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Review article

Update on polymyalgia rheumatica ☆

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ABSTRACT

Polymyalgia rheumatica is an inflammatory disease of unknown etiology affecting individuals aged fifty years and older, mainly of Caucasian ethnicity. Polymyalgia rheumatica is associated with giant cell arteritis more frequently than expected by chance alone. In both conditions, females are affected two to three times more often than males. The clinical hallmark manifestations of polymyalgia rheumatica are aching and morning stiffness in the shoulder girdle and often in the pelvic girdle and neck. Serum inflammatory markers are typically elevated, while the most consistent abnormal finding on imaging studies is bursitis in the symptomatic areas. A dramatic response to glucocorticoids is characteristic of polymyalgia rheumatica. Many patients are able to discontinue glucocorticoids six months to two years after the onset of clinical symptoms, but some patients may require longstanding glucocorticoid treatment. Glucocorticoid-sparing agents may be helpful in patients with chronic relapsing courses and those at high risk of glucocorticoid-related adverse events.

1. Introduction

Polymyalgia rheumatica (PMR) is an inflammatory disease characterized by aching and prolonged morning stiffness in the shoulder girdle and often in the pelvic girdle and neck. The first case of PMR was described 1888 [8], but the term "polymyalgia rheumatica" was coined by Barber in 1957 [3].

2. Epidemiology

PMR typically affects people 50 years of age or older, mostly Caucasians. Its incidence increases progressively with age, peaking between 70 and 80 years of age [60]. Women are affected two to three times more often than men [31]. A population-based study from Olmsted County, Minnesota, US, estimated the prevalence of PMR to be as high as 1 case for 133 persons over 50 years [67]. In Italy, a study based in Reggio Emilia revealed that average annual incidence rates of PMR from 1981 to 1985 were 12.8 per 100,000 individuals aged 50 years or older [70].

PMR is associated with giant cell arteritis (GCA) more frequently than expected by chance. Specifically, approximately 16–21% of patients with PMR have clinical manifestations of GCA, while about 50% of patients with GCA have symptoms of PMR [20,52,68]. PMR can develop before, together with, or after GCA [62]. Mortality is not increased in PMR [6], but there is a significant morbidity, mainly related to complications of glucocorticoid therapy [47].

3. Classification criteria

In clinical practice, the diagnosis of PMR rests on its characteristic manifestations, raised inflammatory markers, a dramatic response to GC, and exclusion of other disorders that may present with similar features [62]. For classification purposes, a number of criteria have been proposed over time, including those by Chuang [16], Healey [34], and Bird [4] (Table 1). However, none of these criteria has been properly validated or received universal acceptance. More recently, new classification criteria have been developed by a group of international specialists with the official endorsement of the American College of Rheumatology and of European League Against Rheumatism [18] (Table 1). These criteria were generated by prospectively evaluating a cohort of 125 patients with new onset of PMR and 169 subjects with a variety of other conditions potentially mimicking PMR. A set of items was agreed upon by at least 70% of the specialists, and statistical models were used to determine the relevance of each item to identify PMR and distinguish it from its mimickers. In patients aged 50 years or older presenting with bilateral shoulder aching and raised inflammatory markers, these criteria had 68% sensitivity and 78% specificity for PMR. The use of ultrasonography is discretionary; when ultrasonography findings consistent with PMR are considered, sensitivity decreases to 66%, but specificity increases to 81%.

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Table 1
Classification criteria for polymyalgia rheumatica.

