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Shared and Distinguishing Features of Late-Onset Rheumatic Diseases Fulfilling Polymyalgia Rheumatica Classification Criteria

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Abstract

Polymyalgia rheumatica (PMR) is a common inflammatory syndrome of older adults, characterised by proximal girdle pain, stiffness, extracapsular inflammation and an initial complete or partial response to moderate-dose glucocorticoids. In the absence of a disease-specific biomarker, PMR classification relies on clinical, laboratory and imaging features, yet its clinical course remains heterogeneous, ranging from self-limiting disease to steroid-refractory disease or subsequent evolving diagnoses. Increasing evidence indicates that a range of immune-mediated and degenerative conditions, including late-onset spondyloarthritis, elderly-onset autoantibody-negative rheumatoid arthritis, autoinflammatory syndromes and immune checkpoint inhibitor–associated arthritis, may fulfil PMR classification criteria at presentation. These conditions do not merely represent well-recognised non-PMR mimics but instead converge on a shared polymyalgic phenotype defined by age, anatomical distribution and elevated acute-phase reactants. Clinical context, including failure to adequately respond to corticosteroids or failure to taper corticosteroids, together with imaging findings, may point towards different underlying diagnoses that are relevant for emerging treatment strategies. Recognising this phenotypic convergence, alongside pathogenic divergence, may improve diagnostic precision, inform prognosis, and support more individualised therapeutic strategies beyond conventional glucocorticoid-based management.

Polymyalgia rheumatica (PMR) is a well-recognised inflammatory syndrome of later life, typically presenting with bilateral shoulder and/or hip girdle pain, prolonged morning stiffness, elevated acute-phase reactants and a rapid response to glucocorticoids [1]. Magnetic resonance imaging (MRI) and positron emission tomography (PET) most characteristically demonstrate pericapsular or periligamentous soft-tissue inflammation without substantial bone-marrow involvement [2, 3]. In the absence of a disease-specific biomarker, the 2012 EULAR/ACR criteria provide a structured clinical framework for PMR classification, incorporating age, characteristic symptom distribution, inflammatory markers, exclusion of alternative diagnoses, and supportive imaging findings [4]. In the derivation study, the clinical criteria demonstrated 68% sensitivity and 78% specificity, with lower specificity in distinguishing PMR from rheumatoid arthritis (RA); the addition of ultrasound modestly improved specificity (~81%) with similar sensitivity [4].

Notably, the inclusion of rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibody (ACPA) negativity reflects the close clinical resemblance between PMR and elderly-onset rheumatoid arthritis (EORA), both of which may present with a polymyalgic distribution of symptoms [4, 5]. Consistent with this, validation studies have shown that the criteria retain limited specificity against inflammatory arthritis, with a proportion of RA cases classified as PMR. While ultrasound improves classification performance [4], the persistence of this overlap supports the concept that these conditions may share not only clinical features but also aspects of anatomical involvement (e.g. extracapsular and periarticular tissues).

Similar presentations occur across spondyloarthritis, connective tissue disease (CTD) and other inflammatory conditions (Figures 1 and 2) [6, 7]. Rather than superficial mimics, these conditions may closely reproduce the age distribution, anatomical localisation and inflammatory response of PMR. We describe this as phenotypic convergence: distinct immune pathways localizing inflammation to a shared periarticular tissue domain. Herein, we examine immune-mediated conditions that converge on the PMR phenotype with sufficient similarity to fulfill PMR classification frameworks yet display shared and distinct features that extend beyond classical mimics. We integrate clinical, imaging and immunological evidence to define this spectrum and identify features that may improve diagnosis, therapeutic stratification and early glucocorticoid-sparing management.

