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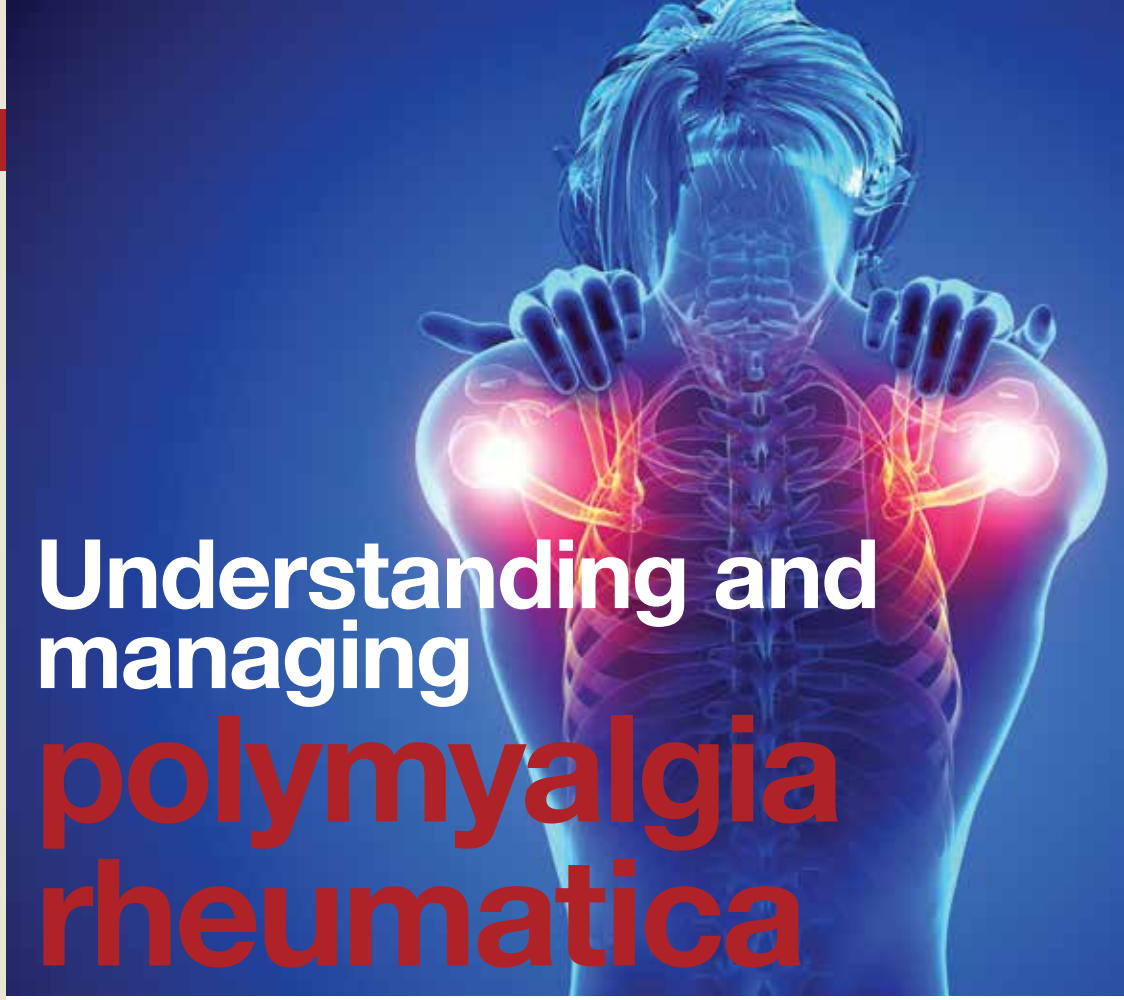

Understanding and managing polymyalgia rheumatica

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Key points

- **Polymyalgia rheumatica (PMR) is the second most common inflammatory disorder affecting men and women over the age of 50 years.**
- **The cardinal features of PMR are sudden-onset bilateral shoulder and pelvic girdle pain and stiffness, in combination with raised inflammatory markers.**
- **About one-half of patients diagnosed with PMR exhibit distal manifestations including peripheral arthritis.**
- **Concomitant giant cell arteritis can occur in 16 to 21% of patients with PMR.**
- **A weaning course of prednisolone over one to two years remains the mainstay of treatment for patients with PMR.**
- **Preventive health measures in patients with PMR should include assessment of bone health and treatment of modifiable cardiovascular risk factors.**

Polymyalgia rheumatica is a chronic inflammatory disorder that affects the shoulder and pelvic girdle. Diagnosis is based on a clinical construct, and prednisolone remains the mainstay of treatment.