Chuang et al. [16]	
1. Patients 50 years or older	
2. Bilateral aching and stiffness persisting for one month or more involving two of the following areas: neck or torso, shoulders or proximal regions of the arms, and hips or proximal aspects of the thighs	
3. Erythrocyte sedimentation rate greater than 40 mm/1st hour	
4. Exclusion of other diagnoses except giant cell arteritis	
The presence of all these criteria defines PMR diagnosis	
Healey et al. [34]	
1. Persistent pain (for at least one month) involving two of the following areas: neck, shoulders, and pelvic girdle	
2. Morning stiffness lasting more than 1 h	
3. Rapid response to prednisone (<20 mg/day)	
4. Absence of other diseases capable of causing the musculoskeletal symptoms	
5. Age over 50 years	
6. Erythrocyte sedimentation rate greater than 40 mm/1st hour	
The diagnosis of PMR is made if all the above criteria are satisfied	
Bird et al. [4]	
1. Bilateral shoulder pain and/or stiffness	
2. Onset of illness within two weeks	
3. Initial erythrocyte sedimentation rate higher than 40 mm/1st hour	
4. Morning stiffness exceeding 1 h	
5. Age older than 65 years	
6. Depression and/or loss of weight	
7. Bilateral upper arm tenderness	
A diagnosis of probable PMR is made if any 3 or more of these criteria are fulfilled. The presence of any 3 or more criteria yields a sensitivity of 92% and a specificity of 80%	
American College of Rheumatology/European League against Rheumatism criteria [18]	
Required criteria: age 50 years or older, bilateral shoulder aching and abnormal C-reactive protein and/or erythrocyte sedimentation rate	
1. Morning stiffness >45 min	2 points
2. Hip pain/limited range of motion	1 point
3. Negative rheumatoid factor and/or anti-cyclic citrullinated peptide antibodies	2 points
4. Absence of peripheral joint pain (with ultrasonography findings)	1 point
5a. At least one shoulder with subdeltoid bursitis and/or biceps tenosynovitis and/or glenohumeral synovitis (either posterior or axillary) and at least one hip with synovitis and/or trochanteric bursitis	1 point
5b. Both shoulders with subdeltoid bursitis, biceps tenosynovitis or glenohumeral synovitis	1 point
A patient with a score of 4 or more (5 or more if ultrasonography findings are considered) can be categorized as having PMR	

4. Etiology and pathogenesis

The etiology of PMR is still obscure. A seasonal pattern with higher incidence rates in winter has been reported [54], suggesting that an infectious agent could act as trigger. The odd case of PMR simultaneously affecting both spouses would also fit with an infectious etiology [57]. However, a bacterial etiology seems unlikely because procalcitonin levels are not raised in PMR [71]. In addition, no specific microorganism has consistently been linked to PMR [56,74].

The higher incidence of PMR in Caucasians with a North–South gradient in Europe may suggest that genetic factors could modulate susceptibility to PMR [31]. However, the role played by genes in the pathogenesis of PMR has yet to be fully unraveled. Among the genes of the major histocompatibility complex, the HLA-DRB1*04 allele is variably associated with susceptibility to PMR in different populations [25,28,60], while polymorphisms of the proinflammatory cytokines tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) cluster genes appear to confer a slightly increased risk of developing PMR [26]. Of note, all of the above genes are risk factors for developing GCA as well, in keeping with the concept that PMR and GCA are closely related disorders.

Other genes further modulate the susceptibility to, and/or severity of PMR. A study reported a significant association between the IL-1RN*2/2 genotype and susceptibility to, although not severity of PMR [1]. Among the tumor necrosis factor (TNF) microsatellite polymorphisms, TNFb3 has been found to be positively and TNFd4 negatively associated with PMR [46], while the allele A within the promoter region of the RANTES (regulated upon activation normal T-cell expressed and secreted) gene at position-403 has been found to be overexpressed in PMR patients relative to controls and GCA patients [45]. In Northern Italy, the G/R 241 polymorphism of intercellular adhesion molecule-1 (ICAM-1) has been linked to susceptibility to PMR and GCA [66], while in Northern Spain the distribution of ICAM-1 polymorphisms at codons 241 and 469 showed no significant differences between patients with isolated PMR and controls [2]. On the other hand, Gonzalez-Gay et al. have reported an association between the IL-6-174 allele C and PMR manifestations in patients with GCA [30], whereas an Italian study showed that the IL-6 promoter polymorphism at position -174 was equally represented in patients with PMR and controls [7]. These findings suggest that a multitude of genes contributes to explain the susceptibility to and/or severity of PMR, and that associations with polymorphisms may vary in different populations.

Histological studies of synovial membranes extracted from patients with active PMR mostly show a nonspecific chronic inflammatory infiltration with a predominance of macrophages and T cells [50]. Activated immune cells, especially macrophages, synthesize proinflammatory molecules such as IL-1β and IL-6, which are increased in the peripheral blood of patients with PMR and are responsible for its constitutional manifestations [19,33]. Dendritic cells in PMR have an activated phenotype, and could thus be arguably involved in setting off the inflammatory process [24]. However, the events leading to dendritic cell activation remain to be elucidated [24].

