Review

Imaging in polymyalgia rheumatica: which technique to use?

F.A. Figus[1], M. Skoczyńska[2], R. McConnell[3], G. Massazza[3], A. Iagnocco[1]

[1]Academic Rheumatology Centre, Università degli Studi di Torino Dipartimento di Scienze Cliniche e Biologiche, MFRU, Turin, Italy; [2]Department and Clinic of Rheumatology and Internal Medicine, Wrocław Medical Hospital, Wrocław Medical University, Poland; [3]Medicina Fisica e Riabilitazione, Dipartimento di Ortopedia, Traumatologia e Riabilitazione, Università di Torino, Turin, Italy.

Fabiana A. Figus, MD
Marta Skoczyńska, MD
Rebecca McConnell, MD
Giuseppe Massazza, MD
Annamaria Iagnocco, MD

Please address correspondence to:
Annamaria Iagnocco,
Academic Rheumatology Center,
MFRU, Dipartimento Scienze Cliniche e Biologiche,
Università degli Studi di Torino,
Regione Gonzole 10,
10043 Orbassano (TO), Italy.
E-mail: annamaria.iagnocco1@gmail.com

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ABSTRACT

Polymyalgia rheumatica (PM) is an inflammatory rheumatic disorder characterised by pain and stiffness, mainly in the neck, shoulders, and pelvic girdle and possible association with giant cell arteritis. Currently, there is no diagnostic gold standard for PM, however, an extensive assessment of patients' inflammatory status aided by imaging evaluation is crucial for disease stratification.

Many imaging techniques study PM features and their possible complications or associations with giant cell arteritis: radiography, ultrasound, scintigraphy, magnetic resonance imaging, and positron emission tomography/computed tomography. Each one has different advantages and disadvantages.

The aim of this review is to clarify the current uses of imaging in PM for diagnosis and follow-up through a literature review of the last 10 years.

Introduction

Polymyalgia rheumatica (PM) is a chronic inflammatory disorder that typically affects individuals over 50 years of age. Several autoimmune and inflammatory rheumatic diseases can mimic PM, including rheumatoid arthritis (RA), spondyloarthropathies (SPA), and remitting seronegative symmetrical synovitis with pitting oedema (RS3PE syndrome), as well as infectious diseases and malignancies (1).

Characteristically, PM presents with symmetrical pain and stiffness in the neck, shoulders, and pelvic girdle, with involvement around the glenohumeral, sternoclavicular, and hip joints. Early pathophysiological understanding of PM focused on articular pathology; however, imaging has broadened this assumption to understand the importance of extra-articular involvement and association to subclinical vasculitis. It has been suggested that inflammatory processes in the extra-articular synovial structures disseminate pro-inflammatory molecules at joint sites resulting in joint synovitis and characteristic joint symptoms (2).

Mackie *et al*. described the importance of using imaging as a diagnostic tool in PM above clinical and laboratory criteria (3). Presently, there is no gold standard test for the diagnosis of PM; clinicians rely on a combination of history, physical examination, laboratory tests, and imaging studies to make the disease diagnosis. The EULAR and ACR provisional classification criteria for PM now include ultrasound (4). Ultrasound inclusion in these classification criteria helps in clinical practice, in particular to discriminate PM from rheumatoid arthritis (RA) and increases the diagnostic specificity from 81.5% to 91.3% (5). Clearly, imaging adds diagnostic value. This narrative review assesses the current uses of imaging in the diagnosis and follow-up of PM through a literature review of the last 10 years. Many imaging techniques study PM and its possible complications or associations: radiography (x-ray), ultrasound, scintigraphy, magnetic resonance imaging (MRI), and positron emission tomography/computed tomography (PET/CT). This review discusses how recognising the advantages and disadvantages of each can help us diagnose, track, and treat PM.

Radiography

X-rays do not show abnormalities in PM (6). Arthritis, when present, is typically non-erosive (7). The British Society for Rheumatology and the Health Professionals in Rheumatology guidelines for the management of PM recommend x-ray in the diagnostic phase to support differential diagnoses and associated conditions (8). For example, in the presence of systemic symptoms, a chest x-ray is recommended to

exclude pulmonary infections or other pulmonary processes associated to PM. In the presence of peripheral symptoms, such as arthritis of the small joints of the hands or feet or oedema of the hands or feet, x-rays of the hands, feet, shoulders, and pelvis help distinguish PM from diseases such as advanced osteoarthritis or erosive inflammatory diseases (*i.e.* RA) (8).

