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 criteria¹. However, the precise pathology underpinning PMR remains unclear². 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) patients⁵. 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 PMR⁶. 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 therapy⁷. 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 condition⁹. 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.

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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 PMR¹⁰. Subsequent to this, Rehak, *et al* investigated the response of prepubic 18F-FDG accumulation to glucocorticoid therapy¹¹. 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-naïve patients, we performed MRI to confirm involvement of the hamstring tendons¹². 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 peritendinitis of the semitendinosus and to a lesser extent gracilis tendons noted at the knee. Using PET/MRI fusion, hamstring peritendinitis 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 PMR¹³. 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 PMR⁸, 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 images¹³. 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 cuff¹⁴. 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 proposed¹⁵. 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 septum¹⁶. 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 perimysium¹⁷. 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 PMR⁴. 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 extra-capsular 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 peritendinitis to newly recognized localized myofascial lesions in a patient with PMR from our own study¹², 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 peritendinitis (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.

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