Temporal arteries from patients with PMR without clinical manifestations of GCA have been found to contain gene-specific transcripts for IL-2, IL-1, and transforming growth factor-β (TGF-β) even in the absence of inflammatory cells [77,78]. However, the Th1 cytokine interferon-γ, which is found in most temporal artery samples from patients with GCA, is characteristically absent in those from patients with PMR [77,78]. This suggests that while PMR and GCA may share some immune pathways, interferon-γ is critical for the development of overt arteritis.

5. Clinical manifestations

The hallmark manifestations of PMR are aching and prolonged morning stiffness in the shoulder girdle and often in the neck and pelvic girdle [62]. Nearly all patients develop shoulder pain, while the neck and pelvic girdle are involved in approximately 70% and 50% of patients, respectively [60,62]. The pain is inflammatory in nature i.e. worse at night and radiates distally toward the elbows and knees. Shoulder and hip pain may initially be unilateral, but as a rule becomes soon bilateral. The onset is quite sudden in some patients, who can name “day and hour” of the onset of their pain, but it can also be gradual. About 40% of patients have systemic symptoms including low-grade fever, depression, fatigue and weight loss, while circa 50% of patients have distal musculoskeletal manifestations [60,62,63]. In particular, one-quarter of patients have arthritis mainly of knees (40%) and wrists (40%); involvement of the metacarpophalangeal joints is less common, but not exceptional (25% of all patients with peripheral synovitis), and may mimic rheumatoid arthritis [63]. However, unlike rheumatoid arthritis, PMR-related arthritis is typically non-erosive, self-limiting, and highly responsive to glucocorticoids. Finally, in a minority (about 12%) of patients, distal tenosynovitis mainly of the extensor tendons of hands and/or feet variably associated with joint synovitis may be the predominant peripheral manifestation, often referred to as RS3PE (remitting seronegative symmetrical synovitis with pitting edema) syndrome [63]. Carpal tunnel syndrome in PMR is probably due to tenosynovitis of wrist flexors [23] and has been noted in 14% of patients [63].

On examination, patients with PMR may have evidence of painful and limited range of active and often passive movements of the

shoulders and hips [62]. Muscle weakness is not a feature of PMR, although patients may be unable to maximally contract involved muscles because of pain. In patients with distal musculoskeletal manifestations there may be some joint tenderness and swelling, while Phalen and Tinel signs may be positive in patients with carpal tunnel syndrome.

There are no established criteria to assess disease activity and response to treatment in PMR. However, the European League against Rheumatism has proposed a core set of response criteria for PMR, which include erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP), pain, physician's global assessment, early morning stiffness, and degree of elevation of the upper limbs [42]. Remission criteria based on the same outcome measures have been proposed [41]. On a similar line, using a Delphi approach the international Work Group for PMR and GCA has identified a number of parameters deemed crucial for definitions of remission and of relapse, i.e. patient's pain assessment, early morning stiffness, ESR, CRP, shoulder and hip pain on clinical examination, limitation of upper limb elevation, and glucocorticoid requirements [21].

6. Investigations

6.1. Laboratory tests

Inflammatory markers, such as the ESR and CRP, are elevated in most patients with PMR [62]. Other laboratory abnormalities associated with active inflammation may include normochromic normocytic anemia, thrombocytosis, hypoalbuminemia, and raised α-2 globulin proteins [73]. However, in a small number of cases the ESR and, rarely, the CRP may be normal despite clinically active disease [22,78]. The CRP is more specific than the ESR in reflecting inflammation and should thus preferentially be used to monitor disease activity over time [61]. Plasma fibrinogen is not inferior to ESR and CRP in supporting the diagnosis of PMR and may be more specific in assessing response to treatment [48]. Clinical flares are typically associated with a rise in serum inflammatory indices [39], whereas the reverse is not always true, i.e. inflammatory indices may sometimes rise in the absence of clinically active disease [60,62]. Therefore, the decision of stepping up glucocorticoid therapy should not be solely based on a rise in inflammatory markers. Autoantibodies, including antinuclear antibodies, anti-cyclic citrullinated peptide antibodies and rheumatoid factor are typically negative, although in approximately 10% of elderly subjects rheumatoid factor may be nonspecifically positive, usually at low titer [43,60].