Scintigraphy

No study published within last 10 years has demonstrated a relevant role of scintigraphy in PM. The precedent publication of O'Duffy *et al.* demonstrated that 24 out of 25 patients with PM at baseline had joint alteration in the shoulders on Technetium pertechnetate scintigraphy, which instead was negative in all of the 26 control patients. After treatment, the alterations disappeared (9).

This study reports a high sensitivity of this technique. However, most likely due to the use of new imaging techniques, unfortunately, there are no other noteworthy articles on this topic (2).

Ultrasonography

Ultrasound has become a useful technique in the assessment and monitoring of rheumatic diseases thanks to its capacity to evaluate both articular and periarticular structures. In addition, the use of power and colour-Doppler has improved the assessment of joint inflammation (10). Ultrasound is feasible, non-invasive, well-accepted by patients, relatively inexpensive and detects inflammatory involvement of both articular and extra-articular synovial structures in PM patients. According to literature data, a typical sonographic PM pattern involves bilateral subacromial/subdeltoid (SAD) bursae with the appearance of bursitis followed by tenosynovitis of the long head of the biceps (LTB). Less frequently, hip synovitis and trochanteric bursitis occur (11). In accordance with the EULAR and ACR provisional classification criteria, suspected cases of PM should have an ultrasound assessment of the shoulder and pelvic girdles (to identify included criteria of subdeltoid bursitis, trochanteric bursitis, LTB tenosynovitis, glenohumeral synovitis, or hip synovitis). By analysing the performance of these criteria in 136 patients affected by various inflammatory diseases (including RA and PM) and 149 healthy controls, Macchioni *et al.* showed that adding US findings increased the diagnostic specificity in all cases from 81.5% to 91.3% and in RA patients from 79.7% to 89.9% (5). In a 2015 systematic review and meta-analysis, Mackie *et al.* evaluated the diagnostic accuracy of imaging tests for PM. They evaluated 26 studies using a combination of ultrasound, PET, MRI, scintigraphy or x-ray on 2370 patients. They suggested that bursitis of the SAD and trochanteric bursae, readily identified by ultrasound, is a more helpful diagnostic finding than synovitis in the shoulder or hip joints. (3). Manzo *et al.* showed that when the erythrocyte sedimentation rate (ESR) is normal, ultrasound can support the diagnosis of PM with evidence of bilateral shoulder bursitis, long head of the biceps exudative tenosynovitis and/or trochanteric bursitis (6, 12). In the past, Weber *et al.* also showed the usefulness of ultrasound in the diagnosis of disease with unusual onset with a case where iliopectineal bursitis found on sonography was the first sign of PM. Thanks to ultrasound, the diagnosis was made, and the patient was started early on an appropriate treatment (13).The presence of the typical PM patterns with ultrasound also helps discriminate PM from other inflammatory joint diseases. Suzuki *et al.* performed ultrasound examinations on 15 patients with elderly RA with a PM-like onset (pm-EORA) and 15 with PM before starting therapy. They found that shoulder bursitis (in particular subacromial bursitis) was more severe in pm-EORA than in PM by using a semiquantitative score of both grey-scale and PD (14). This is in accordance with the different mechanisms of the two diseases where RA is a disorder in which synovial proliferation is greater (15), and PM is a disorder in which synovial exudate prevails (16). The authors concluded that a key feature for discriminating pm-EORA from PM is moderate to severe proliferative synovitis of the shoulder bursae, especially in the subacromial bursa. (15).