Classical PMR

Classical PMR is characterized by predominantly extracapsular inflammation without persistent synovial stromal activation and erosive pannus typical of RA, accounting for marked inflammation without periarticular erosion [2, 3, 6]. Genetic studies show enrichment of HLA-DRB1*04 alleles, which is stronger and more consistent in giant cell arteritis (GCA) but appears more heterogeneous in isolated PMR, supporting the idea of a partially shared antigen-presentation axis across the PMR–GCA spectrum [8]. This overlap aligns with the broader immunologic continuum in which IL-6 and IFN-γ signaling, activated macrophages, and class II–restricted CD4 T-cell responses contribute to systemic inflammation [9]. Immunophenotypically, classical PMR is characterized by macrophage-rich extracapsular inflammation with prominent IL-6 pathway activation, together with evidence of T-cell involvement in affected bursae and tendon sheaths [10]. Variation at the IL-6 −174 promoter is associated with

higher IL-6 production and relapse risk [11]. Furthermore, IL1R1, NEK6 and CCDC88B as susceptibility loci and implicate IL-1-related networks, IL-6 receptor signalling, visceral adiposity and smoking [12]. Mendelian-randomisation findings further associate genetically proxied IL-1 receptor antagonism with lower PMR risk [13].

Aging may further lower the inflammatory threshold through expansion of MHC class II-positive classical monocytes and epigenomic remodelling that sustains antigen presentation, CD4 T-cell activation and responses to sterile danger signals [14-17]. These changes parallel innate–adaptive amplification in GCA and may link periarticular and arterial adventitial inflammation across the PMR–GCA spectrum [9, 18]. Together, these mechanisms may convert an age-conditioned, danger-signal-rich periarticular niche into systemic IL-6-driven inflammation. The efficacy of IL-6 blockade in refractory PMR and GCA provides reverse-translational support for this axis [19, 20]. Other conditions may reproduce this phenotype while remaining immunologically and therapeutically distinct.

Autoinflammatory or Innate Immune Driven PMR

Clonal autoinflammatory disorders such as VEXAS syndrome and myelodysplastic syndromes (MDS) provide a clear example of how myeloid-driven inflammation may converge on the PMR phenotype [21]. In VEXAS, the PMR phenotype is frequently DMARD-refractory and shows dependence on higher-dose glucocorticoids with relapse on taper, rather than the sustained response typical of PMR, consistent with persistent myeloid-driven inflammation [22]. Related presentations approximating the PMR phenotype have also been reported in myelodysplastic syndromes, further supporting a link between clonal myeloid dysregulation and polymyalgic inflammatory phenotypes in older individuals [21]. Somatic UBA1 mutations disrupt cytoplasmic ubiquitylation and protein homeostasis, activating unfolded-protein, NF-κB and cGAS–STING stress pathways in myeloid cells [21, 23]. Typical presentation is in older adults; population-based data estimates UBA1 pathogenic variants in 1 in 4,269 men older than 50 years [24].

Together these pathways sustain high IL-1β, IL-6 and TNF output and license the NLRP3 inflammasome, thereby giving rise to a polymyalgic clinical picture without adaptive autoimmunity and often with poor glucocorticoid responsiveness [21]. Case reports describe patients initially managed as PMR who were later found to carry UBA1 mutations, illustrating that a PMR like presentation can occur in VEXAS.[24, 25] More broadly, age-related clonal haematopoiesis of indeterminate potential, characterised by somatically acquired mutations in myeloid lineages, represents a related but more prevalent mechanism through which myeloid-driven inflammatory priming may lower the threshold for polymyalgic inflammation in older individuals [26]. VEXAS therefore represents a high-penetrance form of somatic myeloid autoinflammation that may closely resemble PMR at presentation but follows a biologically and therapeutically distinct course.