6.2. Imaging techniques

Imaging techniques have greatly contributed to reveal the nature of PMR lesions. Earlier studies based on scintigraphy showed increased articular tracer accumulation thought to reflect synovitis in a high percentage of patients with PMR [9,51]. However, owing to its poor power of resolution, bone scan was not able to pinpoint the exact location of the inflammatory changes. Later on, with the advent of techniques endowed with much better spatial resolution such as magnetic resonance imaging (MRI) and ultrasonography, it became clear that peri-articular bursitis, rather than synovitis, was the most consistent lesion of PMR. In particular, subacromial–subdeltoid, trochanteric, cervical and lumbar bursitis have been detected in patients with PMR that had pain in the shoulders, pelvic girdle, neck, and lumbar spine, respectively [12,59,65]. Ultrasonography and MRI are equally sensitive in revealing bursitis at the shoulder and hip level, but MRI is required to demonstrate bursitis in the spine [12,65]. Bilateral shoulder bursitis has also been detected in PMR patients with normal ESR (Fig. 1)[11]. Some early reports suggested that bilateral shoulder and pelvic bursitis had very high sensitivity and specificity for PMR in patients with shoulder and pelvic girdle pain, respectively [12,65]. However, later studies have shown a more nuanced pattern of imaging alterations in patients with PMR, with changes seen in PMR somewhat overlapping with those seen in RA. More specifically, according to a systematic review, ultrasonography studies published from 2001 to 2011 revealed bilateral shoulder bursitis in 61% to 92% of patients with PMR [9]. Bilateral biceps tenosynovitis was demonstrated in 34% to 100% of PMR patients, while bilateral gleno-humeral synovitis was demonstrated in 16% to 20% of cases [9]. On the same line, a study that compared ultrasonographic findings in patients with PMR and RA disclosed unilateral subachromial–subdeltoid bursitis 55% of patients with PMR versus 18% of RA patients and 25% of controls, while long head biceps tenosynovitis was found in 47% of PMR patients versus 23% of RA patients and 20% of controls; bilateral subachromial–subdeltoid bursitis found in 37% of PMR patients (versus 3% of rheumatoid arthritis patients), and bilateral long head biceps tenosynovitis in 30% of PMR patients versus none of rheumatoid arthritis patients [58]. Therefore, while subachromial–subdeltoid bursitis and tenosynovitis of the long head of the biceps appear to occur fairly frequently in PMR, it is unclear how well these signs are able to discriminate patients with PMR from those with rheumatoid arthritis and from unaffected controls at the individual patient's level. In agreement with this view, the addition of ultrasonographic signs to conventional clinical and laboratory criteria improved only marginally the specificity of the novel classification criteria for PMR proposed by the American College of Rheumatology/European League against Rheumatism [18].

There is limited evidence on the use of ultrasonography to follow up patients with PMR. In a prospective cohort of 53 patients evaluated clinically, by laboratory markers and by ultrasonography at onset of glucocorticoid therapy, at 4 weeks, and at 12 weeks, clinical, laboratory and ultrasonography variables showed a parallel decrease over time [36]. Moreover, after 4 and 12 weeks of treatment with glucocorticoids, ultrasonographic inflammatory findings showed similar or better sensitivity to change than clinical and laboratory markers of PMR activity [36]. However, in another prospective study on 57 consecutive, newly diagnosed patients with PMR, while glucocorticoids significantly reduced the frequency and the severity of subacromial/subdeltoid bursitis, long head biceps tenosynovitis, and glenohumeral synovitis, as many as 59% of the 44 patients judged to be in clinical remission or to have low disease activity had persistent inflammatory lesion on ultrasonography at follow-up [9]. Therefore, at the present, ultrasonography cannot be recommended to assess disease activity including response to therapy in the individual patient.

In the few PMR patients presenting with the RS3PE syndrome imaging studies of the extremities affected disclose tenosynovitis of the digits and of the dorsum of the hands (or feet), which cause the distal swelling [10,37].