In 1888 Dr William Bruce first described polymyalgia rheumatica (PMR) as 'senile rheumatic gout' when he documented a series of elderly patients presenting with disabling proximal joint and muscle pain.[1] Today, PMR is recognised as a common chronic inflammatory disorder characterised by sudden-onset bilateral shoulder and pelvic girdle pain, and early morning stiffness that affects men and women over the age of 50 years.

As a diagnosis of PMR is based on clinical features and raised inflammatory markers, distinguishing it from late-onset rheumatoid arthritis (RA) can be difficult. Although about 50% of patients diagnosed with PMR exhibit distal joint manifestations, the combination of wrist and metacarpophalangeal or proximal interphalangeal synovitis is significantly more common in patients with late-onset RA.[2] Similarly, the related condition giant cell arteritis (GCA) may be characterised by a 'polymyalgic' onset. Clinicians must therefore be vigilant in screening patients with PMR for features suggestive of an alternative pathology. The European League against Rheumatism (EULAR) and American College of Rheumatology (ACR) have recently released classification criteria to aid the differentiation of PMR from other rheumatic diseases (Table).[2]

Research indicates that most cases of PMR are managed exclusively in general practice.[3] For primary care providers, the diagnostic uncertainty associated with PMR can be

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TABLE. THE 2012 EULAR/ACR CLASSIFICATION CRITERIA SCORING ALGORITHM FOR POLYMYALGIA RHEUMATICA.*

Features	Points without ultrasound	Points with ultrasound
Morning stiffness duration >45 minutes	2	2
Hip pain or limited range of motion	1	1
Absence of rheumatoid factor or ACPA	2	2
Absence of other joint involvement	1	1
Ultrasound examination showing:		
• 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	N/A	1
• both shoulders with subdeltoid bursitis, biceps tenosynovitis or glenohumeral synovitis	N/A	1

ABBREVIATIONS: ACPA = anti-citrullinated protein antibody; ACR = American College of Rheumatology; EULAR = European League against Rheumatism; N/A = not applicable.

* Required criteria are age ≥50 years, bilateral shoulder aching and abnormal C-reactive protein level and/or erythrocyte sedimentation rate. A score of 4 or more without an ultrasound examination is categorised as PMR and a score of 5 or more with an ultrasound examination is categorised as PMR.

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particularly disconcerting. Furthermore, treatment dilemmas often arise from an incomplete response to or inability to taper prednisolone therapy. This article will address these common issues and review recent advances in our understanding of the pathophysiology, diagnosis and treatment of PMR. The flowchart on page 49 outlines a suggested diagnostic and treatment pathway for PMR.

EPIDEMIOLOGY AND PATHOPHYSIOLOGY

The incidence of PMR is highest in individuals of Northern European descent, with a prevalence of about six in 1000 people.[5] Women are significantly more likely to be diagnosed with the condition (up to twofold), and rates increase steadily with age until the eighth decade of life. When compared with other inflammatory conditions, PMR ranks second only to RA in terms of its lifetime incidence risk (estimated at 2.43% for women and 1.66% for men).[6]

The pathogenesis of PMR is unknown. Like most autoimmune conditions, it is postulated to result from the interaction of susceptible genetics with as yet unidentified environmental factors.

In patients with GCA, a clear association exists between vasculitis and the genes that lie within the human leukocyte antigen (HLA) class II region.[7] The same is not true for patients with PMR where genetic susceptibility varies from one population to another. For example, although HLA-DRB1*04 is associated with PMR in Northern European populations such as Scandinavia, this allele is infrequently found among Italians who develop PMR.[8] Instead, a polymorphism of the intercellular adhesion molecule 1 is frequently seen in this Southern European group. These observations highlight the genetic heterogeneity that contributes to PMR risk.

Several infectious agents (e.g. *Mycoplasma pneumoniae*, parvovirus B19) have been investigated as possible triggers of PMR. In all cases, no microorganism has been consistently linked to the pathogenesis of the condition.[7] Other studies have reported seasonal variations or cycles of incidence, but their cause remains unclear.[9]

A mild synovitis with macrophage and CD4+ T cell infiltration characterises the pathology of PMR within the glenohumeral joint, although periarticular structures including the bursa and muscle are also affected.[10] In particular, increased cytokine levels have been previously demonstrated in the muscle interstitium of patients with PMR.[11]

CLINICAL FEATURES

Pain and stiffness in the bilateral shoulder girdle is the presenting complaint in 70 to 95% of patients with PMR (Figure 1).[12] Involvement of the neck and hips is less common (50 to 70%). Typically, prolonged early morning stiffness (>45 minutes duration) accompanies these symptoms, and constitutional features such as low-grade fevers and fatigue may also be present. On examination, painful limitation of shoulder and hip movements is observed, without evidence of joint effusion. Muscle strength is normal, unlike in the differential diagnosis of inflammatory myositis.