An interesting recent observational study by Ottaviani *et al.* included 94 patients with polymyalgic syndrome. All of them underwent ultrasound of the shoulders and in 25 of those cases calcium pyrophosphate disease (CPPD) was found. The authors concluded that this finding is quite frequent in suspected PM and the assessment of the acromio-clavicular joint may help the clinician to more accurately distinguish PM from CPPD (85.2% sensitivity; 97.1% specificity) (17). For PMR diagnosis, the most sensitive US features were SAD bursitis (96.3%) and biceps tenosynovitis (85.2%), despite low specificity. Moreover, ultrasonography is a valuable tool to monitor disease activity and treatment response in PM patients. Jiménez-Palop *et al.* studied 53 patients with active PM. Sonography of the shoulders and hips were performed to assess therapy response at baseline and 4 and 12 weeks after corticosteroid treatment. A significant improvement in ultrasound-assessed signs of inflammation was detected at week 4 ($p<0.001$). Overall, ultrasonography demonstrated similar or better sensitivity in detecting residual disease activity of PM compared to laboratory markers and clinical evaluation (18).

Finally, Sakellariou *et al.* found that ultrasound, in conjunction with clinical examination (especially in shoulder examination), is a potentially useful way to integrate information for the management of patients with PM. Its additional value in conjunction with the ACR/EULAR classification criteria should be tested further (19).

Magnetic resonance imaging

MRI is used to evaluate different rheumatic inflammatory diseases in various contexts. Like ultrasonography, it is safe; however, it is more expensive and sometimes not accepted by patients. It remains an important tool because MRI visualises articular synovitis, bursitis, and tenosynovitis, and is more sensitive for pelvic girdle and hip findings than ultrasound (20). Many PM studies used MRI over the past 10 years, and all of them showed extra-articular involvement in a characteristic pattern that includes the entheses, bursae, and periarticular regions.

In particular, Fruth *et al*. in 2018 performed contrast-enhanced pelvic MRIs on 40 patients with a clinical diagnosis of PM. All patients displayed the hallmark peritendinous enhancement of the pelvic girdle tendons. Most patients had bilateral findings with 100% involvement of the proximal rectus femoris origin and 90% involvement of the adductor muscles at the pubic bone. In all patients, ≥4 extracapsular sites were involved. Therefore, using MRI to identify typical PM patterns (such as peritendinous and multi-site extracapsular involvement) may be important for future PM diagnosis (21). Another interesting and recent study by Laporte *et al*. described localised, myofascial inflammations identified by MRI at the shoulder and pelvic girdles in patients with active, recent-onset PM. Myofascial findings might, therefore, aid in PM diagnosis (22). Involvement of muscles on MRI has not been found in RA (23) nor spondyloarthritis (24).

Cimmino *et al*. performed MRI on the hands and wrists of 26 PM patients and 26 healthy controls. The study evaluated the presence of tenosynovitis, articular synovitis, bone marrow oedema, soft-tissue oedema, and erosions. They found that the most prevalent, significant lesion was tenosynovitis (p=0.001) of the wrist extensor tendons (61% in PM and 15% in healthy controls). Except for one PM patient, there was no correspondence between MRI findings and clinical presentation; extensor tendons tenosynovitis was an expression of the subclinical disease process. The other lesions were not significantly different in the two groups. This study then confirms that PM is a disease that predominantly affects extra-articular structures (25).

Consistently, recent studies also demonstrate that periarticular inflammation and soft tissue oedema of extrasynovial structures are typical and more frequent in PM than RA. Ochi *et al*. (26) performed MRI of 25 PM patients (6 hips, 23 shoulders), 43 RA patients (22 hips, 22 shoulders), and 50 controls. The thickness of the supraspinatus tendon and the severity of the rotator cuff tendinopathy was significantly higher in patients with PM (p<0.05 and <0.002, respectively). Soft tissue oedema of extrasynovial structures was more common in PM patients compared to controls or RA patients (p<0.05). Similarly, PM patients had more severe effusions in the shoulder joint, shoulder tendon sheath, and trochanteric bursa (p<0.05). An additional benefit of utilising MRI is the ability to track PM disease progression. In an interesting study by Mackie *et al*., total body MRI was performed on 22 patients with PM and 16 with RA before and after treatment with corticosteroids. In PM patients, the characteristic extra-articular inflammatory pattern (congruent to other MRI studies) and patient-reported symptoms improved after steroid therapy (27).