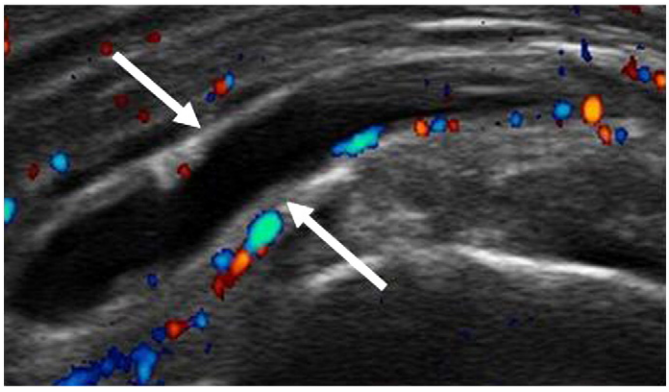

Fig. 1. Ultrasonography: coronal view of the shoulder of a patient with active polymyalgia rheumatica showing marked distension of the subachromial bursa (arrows).

There is no indication to perform ^{18}F-Fluorodeoxyglucose positron emission tomography (PET) in patients with PMR unless GCA with large-vessel involvement is suspected. PET findings in PMR may include increased FDG uptake in the shoulders, hips, as well as the spinous processes of the cervical and lumbar spine (Fig. 2)[5]. PET may also show subclinical vasculitis, especially in the subclavian arteries, in circa 1/3 of PMR patients without clinical features of GCA. But vascular tracer uptake is less intense than that observed in GCA with large-vessel arteritis [5].

7. Association between polymyalgia rheumatica and giant cell arteritis

PMR and GCA are both inflammatory diseases of the elderly that occur together more frequently than expected by chance [60,62]. Circa 16–21% of PMR patients develop GCA; conversely, 40–60% of GCA patients have features of PMR [20,52,68]. PMR may appear before, together with, or after GCA [62]. Mild arteritis has been demonstrated using PET in 1/3 of patients with isolated PMR (i.e. PMR without clinical evidence of GCA) [5], while about 4% of patients with isolated PMR have histological inflammation of the temporal arteries [27]. However, patients with isolated PMR are not at risk for ischemic complications regardless of the presence of subclinical arteritis [5].

8. Management

8.1. Glucocorticoids

Glucocorticoids remain to date the cornerstone of treatment of PMR. There is evidence that initial prednisone doses higher than 10 mg daily are associated with fewer relapses and shorter glucocorticoid requirements than lower dosages [35]. On the other hand, starting prednisone doses higher than 15 mg daily have been linked to higher cumulative glucocorticoid doses and more frequent glucocorticoid-related adverse events [35]. In practice, most patients with PMR respond to a prednisone dosage of 15 mg/day, although a few patients may require up to 20 mg/day. Failure to respond to such prednisone doses should prompt the clinician to question the diagnosis of PMR and to search for alternative diagnoses.

There is no universally accepted treatment regimen for PMR, but the British Society for Rheumatology suggests that prednisolone (or its equivalent) be used at 15 mg/day for 3 weeks, then at 12.5 mg for 3 weeks, then at 10 mg for 4–6 weeks, and subsequently tapered by 1 mg every 4–8 weeks provided no flares occur [17]. Prophylaxis for osteoporosis should be provided to all patients according to current recommendations [17].

Many patients are able to discontinue glucocorticoids six months to two years after the onset of clinical symptoms, but some patients may require longstanding glucocorticoid treatment. In particular, patients

