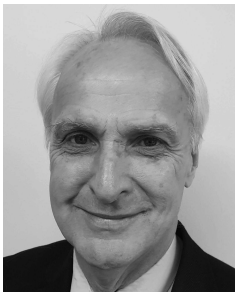
Editorial

Musculotendinous Inflammation: The Defining Pathology of Polymyalgia Rheumatica?





Despite being the most common inflammatory rheumatic disease of the elderly, and despite significant scientific breakthroughs in the related condition giant cell arteritis (GCA), the paradigm of polymyalgia rheumatica (PMR) has failed to progress beyond its earliest descriptions as a glucocorticoid-responsive syndrome of shoulder and pelvic girdle pain and stiffness. In the absence of a gold standard test, diagnosis is based on laboratory evidence of systemic inflammation and the exclusion of other relevant differentials. Ultrasound findings including subacromial bursitis, biceps tenosynovitis, and glenohumeral synovitis at the shoulders, and synovitis and trochanteric bursitis at the hips, improve the specificity of clinical classification criteria[1]. However, the precise pathology underpinning PMR remains unclear[2]. A mild synovitis with CD4+ T cell and macrophage infiltration characterizes arthroscopic biopsies taken from the glenohumeral joints of patients with PMR, while histopathologic studies of muscle have consistently revealed only minor immunologic abnormalities[3,4]. Such uncertainty surrounding disease pathophysiology has undoubtedly hindered therapeutic advances in PMR, with the majority of patients still condemned to longterm prednisolone treatment and its attendant glucocorticoid-related complications.

Modern advances in our understanding of PMR as a distinct disease entity have come largely courtesy of imaging. McGonagle, *et al* first reported an anatomical difference in the distribution of inflammation in their magnetic resonance imaging (MRI) study contrasting the shoulders of PMR and rheumatoid arthritis (RA) patients[5]. Extracapsular soft tissue edema differentiated the PMR group from its RA counterpart, whereas bursitis, tenosynovitis, and joint effusion did not. A subsequent study by the same authors investigating MRI findings at the metacarpophalangeal joints in PMR and RA similarly documented comparable rates of synovitis, tenosynovitis, and even bone erosions, with a much greater degree of gadolinium-enhancement noted in the extracapsular soft tissues of patients with PMR[6]. More recently, a symmetrical extracapsular pattern of inflammation adjacent to the greater trochanter, acetabulum, ischial tuberosity, and/or pubic symphysis has been associated with a complete, patient-reported response to glucocorticoid therapy[7]. Taken together, these findings implicate extracapsular inflammation as a point of difference between PMR and other rheumatic conditions, with utility in both diagnostic and prognostic settings. Delineation of the inflamed anatomical structures responsible for this imaging pattern also possesses the very real potential to shed new light on the mystery that is PMR's true pathology.

In this edition of *The Journal*, Laporte, *et al*[8] provide first documentation of the prevalence of localized myofascial lesions in patients with active PMR and their response to the interleukin (IL)-6 receptor blocker tocilizumab (TCZ), which has previously been established as an effective therapy for this condition[9]. T1– and T2–short-tau inversion recovery (STIR)-weighted MRI of the shoulder and pelvic girdle were undertaken at baseline and at weeks 2 and 12 posttreatment, with myofascial inflammation defined as high T2-STIR signal within the affected muscle or forming a line around it. In addition to an anticipated high frequency of synovitis and bursitis, at least 1 shoulder girdle and at least 1 pelvic girdle myofascial inflammatory lesion was detected at baseline in 71.4% and 86.7% of cases, respectively. The hip musculature was most commonly involved (86.7%), followed by the adductors at the pubic symphysis (80.0%), shoulder musculature (71.4%), and muscles adjacent to the ischial tuberosities, specifically semitendinosus, semimembranosus, and the long head of biceps femoris (60.0%). Improvement in these lesions was subsequently noted in 64.1% of muscle groups following 12 weeks of TCZ, thereby confirming the responsiveness of this newly identified pathology in PMR to biologic therapy.

