Inflammatory Musculoskeletal Disease: Identification and Assessment

PHILIP J. MEASE

ABSTRACT. Diagnosis of psoriatic arthritis (PsA) is complex because not all patients with psoriasis and musculoskeletal symptoms of pain, stiffness, and dysfunction have PsA. Instead, they may have other inflammatory conditions such as rheumatoid arthritis, gout, or septic arthritis, or noninflammatory conditions such as osteoarthritis, recurrent tendonitis, mechanical back pain, or a myriad other musculoskeletal conditions. To acquire skill in diagnosing and monitoring the disease course of PsA, a clinician must recognize that there are multiple clinical domains that may be affected, including peripheral joints, enthesal insertion sites, dactylitis, and the spine. They must also appreciate the clinical features (history and physical examination) that are characteristic of immunologic inflammation and know how to utilize and interpret laboratory and imaging studies. Rheumatologists are expected to be skilled in these assessments. It is also helpful for dermatologists, primary care physicians, and other clinicians who work with psoriasis patients to have a working knowledge of assessments in PsA in order to identify and triage the patient for optimal management. Features that assist identification and assessment of PsA are reviewed in this article. (J Rheumatol 2011;38:557-61; doi:10.3899/jrheum.101121)

Key Indexing Terms:
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ENTHESITIS
INFLAMMATORY ARTHRITIS
DACTYLITIS
SPONDYLITIS

The CASPAR (CLASsification of Psoriatic ARthritis) criteria for classification of psoriatic arthritis (PsA), currently the most widely accepted criteria, require that the patient have evidence of inflammatory arthritis, enthesitis, and/or spine disease in addition to other clinical elements suggesting PsA (Table 1)1. Determination of inflammation in joints, entheses, and the spine is intuitive to a skilled rheumatologist, but not necessarily to other clinicians, including dermatologists and primary care physicians. Indeed, it may be difficult for such clinicians, and occasionally rheumatologists, to distinguish whether pain arising from a joint, tendon or ligament insertion, or the spine is related to degenerative disease, biomechanical problems, or trauma, in contrast to an immunologic inflammatory process. Additionally, it takes clinical acumen to distinguish the inflammation of a joint due to an immunological disease from that due to a crystalline arthritis such as gout or septic arthritis. Even experienced rheumatologists may have problems distinguishing between these disorders.

The classic hallmarks of inflammation are pain, swelling, erythema, and potentially, heat. These can be visible and felt in peripheral joints and entheses, but not in spinal joints and entheses. The features of PsA arthritis include persistent pain; and instead of the bony crepitus and joint enlargement characteristic of osteoarthritis (OA), a swollen joint in PsA tends to be more “spongy” to palpation, as if there were a thin layer of bread dough between the skin and the bony margins of the joint. Tenderness is present with direct palpation of the joint line. The joint distribution in PsA also tends to be distinct from other forms of arthritis. Occasionally, PsA will present in an oligoarticular (fewer than 5 joints involved) or even monoarticular fashion, often asymmetrically, but most frequently in a polyarticular pattern. As in OA, the distal interphalangeal (DIP) joints may be involved, which helps distinguish both these diseases from rheumatoid arthritis (RA), where the DIP joints are virtually never involved. A telltale element often associated with PsA DIP involvement is psoriatic nail disease. Unlike OA, the metatarsophalangeal joints (wrists, elbows, shoulder, acromio-clavicular, sterno-clavicular, ankles, tarsus) may be involved in PsA. A patient with crystalline arthritis or septic arthritis will most often display intense pain and inflammation of a single joint, which tends to be transient, although some of these patients may have chronic polyarticular gout.

Another telltale feature of inflammatory arthritis is the presence of stiffness, particularly noted after the body has been still for a while, such as in the morning or after prolonged travel. The stiffness of inflammatory arthritis is experienced as a “gelling” phenomenon (like the “Tin Man”), and often will take 30 minutes to several hours to resolve, whereas the stiffness associated with OA may be only minutes in duration. A typical question asked of patients, in ascertaining therapeutic response when a treat-
ment is being tried, is how long morning stiffness endures. Often, pain is increased when an inflamed joint has been still and may be less painful once it is used, whereas the opposite tends to be the case with OA.