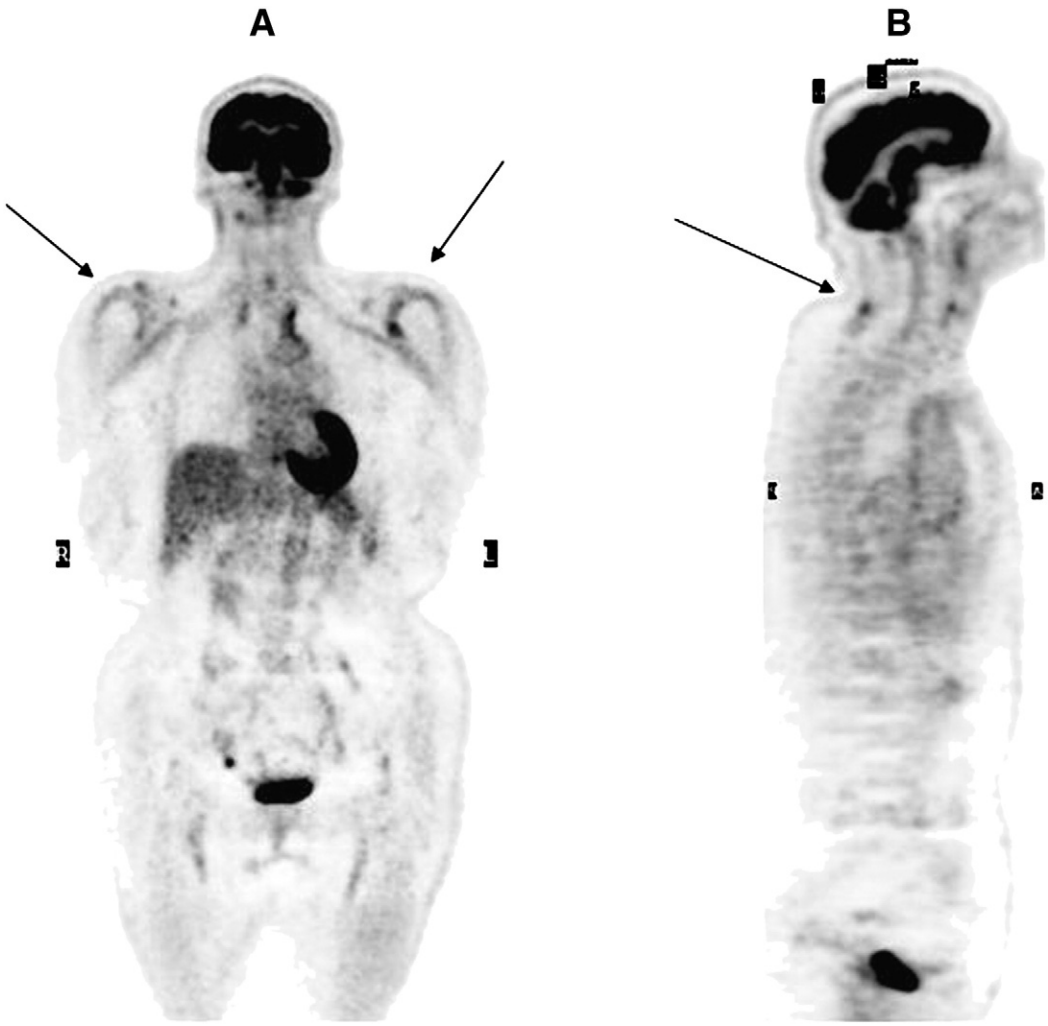

Fig. 2. ^{18}F-Fluorodeoxyglucose (FGD) positron emission tomography (PET): increased FDG uptake (arrows) in the shoulder (A, coronal view) and cervical spine (B, sagittal view) regions in a patient with polymyalgia-related shoulder and cervical pain.

with coexisting GCA and PMR appear to need longer glucocorticoid treatment than those with isolated PMR or GCA [40,44].

8.2. Immunosuppressive agents

Despite their remarkable efficacy, glucocorticoids are fraught with a whole slew of potential adverse events. In a study on 222 patients with PMR treated with glucocorticoids for a mean of forty-six months, 95 patients (43%) suffered at least one glucocorticoid-related adverse event [47]. In particular, 55 patients developed osteoporosis, 31 had fragility fractures, 27 developed arterial hypertension, 11 diabetes mellitus, 9 acute myocardial infarction, 3 stroke, and 2 peripheral vascular disease. Therefore, in patients with longstanding disease and in those at high risk for glucocorticoid-related adverse events, the use of glucocorticoid-sparing agents should be considered.

8.3. Methotrexate

Two randomized controlled trials have investigated the efficacy of methotrexate in patients with new onset of PMR with conflicting results [13,76]. In one study, forty patients with PMR, six of whom also had clinical symptoms of GCA, received prednisone 20 mg/day plus oral methotrexate 7.5 mg/week or a matched placebo. The prednisone dose was tapered as soon as clinical symptoms resolved and inflammatory markers normalized. Patients were followed up every 3–6 weeks until attainment of remission, and subsequently every three months up to two years or at least one year after treatment discontinuation. Nineteen patients dropped out of the study, nine in the methotrexate group and ten in the placebo group. In this study, methotrexate proved no better than placebo in reducing time to remission, the number of relapses, and the cumulative prednisone dose [76]. In another study, seventy-two patients with PMR were treated with prednisone at a starting dose of 25 mg/day plus oral methotrexate 10 mg/week for 48 weeks. The prednisone dose was tapered off within 24 weeks, but dose adjustment was allowed if flares occurred. 92% of patients in the methotrexate group and 86% of patients in the control group completed the trial. In this study, methotrexate was superior to placebo in reducing the number of flares and the cumulative glucocorticoid dose as well as in allowing discontinuation of glucocorticoid therapy in a larger number of patients [13]. However, the rates and severity of glucocorticoid-related adverse events were similar in patients treated with methotrexate and placebo. The lack of efficacy of methotrexate in the former study [76] may arguably by explained by the lower methotrexate dosage, the shorter duration of treatment, and the higher number (48%) of patients that failed to complete the study protocol. Nevertheless, it still remains to be established whether methotrexate, perhaps at higher doses, might significantly decrease the burden of glucocorticoid-related complications.