See Polymyalgia rheumatica and TCZ therapy, *page 1619*

The Journal of Rheumatology 2019; 46:12; doi:10.3899/jrheum.190367

The close parallels between the anatomic distribution of the myofascial inflammatory lesions seen by Laporte, *et al*[8] and the previously described extracapsular pattern of inflammation typical of PMR cannot be denied. These findings similarly add to a growing body of evidence from other recent imaging studies documenting the involvement of musculotendinous structures in this condition. A Japanese whole-body positron emission tomography/computed tomography (PET/CT) study first noted abnormal fluorodeoxyglucose (FDG) uptake at the tendon attachment sites of the pelvic girdle as a feature unique to PMR[10]. Subsequent to this, Rehak, *et al* investigated the response of prepubic 18F-FDG accumulation to glucocorticoid therapy[11]. Like Laporte, *et al*[8], improvement in these abnormalities was noted in all treated patients, with the authors hypothesizing that the observed PET findings represented "another type of extra-articular inflammation" in PMR (i.e., enthesitis and tenosynovitis of the pectineus and adductor longus muscles).

The low image resolution typical of whole-body PET/CT, however, has represented a barrier to the identification of precise anatomic correlates of abnormal 18F-FDG uptake in PMR. Having observed a distinctive pattern of PET avidity adjacent to the ischial tuberosities and of posteromedial knee structures in our own prospective study of 22 newly diagnosed, steroid-naive patients, we performed MRI to confirm involvement of the hamstring tendons[12]. Bilateral and symmetric high T2 signal surrounding the proximal hamstring tendon origins of the semimembranosus and the conjoint tendon of the semitendinosus and biceps femoris was subsequently visualized at the pelvis, with peritendonitis of the semitendinosus and to a lesser extent graciliis tendons noted at the knee. Using PET/MRI fusion, hamstring peritendonitis was identified as the anatomical correlate of 18F-FDG uptake adjacent to the ischial tuberosities and of posteromedial knee structures, and PMR's predilection for tendinous structures was confirmed.

Most recently, Fruth, *et al* has replicated these findings at the hamstrings and proposed peritendinous enhancement of the pelvic girdle tendons as the imaging hallmark of PMR[13]. In a retrospective study of 40 patients with PMR who underwent contrast-enhanced pelvic MRI as part of their diagnostic investigation, areas of previously mentioned extracapsular inflammation were studied in detail in the hopes of identifying a disease-specific pattern. Mostly bilateral enhancement of tendinous structures in the pelvis corresponded with these regions of interest in all cases and the pathology identified encompassed a spectrum ranging from circumferential peritendinous inflammation to complete intratendinous involvement up to the level of the musculotendinous junction. While Laporte, *et al* have documented the prevalence of localized myofascial lesions for the first time in PMR[8], this publication also notably recorded the presence of linear enhancement of the intramuscular perimysium at the gluteus maximus in 2 patients.

It is with good reason that Fruth, *et al* highlight the contiguous relationship that exists between peritendineum and perimysium, with inflammation of the hip capsule similarly observed to merge seamlessly with peritendinous enhancement of adjacent muscles in the provided images[13]. The close anatomic proximity of the subacromial bursa to the supraspinatus tendon of the shoulder should also be remembered in this context. This bursa does not consist of a distinct sac, but rather its synovial layers blend with and are firmly attached to the underlying rotator cuff[14]. The possibility that the mild joint synovitis associated with PMR may represent a secondary phenomenon that arises from adjacent extra-articular inflammation has been previously proposed[15]. That bursitis in this condition could similarly reflect a primary pathology within the tendon itself should now be considered. Certainly there can be little doubt, amid this accumulating evidence, of the involvement of the connective tissues surrounding the tendons and muscles of the shoulder and pelvic girdle in the pathogenesis of PMR. Musculotendinous inflammation as the defining pathology of PMR not only provides a unifying anatomic basis for established disease manifestations including capsulitis and bursitis, but also goes some way toward finally explaining the profound myalgia experienced by patients with PMR, which has been so inadequately accounted for by our understanding of this condition to date.