Viral Infections and PMR Phenotypes

Viral infections can trigger type I interferon-mediated musculoskeletal inflammation that may present with proximal girdle pattern similar to PMR [27]. Resident plasmacytoid dendritic cells in periarticular structures,

including interspinous ligamentous tissue, can produce type I interferon, providing a potential tissue context for virus-associated polymyalgic inflammation in older individuals [28]. Parvovirus B19 infection may present with symmetric arthralgia and, in older adults, shoulder and pelvic girdle pain similar to PMR [29]. Alphaviruses such as Chikungunya are characterised by severe acute myalgia and arthritis, with imaging studies demonstrating tenosynovitis and sub-deltoid bursitis, particularly in older patients [30-33]. Similarly, viral immune dysregulation in HIV infection and following immune reconstitution has been associated with proximal girdle pain and peri-articular inflammation resembling PMR [34]. Transient polymyalgia-like syndromes have also been reported following influenza and other respiratory viral infections [35].

New-onset PMR has been reported following SARS-CoV-2 infection and COVID-19 vaccination, raising the possibility that coronavirus-related immune activation may act as a trigger for classical PMR in susceptible older individuals[36, 37]. Whether these cases represent triggered classical PMR or a transient post-viral syndrome remains uncertain; they nevertheless support the possibility that acute immune activation can precipitate PMR-classifying presentations in susceptible older adults, potentially with a shorter and more self-limiting course.

Reactive arthritis converging on the PMR phenotype

Reactive arthritis following bacterial infection may present with proximal girdle pain and prolonged morning stiffness approximating the PMR phenotype [38], reflecting an enthesitis-driven pattern of inflammation. Case-based observations illustrate how this presentation may initially raise suspicion for PMR but ultimately be classified as reactive arthritis, which generally has a favorable and often self-limiting course, particularly in HLA-B27–negative cases [38].

Importantly, data indicate that FDG-PET patterns typically associated with PMR, including uptake at the shoulders, hips, ischial tuberosities and spinal processes, may also be observed in post-infectious or reactive arthritis [39] Thus, transient IL-23/IL-17-mediated entheseal inflammation may reproduce both the clinical and PET phenotype of PMR despite a distinct pathogenesis [39, 40].

The Interface Between PMR and Spondyloarthritis

While PMR and SpA differ in HLA predisposition, imaging pattern, cytokine networks, and therapeutic response, the clinical and pathological overlap between these diseases is increasingly recognised. SpA is typically HLA class I-restricted and IL-23/17-driven, showing bone marrow edema at entheses and sacroiliac joints, whereas PMR is HLA class II-linked, IL-6-dominant, and characterized by bursitis and peritendinous and pericapsular inflammation on MRI. Unlike classical ankylosing spondylitis, psoriatic arthritis often adopts a ligament-centric axial pattern, with inflammation tracking the enthesis–annulus–longitudinal ligament complex; this ligamentous topography places it closer in anatomical pattern to the extracapsular, peritendinous signature of PMR, even though their cytokine programs and HLA anchors diverge [41, 42]. The clinical boundaries between these entities may blur in selected patients, raising the possibility of convergent mechano-inflammatory pathways rather than a shared disease mechanism.

A recent cohort of 31 patients aged over 50 who initially fulfilled PMR classification criteria later evolved into a clear late-onset spondyloarthritis phenotype. These individuals typically presented with bilateral shoulder and hip girdle symptoms and elevated inflammatory markers but were unable to taper glucocorticoids and subsequently demonstrated imaging features characteristic of spondyloarthritis. MRI frequently showed subacromial–subdeltoid and hip-region bursitis, and FDG-PET often revealed periarticular uptake consistent with PMR. Some patients also demonstrated features suggestive of concomitant GCA. During follow-up, many patients developed additional features associated with spondyloarthritis such as psoriasis, inflammatory bowel disease, uveitis or a relevant family history, and sacroiliac joint imaging often demonstrated bone marrow or spinal edema consistent with ASAS criteria. Although several patients showed an initial symptomatic response to glucocorticoids, relapse during tapering was common, and a substantial proportion ultimately required DMARDs or biologic therapy including TNF or IL-17 inhibition for sustained benefit. [7]

Earlier reports similarly described late-onset undifferentiated SpA presenting as PMR but later developing sacroiliitis and poor glucocorticoid responsiveness [43]. Positive topline results from the phase III REPLENISH trial of secukinumab in glucocorticoid-resistant PMR further suggest that IL-17-driven disease may exist within the broader PMR-classifying spectrum. Relapse during glucocorticoid tapering, bone-marrow edema and SpA-specific clinical features should therefore prompt consideration of early glucocorticoid-sparing treatment.