8.4. TNF-α inhibitors

A randomized controlled trial demonstrated that add-on infliximab to prednisone provided no significant benefit over and above that provided by prednisone alone in patients with newly diagnosed PMR [69]. Another randomized controlled trial demonstrated only a modest benefit of etanercept 25 mg twice weekly for two weeks over placebo in glucocorticoid-naïve patients with PMR [38]. In particular, etanercept significantly improved shoulder mobility, physician's global assessment and CRP levels, while duration of morning stiffness and patient's assessment of pain did not significantly change. These findings suggest that TNF-α inhibitors have, at best, a very limited efficacy in patients with new onset of PMR.

In contrast, TNF-α blocking agents might have a role in the treatment of patients with relapsing disease. In this regard, two open-label studies have shown that TNF-α blockade with infliximab or etanercept was effective in reducing glucocorticoid requirements in patients with longstanding, relapsing PMR [14,64].

8.5. Tocilizumab

The IL-6 receptor antagonist monoclonal antibody tocilizumab has recently been used to treat PMR on the basis of the demonstration of raised levels of circulating IL-6 in patients with active disease [19]. Altogether, four papers have reported on the use of tocilizumab in a total of nine patients [15,32,72,75]. Tocilizumab was used at 8 mg/kg monthly in all patients except in one who received 4 mg/kg monthly. One patient had newly diagnosed PMR, one had relapsing PMR, while seven patients had developed PMR during the tapering of glucocorticoids prescribed for GCA. Three patients (one with PMR and two with PMR/GCA) were glucocorticoid-naïve. Tocilizumab was able to induce clinical and serological remission in all nine patients. Eight patients responded to tocilizumab within 2 months and one within 5 months. In the three glucocorticoid-naïve patients glucocorticoids were not required at follow-up, while the dosage of glucocorticoids could be tapered in four patients and glucocorticoids discontinued altogether in two other patients. However, controlled trials are warranted to confirm these initial favorable results. In addition, the high costs of tocilizumab probably do not justify its routine use in patients with isolated PMR (without associated GCA).

9. Differentials of polymyalgia rheumatica

A number of diseases can potentially present with clinical features mimicking PMR [55]. PMR mimickers include elderly-onset rheumatoid arthritis, late-onset seronegative spondyloarthropathy, myositis, fibromyalgia, calcium pyrophosphate disease, viral myalgia, bilateral rotator cuff syndrome, bilateral adhesive capsulitis, osteoarthritis of the cervical spine and shoulders, tumors including multiple myeloma, hypothyroidism, and neurological disorders such as Parkinson's disease.

Elderly-onset rheumatoid arthritis presents more frequently than adult-onset rheumatoid arthritis with shoulder pain and systemic manifestations resembling PMR [20], while approximately 25% of patients with PMR have peripheral synovitis, which in one-fourth of cases affects the metacarpo-phalangeal joints, thus mimicking rheumatoid arthritis [63]. Positive anti-cyclic citrullinated peptide antibodies and rheumatoid factor point away from PMR and to elderly-onset rheumatoid arthritis, although low-titer rheumatoid factor positivity may be nonspecific [43]. On the other hand, response to glucocorticoids is usually far more dramatic in PMR than in rheumatoid arthritis. The presence of GCA features would strengthen the clinical suspicion of PMR, although GCA may occasionally affect patients with rheumatoid arthritis, too. In contrast, the presence of extra-articular manifestations of rheumatoid arthritis such as rheumatoid nodules and the development of joint erosions would strongly support a diagnosis of elderly-onset rheumatoid arthritis [63].