Heterogeneity in the clinical features and disease course of PMR is well recognised. About one-half of patients diagnosed with PMR show distal manifestations, including peripheral arthritis (classically nonerosive, self-limited and asymmetrical), carpal tunnel syndrome and peripheral oedema.[2] In this group, distinguishing PMR from the differential diagnosis of late-onset RA is vital to facilitate early initiation of disease-modifying antirheumatic drugs (DMARDs) in the latter. The combination of wrist and metacarpophalangeal or proximal interphalangeal synovitis is significantly more common in patients with late-onset

SUGGESTED DIAGNOSTIC AND TREATMENT ALGORITHM FOR POLYMYALGIA RHEUMATICA

Patient presents with bilateral shoulder and/or pelvic girdle pain

Are the following clinical features also present?
- Age ⩾50 years
- Early morning stiffness >45 minutes
- No headache, scalp tenderness, jaw claudication, visual change
- No rigors, nightsweats or profound loss of weight

Yes

Do investigations show the following results?
- Elevated ESR and CRP levels
- Normal FBC, UEC, LFT, calcium, TSH, creatine kinase
- Negative rheumatoid factor and ACPA
- Optional ultrasound results consistent with classification criteria for PMR (Table)

Yes

Start treatment for polymyalgia rheumatica
- Prednisolone 15 mg/day for 3 weeks, wean as per BSR guidelines[4]

- Follow up at 1 to 3 and 6 weeks, and 3, 6, 9 and 12 months
- If relapse occurs (symptom recurrence with elevated ESR/CRP), reinstate previous prednisolone dose for 4 weeks, then resume weaning schedule
- If there is recurrent relapse, consider DMARD initiation

No

Investigate for the presence of other inflammatory conditions, metabolic disorders, infection or malignancy

No

Investigate for the presence of other inflammatory conditions, metabolic disorders, infection or malignancy

ABBREVIATIONS: ACPA = anti-citrullinated protein antibody; BSR = British Society for Rheumatology; CRP = C-reactive protein; DMARD = disease-modifying antirheumatic drugs; ESR = erythrocyte sedimentation rate; FBC = full blood count; LFT = liver function tests; TSH = thyroid-stimulating hormone; UEC = urea, electrolytes and creatinine.

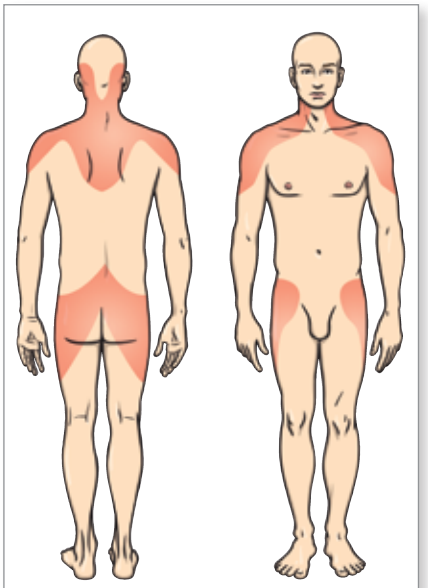

Figure 1. Typical sites of pain in patients with polymyalgia rheumatica. Shaded areas demonstrate the distribution in the shoulder and pelvic girdle.

RA than PMR and should prompt consideration of referral of the patient to a specialist.[13] Conversely, hip pain with a limited range of movement on examination has been identified as more typical of patients with PMR.[2]

Although the link is poorly delineated, PMR and GCA occur together more frequently than expected by chance.[14] Concomitant large vessel vasculitis is found in 16 to 21% of patients with PMR, and up to 50% of patients diagnosed with GCA have musculoskeletal symptoms consistent with PMR.[15] GCA can develop before, during or after PMR. Symptoms such as headache, scalp tenderness, jaw claudication and visual change must therefore be screened for at diagnosis and follow up in all patients with PMR. If suspicions of GCA arise, high-dose prednisolone should be initiated and urgent temporal artery biopsy arranged.

Other 'red flags' such as rigors, night sweats and profound loss of weight are inconsistent with PMR and should prompt evaluation for mimics such as infection and malignancy.