Immune checkpoint inhibitor–associated PMR phenotypes

Immune checkpoint inhibitor (ICI)–associated inflammation provides a clear example of how T-cell–driven immune activation may converge on the PMR phenotype. ICIs enhance antitumor immunity by releasing cytotoxic T-cell responses, particularly $CD8^+$ effector cells, through blockade of the PD-1/PD-L1 and CTLA-4 pathways. While effective against malignancy, this mechanism can precipitate musculoskeletal immune-related adverse events (irAEs) through loss of peripheral tolerance [44]. In the Leeds cohort of 60 patients with musculoskeletal irAEs, 19 (31.7%) whole body MR imaging showed a PMR–like uptake pattern. Of these, 12 presented with concomitant peripheral arthritis and 7 with isolated PMR-like disease. Patients with overlap required higher cumulative glucocorticoid doses and frequent DMARD initiation; those with isolated PMR-like features generally had a milder course, lower CRP, less glucocorticoid exposure and no DMARD requirement [45]. Similarly, in the a series of 61 patients with rheumatic irAEs, 3 developed de novo PMR-like syndrome and 1 had a PMR flare [46]. Calabrese and colleagues reported 49 patients with ICI-associated PMR-like syndrome [47]; 37 had complete clinical data and 28 (75%) fulfilled 2012 EULAR/ACR criteria for PMR; 9/20 (45%) displayed peripheral joint involvement and 6/20 (30%) had normal acute-phase reactants. Nearly all patients (94%) received glucocorticoids, with (37%) requiring > 20 mg prednisone daily and (20%) receiving a glucocortoicoid-sparing agent [47].

Studies of synovial fluid and tissue from ICI-associated arthritis demonstrate clonally expanded cytotoxic CD8 T cells expressing perforin, granzyme B, IFN-γ and TNF [48]; as these findings did not derive from a PMR-like phenotype, direct extrapolation to ICI-associated PMR requires caution. Recent single-cell transcriptomic analyses show enrichment of CD38-high cytotoxic CD8 T cells and an interferon-stimulated gene signature characteristic of checkpoint-related inflammation[48, 49]. HLA-DRB1 associations remain inconsistent, although class II-restricted antigen presentation indirectly supports cytotoxic CD8 T-cell responses [50, 51]. Compared to classical

PMR, ICI-associated polymyalgic presentations have more frequent peripheral arthritis, variable inflammatory markers and a more heterogeneous therapeutic course.

Difficulties in Distinguishing Late onset Rheumatoid Arthritis from PMR

Late-onset inflammatory arthritides such as elderly-onset seronegative RA and remitting seronegative symmetrical synovitis with pitting edema (RS3PE) provide clear examples of how distinct immunological mechanisms may converge on the PMR phenotype. RS3PE was originally described as a distinct form of RA, with abrupt-onset seronegative symmetrical synovitis, pitting oedema and favourable glucocorticoid responsiveness and a good prognosis [52]. Prominent distal extremity swelling, extensor tenosynovitis and peripheral edema provide distinguishing features and indicate a different anatomical emphasis from classical RA, with closer similarities to PMR[53]. MRI studies support this anatomical distinction: RA shows predominantly synovial-centred phenotype, whereas PMR and RS3PE are characterised by capsular, extracapsular and tenosynovial involvement [6, 54, 55].