Late-onset seronegative spondyloarthropathy may at times resemble PMR when presenting with clinical features such as constitutional manifestations, shoulder involvement, and distal pitting edema. However, the presence of dactylitis, enthesitis, and uveitis would tip the balance in favor of a diagnosis of seronegative spondyloarthropathy. Additional aid in the differential diagnosis may come from imaging techniques showing bursitis, which would suggest PMR, or bone edema of axial joints, which would be in keeping with seronegative spondyloarthropathy. However, the use of imaging techniques in the differential diagnosis of PMR from seronegative spondyloarthropathy remains to be validated.

Myositis can infrequently cause myalgia on top of the more typical muscle weakness. However, myositis is not associated with morning stiffness, while muscle strength is normal in PMR. In doubtful cases measurements of muscle enzymes, electromyography and occasionally a muscle biopsy can clarify the diagnosis.

Fibromyalgia is a common cause of muscle pain variably associated with a feeling of stiffness in the neck and shoulder area aggravated by stress and exposure to cold. Like PMR, fibromyalgia may also be associated with generalized fatigue. However, differently from PMR, inflammatory indices are normal. Physical examination in fibromyalgia reveals positive tender points, whereas the range of motions of the shoulders is not restricted.

Viral myalgia can accompany various viral infections, and be associated with systemic manifestations and raised inflammatory markers. However, viral myalgia is usually widespread and symptoms clear spontaneously quite rapidly.

Calcium pyrophosphate disease may occasionally present with polymyalgic symptoms [53]. The identification of calcium pyrophosphate dihydrate crystals in the synovial fluid, the demonstration of the typical imaging findings of calcium pyrophosphate disease, or both, can aid at arriving at the correct diagnosis.

Bilateral rotator cuff tendinitis can cause shoulder pain radiating distally to the elbows resembling PMR. However, in rotator cuff tendinitis the symptoms are often initially unilateral, the pain is more mechanical in nature, and inflammatory markers are not elevated.

Adhesive capsulitis can mimic PMR in the odd case when both shoulders are simultaneously affected, since in the early stages adhesive capsulitis is characterized by inflammatory shoulder pain, and the typical restriction of joint movements occurs only weeks to months later. The absence of raised inflammatory markers and of bursitis on ultrasonography can help in differentiating adhesive capsulitis from PMR.

Symptomatic osteoarthritis of the cervical spine and/or shoulders may sometimes mimic PMR. However, unlike PMR, the pain is mechanical in nature, morning stiffness is absent or of very limited duration, and inflammatory markers are not elevated.

Hypothyroidism can cause pain and stiffness in the muscles including those in the shoulder area. However, differently from PMR, in hypothyroidism muscle stiffness does not ease with the passing hours of the day. The diagnosis can easily be verified by checking thyroid function tests.

Tumors, particularly multiple myeloma and renal adenocarcinoma, can very occasionally simulate PMR. However, in these cases there is usually limited or absent early morning stiffness, no significant restriction of joint movements, and no ultrasonographic evidence of shoulder bursitis. Response to glucocorticoids is also quite poor [29].

Some neurological disorders, particularly Parkinson's disease, may rarely mimic PMR. However, in patients with neurological complaints, stiffness is continuous throughout the day rather than being limited to the morning, other neurological signs are often discernible, and inflammatory markers are not raised.

RS3PE is a known manifestation of PMR. However, it can also occur in association with vasculitis, SpA, neoplasm's, or else be idiopathic [49].

10. Conclusions

Various criteria have been proposed to classify PMR, but in practice the diagnosis of PMR still eminently rests on its characteristic clinical features, elevated inflammatory markers, and a dramatic response to glucocorticoids. Imaging findings may support the clinical diagnosis of PMR, but their role in the individual diagnostic process is not fully clarified. Glucocorticoids remain the mainstay of treatment of PMR, but immunosuppressants may be useful in relapsing cases and in those at high risk for glucocorticoid-related complications.

Learning points

- Various criteria have been proposed to classify PMR, but in practice the diagnosis of PMR still eminently rests on its characteristic clinical features, elevated inflammatory markers, and a dramatic response to glucocorticoids.
- Imaging findings may support the clinical diagnosis of PMR, but their role in the individual diagnostic process is not fully clarified.
- Glucocorticoids remain the mainstay of treatment of PMR, but immunosuppressants may be useful in relapsing cases and in those at high risk for glucocorticoid-related complications.

Conflict of interests

We declare no conflicts of interest.

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