INVESTIGATIONS

Laboratory tests

The inflammatory markers, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level, are typically elevated by two to 10 times the upper limit in

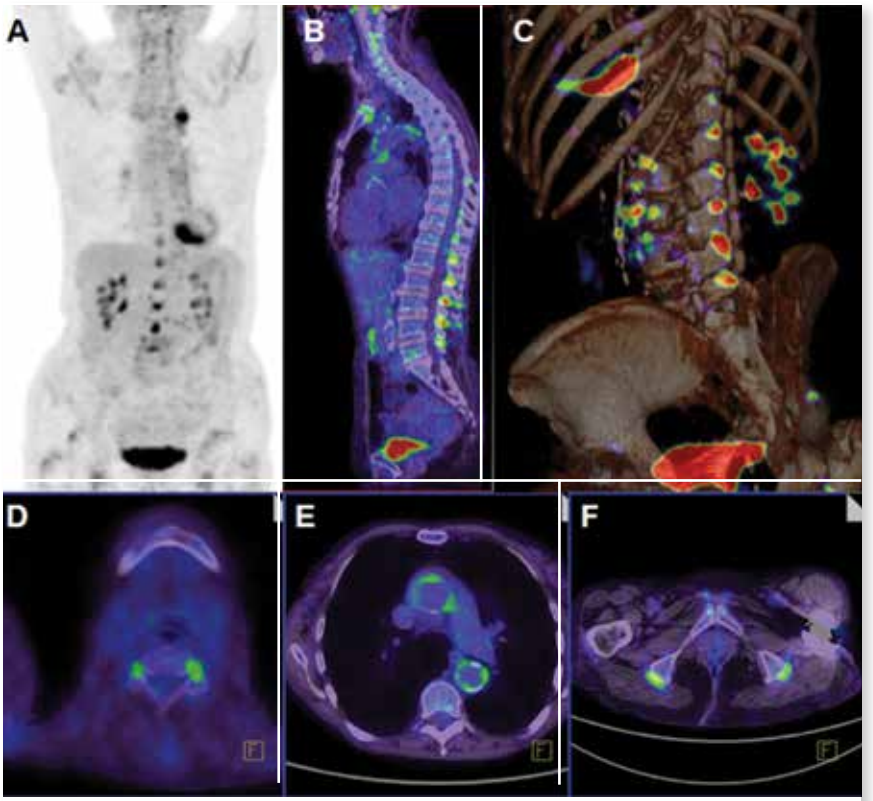

Figure 2. Fluorodeoxyglucose positron emission tomography (PET)/CT scanning in a patient with unsuspected polymyalgia rheumatica.[19] a (top, left). Maximum intensity projection image providing a whole-body overview. b (top, middle) and c (top, right). Coronal and three-dimensional PET/CT bone scans showing interspinous bursitis. d (bottom, left) and e (bottom, middle). Vasculitis of large and medium-sized vessels, with high uptake in the aortic arch and great vessels. f (bottom, right). Widespread bursitis and enthesopathy.

Courtesy of Associate Professor Michael Hofman.

patients with PMR, although patients with normal results have been infrequently reported.[16] ESR and CRP levels should respond and eventually normalise following treatment with prednisolone. Therefore, persistently abnormal ESR and CRP values are concerning and may represent an alternative diagnosis, including GCA (even in the absence of symptoms localising to the temporal arteries). Disease relapse following clinical remission may also be preceded by rising inflammatory markers.[17]

Additional investigations should aim to exclude conditions that may mimic PMR, including other inflammatory conditions (e.g. myositis), metabolic disorders (e.g. hypothyroidism), infection and malignancy. Simple measures such as a full blood count, measurement of calcium and creatine kinase levels, and thyroid function tests are advisable. Testing for the presence of rheumatoid factor and anti-citrullinated peptide autoantibodies (ACPA) should also be performed, and these results are expected to be negative in patients with PMR.

Imaging

Bilateral subacromial-subdeltoid bursitis is the hallmark lesion of PMR, being associated with 92.9% sensitivity and 99.1% specificity.[18] Both ultrasound examination and MRI can detect this bursitis, along with biceps tenosynovitis and glenohumeral synovitis of the shoulders, and trochanteric bursitis of the hips. However, none of these observations can be relied upon solely to distinguish PMR from late-onset RA.[13]

Whole-body positron emission tomography (PET)/CT scanning is an evolving investigative tool in patients with PMR and was recently suggested as a 'one-stop shop' for diagnosis (Figure 2).[19] A characteristic distribution of increased fluorodeoxyglucose uptake at the shoulders (93.4%), interspinous processes (51.4%) and large vessel vasculature (31.4%) is seen.[20] Consequently, this modality offers a tool with which to document the distribution of disease activity (bursitis, synovitis, concomitant GCA) and effectively exclude differential diagnoses such as infection and malignancy. However, at present, the use of whole-body PET/CT is predominantly limited to research settings.