Non- RS3PE seronegative elderly-onset RA can fulfill PMR classification criteria based on shoulder and hip girdle involvement and systemic inflammation. With longitudinal follow-up, however, these patients have more persistent synovitis, less dramatic glucocorticoid response, and articular erosions (~ one-third of patients), in contrast to the shorter lived, non-erosive, steroid responsive arthritis seen in PMR [56]. In the Leeds elderly-onset RA cohort, shoulder involvement occurred in 64% versus 38% of young-onset RA, and hip involvement in 24% versus 12%, respectively [56].

In a whole-body MRI study from our center, extracapsular inflammation was detected in 14 of 22 (64%) PMR patients; RA showed this pattern in 1 of 16 cases (6%). Conversely, predominant synovial inflammation was present in 15 of 16 RA (94%) but in only 8 of 22 PMR (36%), supporting the concept that PMR exhibits more capsular and extracapsular inflammation, while RA remains predominantly synovial. The extracapsular pattern in PMR also correlated with higher IL-6 levels (median 25.8 pg/mL vs 6.0 pg/mL) and a higher rate of complete early patient-reported glucocorticoid response (86% vs 13%), although this group was less likely to discontinue glucocorticoids within the first year [2]. Severe shoulder- or hip-centered RA synovitis may extend into age-altered capsular and extracapsular tissues, producing a clinical PMR pattern. However, the advent of ACPA testing means that this ACPA-positive RA clinical pattern is now less commonly misdiagnosed as PMR (Figure 1). Low-level RF positivity is common in older adults, so definitive classification of seronegative late-onset RA may still depends on longitudinal evolution.

Interferon predominant autoimmune polymyalgic presentations in CTDs

CTDs provide another example of how interferon-driven immune responses may converge on the PMR phenotype, particularly through involvement of periarticular and extracapsular structures. ANA positivity is not uncommon in healthy individuals so initial presentations with dominant joint disease may lead to a positive ANA being ignored with the patient treated for PMR and developing the CTD phenotype later [57]. CTD-related arthropathy may initially manifest with hand swelling or periarticular oedema, pointing to an epicentre outside the synovial cavity [58]. Early imaging studies of lupus hand arthropathy reported periarticular edema as a prominent finding in small joint disease [58]. The joint microanatomy of SLE offers a crucial lens. Some forms of lupus arthritis are typically

non-erosive, with synovitis and tenosynovitis rather than bone destruction [59]. Advanced imaging has demonstrated that periarticular soft tissues, particularly tendon sheaths and capsular structures, are frequent targets [60].

Jaccoud's arthropathy represents the extreme of this spectrum: reducible deformities such as ulnar deviation and swan-neck configurations arise not from erosions, but from ligamentous laxity, capsular fibrosis, and extensor tendon instability or subluxation at the MCP level,[61] with MRI studies confirming sagittal band pathology and peri-tendinous inflammation.[62] Although the immunological programs of SLE (type I interferon signalling, B-cell autoreactivity and autoantibodies) and PMR (innate-driven IL-6 predominance with minimal B-cell involvement) differ fundamentally, their micro-anatomic footprints can converge on periarticular soft tissue, capsular and tendon domains [62].

We recently demonstrated that resident plasmacytoid dendritic cells within ligamentous entheseal tissue, including interspinous structures implicated in PMR, are capable of robust type I interferon production following TLR7/9 stimulation, suggesting that ligamentous and peri-entheseal tissues can act as initiators of IFN-driven inflammation [28]. These observations support a model in which interferon-driven immune activation may act on periarticular tissues to reproduce key elements of the PMR phenotype, particularly in older individuals.