Positron emission tomography/computed tomography

PET/CT with the glucose analogue 2-[fluorine-18]-fluoro-2-deoxy-D-glucose (18F-FDG-PET/CT) is an imaging technique prevalently used in the oncological field. However, the clinical applications go beyond that specialty. FDG accumulates not only in malignant tissues but also concentrates in inflamed tissues due to increased activity of inflammatory cells, such as lymphocytes, neutrophils, and macrophages. (28, 29). In 2018, Slart *et al*. (30) developed guidelines for the use of ^{18}F-FDG-PET/CT in patients with large-vessel vasculitis (LVV) and PM to improve diagnosis and monitoring. This imaging technique is particularly effective in diagnosing vascular involvement and identifying possible complications (stenosis, organ ischaemia, aneurysm formation, and dissection) that other imaging tools may report falsely as negative. Studies using ^{18}F-FDG-PET/CT have found significant co-occurrence of LVV in cases previously thought to have isolated PM symptoms (approximately 20%). Other diagnostic techniques, such as temporal artery biopsy, ultrasound, and MRI, do not definitively exclude LVV and may miss widespread inflammation. Though it is not routinely used in PM, ^{18}F-FDG-PET/CT may be used for detection of mural inflammation and/or luminal changes in extracranial arteries to support the diagnosis of LV-GCA as stated in the EULAR Recommendations for the use of imaging in LVV (31) and reveals PM lesions that are elusive with other techniques (32, 33).

Different studies have attempted to identify a specific pattern of ^{18}F-FDG uptake that helps in the diagnosis. Yuge *et al*. studied 60 patients with suspected PM, enthesitis, arthritis, or myopathy. Sixteen of them were classified as having PM based on 2012 ACR and EULAR criteria. The incidence of significant ^{18}F-FDG uptake in the definitive PM group was 88% for glenohumeral and sternoclavicular joints, 81% for spinous processes, 69% for ischial tuberosities, 81% for greater trochanters, 25% for acromioclavicular joints, and 6% for wrists and elbows. A typical pattern for the PM patients (38% *vs*. 9%) (p=0.016) was an increased "Y-shaped" uptake along the interspinous bursae (34). In agreement with other studies, Kaneko *et al*. and Rehak *et al*. described the abnormal ^{18}F-FDG accumulations in PM (35, 36, 37). Kaneko *et al*. enrolled 20 patients with PM and demonstrated tracer accumulation particularly in the proximal articular structures (96.7% in the shoulder, hip, and sternoclavicular joints) and in extra-articular synovial structures (91.4% in the ischial tuberosity, trochanteric, and spinous process regions) (35). In addition to these locations, another study by Rehak *et al*. detected the increase of the tracer in the prepubic region in some patients, probably secondary to pectineus and adductor longus enthesitis. Furthermore, the authors showed that the affected localisations resolved after PM treatment. This supports the use of ^{18}F-FDG-PET/CT not only for diagnosis but also for monitoring therapy in PM (37). Palard *et al*. studied 18 PM patients undergoing treatment with Tocilizumab (TCZ) as a first-line treatment. The patients performed ^{18}F-FDG-PET/CT at baseline, at 1 month, and at 3 months after therapy. Bioclinical parameters and ^{18}F-FDG uptake significantly reduced after treatment with TCZ, reflecting disease activity improvement (38).

With the use of ^{18}F-FDG-PET/CT, Lund-Petersen *et al*. found a sensitivity of 79% for PM when the ^{18}F-FDG uptake increased in any two of these three

Table I. Summary of the main characteristics of imaging methods.

	Technique		
	Ultrasound	MRI	18F-FDG-PET/CT
Observable PM features	B-mode (grey scale), power Doppler and colour Doppler changes showing bursitis, synovitis and tenosynovitis in the shoulders and hips.	Imaging features showing bursitis, synovitis, tenosynovitis, enthesitis, and myofascial inflammation. Characteristic regions for inflammation include the spinous processes and proximal origin of rectus femoris.	Abnormal tracer accumulation in the glenohumeral, sternoclavicular, hip and knee joints, as well as trochanteric bursae, prepubic bursae, ischial tuberosities region, and spinous processes with or without vessel involvement
Main drawbacks	Operator-dependent Limited deep structures visualisation Low sensitivity	Expensiveness Low accessibility Risk of contrast administration-related adverse effects	Operator-dependent Expensiveness Low accessibility Risk of tracer administration-related adverse effects
Main advantages	High specificity in bilateral involvement of two girdles Non-invasiveness Accessibility Dynamic evaluation Rapidity	High sensitivity High specificity Visualisation of deep structures (bursae)	High sensitivity Visualisation of deep structures (bursae, vessels)