DIAGNOSIS – CLASSIFICATION CRITERIA

In 2012, the EULAR/ACR classification criteria for PMR were released in order to classify this clinical syndrome as a distinct disease entity and thereby differentiate PMR from other rheumatic diseases. Age at onset of 50 years or older, bilateral shoulder aching and abnormal ESR and/or CRP levels represent required criteria, with an additional scoring algorithm as outlined in the Table.[2] In the absence of competing diagnoses, a score of four or more points is indicative of PMR (sensitivity 72% and specificity 65%).

The algorithm can be extended to include ultrasound results where possible, and a score of five or more points is then required for a diagnosis of PMR. Findings of bilateral shoulder abnormalities or abnormalities in one shoulder and hip significantly improve the specificity (70%) of the clinical criteria.[2]

TREATMENT

Despite certain advances, PMR is still subject to wide variations of clinical practice. Prednisolone represents the mainstay of treatment, but randomised controlled trials are lacking. As a result, the efficacy of different initial doses or drug-tapering regimens of prednisolone are unknown.

The British Society for Rheumatology (BSR) guidelines for the management of patients with PMR represent a recently developed consensus-based regimen for treatment. Prednisolone 15 mg/day is initiated for three weeks, weaned to 12.5 mg/day for a further three weeks, then 10 mg/day for four to six weeks, and finally reduced by 1 mg/day every four to eight weeks thereafter.[4] Frequent follow up should be arranged (at 0, one to three, and six weeks, and three, six, nine and 12 months) to monitor the patient's treatment response and assess disease activity. In the event of relapse (arbitrarily defined by the recurrence of symptoms and raised ESR or CRP levels), the prednisolone dose should be increased to the previous higher dose for four weeks before the weaning schedule is reinstated.[4]

However, even patients with a classic presentation of PMR may vary in their response to therapy with three distinct groups identified in one study:[21]

- those who responded rapidly and required prednisolone for less than one year duration
- those who responded well initially but did not tolerate prednisolone weaning
- those who had only a partial response to the initial prednisolone dose.

Treatment dilemmas therefore arise in patients with nonresponse, inability to taper and the need for prolonged therapy beyond two years; specialist referral of these patients should be considered.

The role of DMARDs in managing patients with PMR is unclear with mixed results (two positive, one negative) from randomised clinical trials assessing the efficacy of methotrexate for initial treatment.[22] A small case series recently reported promise with leflunomide treatment, but there were limitations with the study's design.[23] Similarly, case reports suggest that tumour necrosis factor-inhibitors may have a corticosteroid-sparing effect.[24] DMARD initiation should be considered in the event that a patient has relapsed on more than two occasions.[4]

PROGNOSIS AND COMPLICATIONS

Early studies indicate that the natural history of PMR involves symptom resolution after a period of about two years.[25] Having said this, up to 50% of patients require prednisolone therapy beyond this time for persistent disease manifestations.[26]

In the long term, a diagnosis of PMR is associated with an increased prevalence of cardiovascular comorbidities, including coronary artery disease, peripheral arterial disease and cerebrovascular disease.[27] As in other inflammatory conditions (e.g. RA and systemic lupus erythematosus), disease control is the basis for prevention of this outcome, but modifiable risk factors should also be treated. However, mortality is not increased in patients with PMR compared with unaffected individuals.[28] Conversely, complications of therapy such as diabetes mellitus, vertebral and hip fractures (associated with a 2.5-fold increased risk) must be minimised.[29] A baseline dual energy x-ray absorptiometry (DEXA) scan is recommended to assess bone mineral density (BMD) before starting prednisolone treatment. Bisphosphonate therapy is indicated when the patient's BMD T score is -1.5 or less in patients receiving prednisolone 7.5 mg/day or more for three months or longer. Calcium and vitamin D supplementation should also be initiated where necessary.

CONCLUSION

PMR is a common, chronic inflammatory condition that can exhibit significant heterogeneity in its clinical presentation and in patients' responses to prednisolone therapy. In particular, evolution to an alternative diagnosis such as late-onset RA or the development of concomitant GCA must not be missed. New developments such as the 2012 EULAR/ACR classification criteria and the BSR guidelines for the management of patients with PMR have helped further characterise this disease entity and standardise its treatment. Preventive health measures in patients with PMR should include assessment of bone health and treatment of modifiable cardiovascular risk factors. MT

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A list of references is included in the website version (www.medicinetoday.com.au) and the iPad app version of this article.

COMPETING INTERESTS: None.

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