Imaging, of course, cannot characterize histopathology, and dedicated studies are needed to confirm the existence of musculotendinous inflammation in PMR. Some of the very first biopsy reports in this condition did document edema and perivascular chronic inflammatory cell infiltration of the muscular fascia and its tendinous septum[16]. Similar inflammatory changes were identified at the shoulder joint capsule and bursa, while many arterioles exhibited active intimal endothelial cell proliferation, raising a possible pathoetiological link between PMR and GCA. An immunofluorescence study of biceps biopsy samples similarly revealed immune complex and fibrinogen deposition in the perifascicular areas of the perimysium[17]. The authors concluded that muscle pathology in PMR was likely characterized by inflammation of the interstitial tissues. Finally, a more recent microdialysis study documented increased interstitial concentrations of key cytokines including IL-6 in the symptomatic trapezius and vastus lateralis muscles of patients with PMR[4]. Once again, these abnormal levels normalized after prednisolone treatment and this correlated with complete symptom resolution, providing further proof of the response of inflammation within muscle connective tissues in PMR to conventional therapy and linking its resolution to positive clinical outcomes.

It is increasingly apparent from recent publications including Laporte, *et al*[8] that the extracapsular pattern of inflammation previously identified on imaging in PMR corresponds with musculotendinous structures of the shoulder and

pelvic girdle. Musculotendinous inflammation therefore represents the defining pathology of PMR, given that extracapsular abnormalities have previously been identified as the point of difference between PMR and other rheumatic conditions. The connective tissues surrounding the tendons and muscles (peritendineum and perimysium) appear to represent the anatomic basis of PMR's pathology, with secondary involvement of adjacent structures including the joint capsule and bursa. In Figure 1, we note the close proximity of hamstring peritendonitis to newly recognized localized myofascial lesions in a patient with PMR from our own study[12], and present a detailed illustration depicting sites of musculotendinous inflammation in this condition. Ultimately, more detailed histological studies are necessary to elucidate

