent developments in the field of PMR are summarized and proposed to assist our rheumatologists, geriatrics, and other specialty colleagues. Lectori salutem!

Author Contributions

Dr. Schmidt Z: Topic selection, literature review and analysis (research and experience of the Hungarian PMR team is also included), manuscript preparation Prof. Dr. Poór G: Collaboration, manuscript review and approval. Final approval has been confirmed by both of the authors.

Competing Interests

The authors have declared that no competing interests exist.

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