Clinically, polymyalgic presentations in CTDs are often accompanied by features that distinguish them from classical PMR. The CTDs and PMR can coexist, most often in primary Sjogren's disease and in late-onset SLE; accompanying features help distinguish these overlaps from classical PMR. In a longstanding primary Sjogren cohort of 547 patients, PMR prevalence was about ~3%, usually developing years after the Sjogren diagnosis in older women. Clinical profiles were enriched for glandular disease, more frequent ANA positivity, and relative hypogammaglobulinemia rather than the hypergammaglobulinemia often seen in primary Sjogren cohorts [63]. A French multicentre series of seventeen primary Sjogren's disease with PMR cases reported less dry mouth and lower anti-SSA positivity compared with isolated primary Sjogren. Compared with isolated PMR, there was more peripheral joint involvement and fewer typical shoulder and hip ultrasound lesions, and relapse rates were similar to isolated PMR [64]. In SLE, older adults may present with a PMR-like picture that later fulfils full SLE criteria. In such cases, proximal girdle pain and morning stiffness are frequently accompanied by extra-articular or atypical features, including myositis, serositis, interstitial lung disease, Raynaud phenomenon, and occasionally non-classical temporal arteritis [65]. Taken together, these findings indicate that interferon-driven CTDs may approximate the PMR phenotype at presentation, but are typically distinguished by additional systemic features, autoantibody profiles and atypical imaging patterns, supporting targeted evaluation for underlying autoimmune disease when these features are present.

Other conditions

Several systemic disorders may initially resemble PMR despite lacking its characteristic periarticular pathology. In a case-control study, 13% of patients with biopsy-proven ANCA-associated vasculitis had previously been diagnosed with PMR, reflecting diagnostic overlap rather than shared biology [66]. Myeloma and metastatic bone disease may cause musculoskeletal pain and elevated inflammatory markers through marrow cytokine activity,

osteoclast activation or tumour-induced osteolysis, rather than primary extracapsular inflammation [1, 67]. Collectively, these conditions may resemble the PMR phenotype clinically but remain biologically distinct, as they do not primarily involve the periarticular and extracapsular tissues typical of classical PMR.

Why do diverse inflammatory conditions present with a polymyalgic shoulder and hip phenotype?

The recurrence of a shoulder- and hip-centred PMR pattern across distinct diseases suggests that clinical expression is constrained by a shared anatomical substrate. Bursae, tendon sheaths, capsular insertions and ligamentous tissues may permit myeloid, interferon, IL-17 and cytotoxic T-cell pathways to produce a similar extracapsular phenotype.

Aging may increase susceptibility through cumulative mechanical loading, matrix remodelling, collagen disorganisation, reduced elasticity and advanced glycation, while resident fibroblast and immune-cell heterogeneity provides context-dependent inflammatory responses [68-71]. Age-associated inflammaging and myeloid skewing may further lower the threshold for tissue-level amplification of diverse inflammatory stimuli [72]. Thus, PMR-like disease may arise through interactions between systemic immune activation and an age-conditioned periarticular microenvironment rather than from a single unifying pathway. While this review focuses on the shoulder and hip girdles, peripheral joint synovitis may also occur in a subset of PMR patients, as shown by imaging [56, 73]. The age-related prevalence of shoulder pain and degenerative periarticular pathology further supports large-joint tissue susceptibility as a determinant of this phenotype [74, 75].

Future Directions

Future studies should combine longitudinal imaging, detailed clinical phenotyping and tissue-level profiling to distinguish classical PMR from biologically distinct PMR-like syndromes. Defining how age-related tissue vulnerability interacts with disease-specific immune pathways may enable earlier diagnostic stratification and prognosis-based treatment approaches.

Conclusion

Diverse immune-mediated diseases may fulfill PMR classification criteria by converging on an age-conditioned periarticular phenotype. This clinical similarity should not be interpreted as shared pathogenesis: underlying biology, disease trajectory, treatment response and extra-musculoskeletal involvement may differ substantially. Recognising steroid-taper failure, atypical imaging, peripheral arthritis and systemic features may therefore improve diagnostic precision and support earlier mechanism-informed, steroid-sparing management.

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