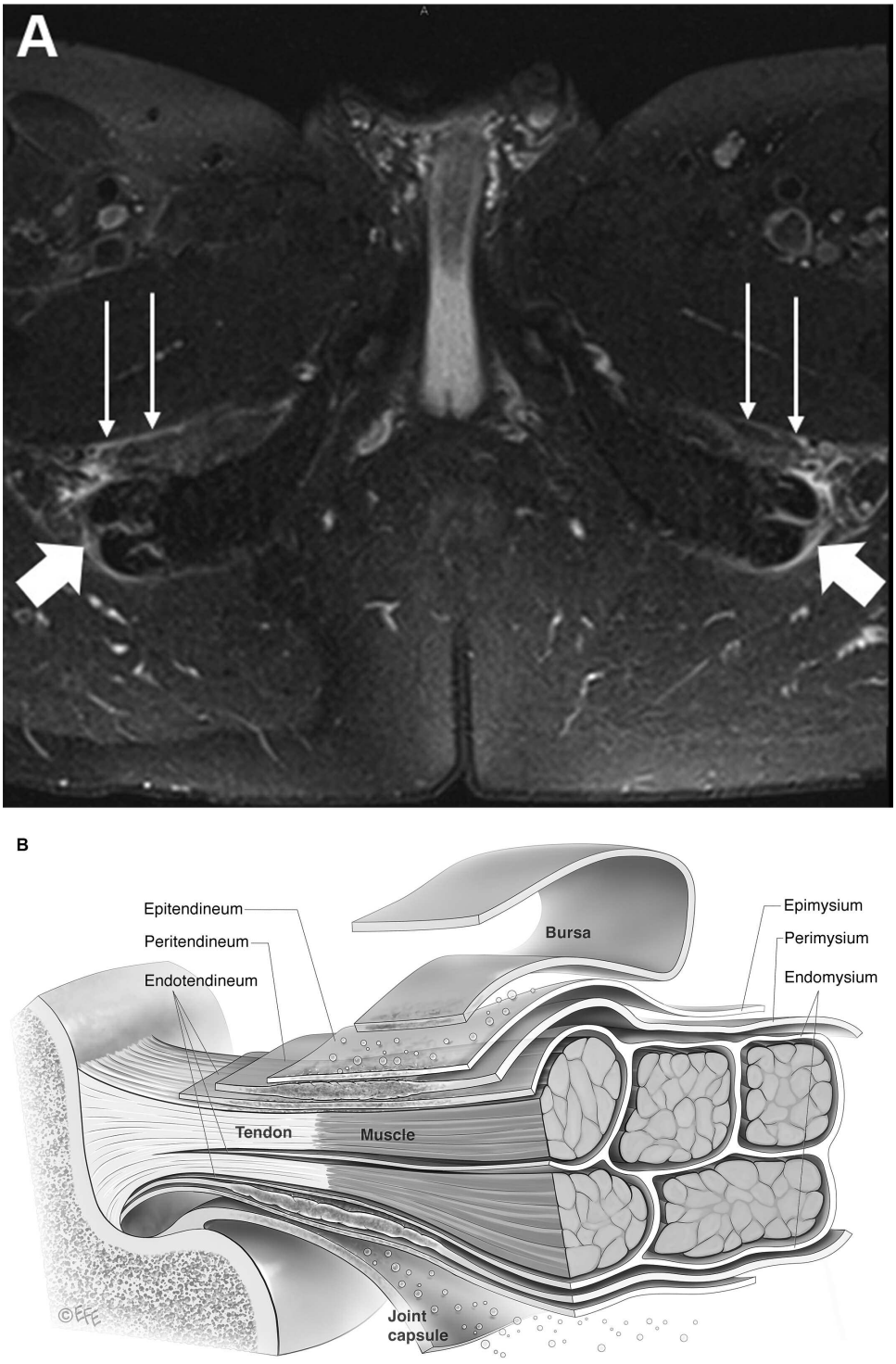


Figure 1. Musculotendinous inflammation in polymyalgia rheumatica (PMR). A. T2-weighted FS MRI reveals the close anatomical relationship between previously documented proximal hamstring peritendonitis (thick arrows) and newly recognized localized myofascial inflammation of the obturator externus (thin arrows) in a patient with PMR. B. A depiction of musculotendinous pathology in PMR arising from the connective tissues of the tendons and muscles (peritendineum and perimysium) to involve adjacent structures including the joint capsule and bursa. Used with permission.

the precise immunopathologic profile of PMR and enable long-overdue therapeutic advances in this condition. In the interim, PMR should be recognized for what it truly is — not a syndrome of shoulder and pelvic girdle pain and stiffness, but a chronic, inflammatory disease of musculotendinous structures.

ACKNOWLEDGMENT

The authors thank Dr. Lee Pheng Yap for her assistance with the included MRI figure and Dr. Levent Efe for his illustration depicting musculotendinous inflammation in PMR.

CLAIRE E. OWEN, FRACP,
Consultant Rheumatologist,
Department of Rheumatology,
Austin Health, Heidelberg, Victoria,
and Department of Medicine,
University of Melbourne,
Parkville, Victoria;
DAVID F.L. LIEW, FRACP,
Consultant Rheumatologist
and Clinical Pharmacologist,
Department of Rheumatology,
and Department of Clinical Pharmacology,
Austin Health, Heidelberg, Victoria,
and Department of Medicine,
University of Melbourne,
Parkville, Victoria;
RUSSELL R.C. BUCHANAN, MD,
Director of Rheumatology,
Department of Rheumatology,
Austin Health, Heidelberg, Victoria,
and Department of Medicine,
University of Melbourne,
Parkville, Victoria, Australia.

Address correspondence to Dr. C.E. Owen, Rheumatology Department, Austin Health, Repatriation Campus, Level 1, North Wing, 300 Waterdale Road, Heidelberg West, Victoria, Australia 3081.
E-mail: claire.owen@austin.org.au