MRI: magnetic resonance imaging; ^{18}F-FDG-PET/CT: glucose analogue 2-[fluorine-18]-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography.

locations: the shoulder, the hip, and the spinous processes (39). Sondag *et al*., at the same time, showed that significant uptake in three or more sites in the joints, bursae, or entheses (acromioclavicular, sternoclavicular, glenohumeral; ischial, trochanteric, iliopectineal, and interspinous; pubic symphysis, respectively) was correlated with the diagnosis of PM with 74% sensitivity and 79% specificity (OR=10.8) (40).

This technique also helps us with the differential diagnosis between PM and RA (32), in particular EORA. Takahashi *et al*. proposed a typical pattern for each pathology. For PM patients, they observed a high sensitivity (92,6%) and high specificity (90%) when 3 out of 5 characteristic regions showed increased or absent ^{18}F-FDG uptake: increased in ischial tuberosities, vertebral spinous processes, shoulder, and iliopectineal bursitis; absent in the wrists. Identifying variations in the uptake rate and patterns are potentially helpful in reaching a conclusive diagnosis of PM (41).

Wakura *et al*. performed ^{18}F-FDG-PET/CT in 15 patients with PM and 7 with EORA. Abnormal ^{18}F-FDG accumulations in PM patients was significantly higher than those in the EORA group in the periarticular region, spinous process of the lumbar and C5-C7 cervical vertebra (42). The typical PET/CT pattern for PM (described above) can also be confused with SPA. Yamashita *et al*. studied 16 patients with PM, 16 with RA, and 21 with SPA. They found that uptake of spinous processes and greater trochanters was considerably higher in both SPA and PM. In SPA, ^{18}F-FDG/PET is helpful for early detection of sacroiliitis (43).

Another important role of ^{18}F-FDG-PET/CT is to help identify PM-like paraneoplastic syndrome. In its early stages, malignant or benign tumours may manifest with symptoms similar to PM. In 2016, a case demonstrated the co-occurrence of RS3PE, PM, and prostate cancer, suggesting a similar trigger (44). In a recent case report, Umetsu *et al*. described an interesting case of a 70-year-old woman who had atypical features of PM with asymmetric symptoms and an ^{18}F-FDG-PET/CT pattern of PM. After endoscopic removal of oesophageal carcinoma, the musculoskeletal symptoms improved, and the ^{18}F-FDG-PET/CT findings decreased (45). Mege *et al*. showed how the association of ^{18}F-DG-PET/CT and the detection of microparticle fibrin positives by flow cytometry may help distinguish essential PM from paraneoplastic PM (46). Therefore, positive findings on ^{18}F-FDG-PET/CT may indicate PM but may also suggest paraneoplastic syndrome and additional tests may be warranted.

Conclusions

This narrative review describes the current literature data on the role of imaging in PM over the last 10 years. Ultrasonography, MRI, and ^{18}F-FDG-PET/CT are the most helpful imaging modalities to differentiate PM from most of the other inflammatory conditions (*e.g*. early RA). The most common and easy-to-use technique remains ultrasound. ACR and EULAR recognised the benefit of ultrasonographic findings and added ultrasound findings to their PM classification criteria (4).

In atypical cases, imaging can help identify alternative pathologies or associated conditions. ^{18}F-FDG-PET/CT seems to be the most complete method to study PM presentation because, in addition to highlighting the sites commonly involved in inflammation, it helps in the early diagnosis of paraneoplastic syndrome and identifies associated vasculitis (*e.g*. giant cell arteritis) (40). MRI and ^{18}F-FDG-PET/CT can help in the diagnostic process in challenging and selective cases, but they are not frequently used in the initial diagnosis given the cost and limited availability of these methods (Table I).

Increased use of imaging techniques in the future could continue to expedite diagnosis, track treatment, and better serve PM patients.

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