REFERENCES

1. Dasgupta B, Cimmino MA, Kremers HM, Schmidt WA, Schirmer M, Salvarani C, et al. 2012 provisional classification criteria for polymyalgia rheumatica: A European League Against Rheumatism/American College of Rheumatology collaborative initiative. Arthritis Rheum 2012;64:943-54.
2. Dejaco C, Duftner C, Buttgereit F, Matteson EL, Dasgupta B. The spectrum of giant cell arteritis and polymyalgia rheumatica: revisiting the concept of the disease. Rheumatology 2017; 56:506-15.
3. Meliconi R, Pulsatelli L, Uguccioni M, Salvarani C, Macchioni P, Melchiorri C, et al. Leukocyte infiltration in synovial tissue from the shoulder of patients with polymyalgia rheumatica. Quantitative analysis and influence of corticosteroid treatment. Arthritis Rheum 1996;39:1199-207.
4. Kreiner F, Langberg H, Galbo H. Increased muscle interstitial levels of inflammatory cytokines in polymyalgia rheumatica. Arthritis Rheum 2010;62:3768-75.
5. McGonagle D, Pease C, Marzo-Ortega H, O'Connor P, Gibbon W, Emery P. Comparison of extracapsular changes by magnetic resonance imaging in patients with rheumatoid arthritis and polymyalgia rheumatica. J Rheumatol 2001;28:1837-41.
6. Marzo-Ortega H, Rhodes LA, Tan AL, Tanner SF, Conaghan PG, Hensor EM, et al. Evidence for a different anatomic basis for joint disease localization in polymyalgia rheumatica in comparison with rheumatoid arthritis. Arthritis Rheum 2007;56:3496-501.
7. Mackie SL, Pease CT, Fukuba E, Harris E, Emery P, Hodgson R, et al. Whole-body MRI of patients with polymyalgia rheumatica identifies a distinct subset with complete patient-reported response to glucocorticoids. Ann Rheum Dis 2015;74:2188-92.
8. Laporte JP, Garrigues F, Huwart A, Jousse-Joulin S, Marhadour T, Guelle D, et al. Localized myofascial inflammation by magnetic resonance imaging in recent-onset polymyalgia rheumatica and effect of tocilizumab therapy. J Rheumatol 2019;46:1619-26.
9. Devauchelle-Pensec V, Berthelot JM, Cornec D, Renaudineau Y, Marhadour T, Jousse-Joulin S, et al. Efficacy of first-line tocilizumab therapy in early polymyalgia rheumatica: a prospective longitudinal study. Ann Rheum Dis 2016;75:1506-10.
10. Wakura D, Kotani T, Takeuchi T, Komori T, Yoshida S, Makino S, et al. Differentiation between polymyalgia rheumatica (PMR) and elderly-onset rheumatoid arthritis using 18F-fluorodeoxyglucose positron emission tomography/computed tomography: is enthesitis a new pathological lesion in PMR? PLoS One 2016;11:e0158509.
11. Rehak Z, Sprlakova-Pukova A, Bortlicek Z, Fojtik Z, Kazda T, Joukal M, et al. PET/CT imaging in polymyalgia rheumatica: Praepubic 18F-FDG uptake correlates with pectineus and adductor longus muscles enthesitis and with tenosynovitis. Radiol Oncol 2017;51:8-14.
12. Owen CE, Poon AMT, Lee ST, Yap LP, Zwar RB, McMenamin CM, et al. Fusion of positron emission tomography/computed tomography with magnetic resonance imaging reveals hamstring peritendonitis in polymyalgia rheumatica. Rheumatology 2018;57:345-53.
13. Fruth M, Buehring B, Baraliakos X, Braun J. Use of contrast-enhanced magnetic resonance imaging of the pelvis to describe changes at different anatomic sites which are potentially specific for polymyalgia rheumatica. Clin Exp Rheumatol 2018;36 Suppl 114:86-95.
14. Dalton S. Section 5: Regional and widespread pain: The shoulder: Bursae. In: Hochberg MC, Smolen JS, Weinblatt ME, Weisman MH, editors. Rheumatology, 5th ed. Philadelphia, USA: Mosby Elsevier; 2011.
15. Salvarani C, Olivieri I, Cantini F, Hunder GG. Classification of inflammatory arthritis. Lancet 1998;352:1938.
16. Gordon I, Rennie AM, Branwood AW. Polymyalgia rheumatica: biopsy studies. Ann Rheum Dis 1964;23:447-55.
17. Shintani S, Shiigai T, Matsui Y. Polymyalgia rheumatica (PMR): clinical, laboratory, and immunofluorescence studies in 13 patients. Clin Neurol Neurosurg 2002;104:20-9.

J Rheumatol 2019;46:1552–5; doi:10.3899/jrheum.190367