Laboratory markers of inflammation, such as C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR), are helpful in detecting the presence of inflammation when abnormal, but unlike in RA, these markers are elevated in PsA in less than 50% of patients, even when active inflammation is present.2

 Imaging joints with radiographs may demonstrate periarticular erosive change of the bone in inflammatory arthritides as well as joint space narrowing, whereas in OA, periarticular bony spurs develop. Occasionally, in PsA, joint ankylosis or periarticular osteitis (new bone formation) will be present, both distinctive features that do not occur in OA or RA. More advanced techniques such as ultrasound and magnetic resonance imaging (MRI) may help distinguish the presence of inflammation. Both techniques can detect the presence of synovitis and increased joint fluid. When power Doppler is added to ultrasound, increased vascularity is revealed by color change. Portable ultrasound is a technology that is widely used by rheumatologists in Europe and gaining popularity in the United States, partly because of ease of use in the clinic, ability to quickly assess multiple sites, and lower cost than MRI. T2 STIR technique or addition of gadolinium in the clinic, ability to quickly assess multiple sites, and lower cost than MRI. T2 STIR MRI and pathologic studies10,11,12. The GRAPPA group has determined that the appropriate procedure to assess joints when following a patient in a clinical trial, registry, or in clinical practice is the 68-tender and 66-swollen joint count utilized in the American College of Rheumatology (ACR) scoring system for joint response4,5. Although other joint scoring systems such as the Disease Activity Score (DAS 28), which requires examination of fewer joints, are more practical in the clinic, it is not as reliable for showing full-joint involvement in PsA, especially if the patient has oligoarticular and predominantly lower extremity joint involvement. As for treatment options for peripheral arthritis, effectiveness of nonsteroidal antiinflammatory drugs (NSAID), corticosteroids, oral disease-modifying antirheumatic drugs (DMARD), biologic therapies has recently been reviewed6,7.

A unique feature of PsA and other spondyloarthropathies is the occurrence of enthesitis, which is typically reported in 35%-50% of patients with PsA2,8. Enthesitis is defined as inflammation at sites where tendons, ligaments, and joint capsule fibers insert into bone. Classically, this is most symptomatic in lower extremity sites such as the insertion of the Achilles tendon or plantar fascia in the heel (calcaneus). Other sites that may be involved include tendon attachments at the superior and inferior pole of the patella, and tendon or ligament insertion sites around the elbows, pelvis, and ribs.9 Sometimes the pain will begin as a routine sports, work, or yardwork injury, but then will be more severe and persistent than usual for such a routine injury. Much of our understanding about enthesopathy comes from the work of Dennis McGonagle and colleagues, including Michael Benjamin, who have carefully evaluated enthesitis using the technique of T2 STIR MRI and pathologic studies10,11,12. McGonagle posits that much of the inflammatory burden in PsA is represented by enthesitis both in peripheral joints and in spine. For example, when a PsA patient presents with knee pain, MR imaging may reveal that inflammation is pri-
arily occurring in enthesal attachment sites around the knee rather than in the synovium of the joint. In the Achilles tendon insertion, it appears there is a sliver of synovial tissue at the junction site that contributes to the immunologically reactive tissue in this area. A hypothesis is that micro-injury at these sites leads to epitope exposure, immunological response, and persistent inflammation or triggering of an autoinflammatory response. There are unanswered questions about the cellular and cytokine milieu of enthesial inflammation and adjacent osteitis and whether these clinical domains are more resistant to some forms of immunotherapy than others.

The simplest assessment of enthesitis is palpation at insertion sites of tendons and ligaments. A historical multi-entheseal assessment measure from Mander, et al has proven too cumbersome to employ in clinical trials, since it calls for assessment of 66 sites. A number of other measures have been proposed that involve assessment of fewer sites, and are currently being used and validated in clinical trials of PsA and ankylosing spondylitis (AS) or in clinical registries. In the INSPIRE (INTERNATIONAL SPONDYLOARTHITIS INTEROBSERVER RELIABILITY EXERCISE) study, organized by Gladman, experts evaluated patients with PsA and AS to assess the reliability of various entheses (Table 214). The Leeds Enthesitis Instrument (LEI)15 and a Canadian instrument, the Spondyloarthritis Research Consortium of Canada (SPARC), which involved assessment of 6 and 8 sites, respectively, appeared to perform the best in PsA in this exercise, perhaps because they focus on more peripheral sites. Others, such as the Maastricht AS Enthesitis Score (MASES), originally developed in patients with AS and involving evaluation of 13 sites, also performed nearly as well. Imaging of enthesal sites has not been systematically performed in clinical trials. Plain radiography may show calcific spurs in sites of longstanding enthesal inflammation, but this technique is highly insensitive for detecting soft tissue inflammatory changes. As previously noted, McGonagle has demonstrated the sensitivity of MRI in illuminating the presence of inflammation in the entheses and adjacent bone. Ultrasound can also detect inflammatory change in entheses, especially when power Doppler is used, and is more practical than MRI, since multiple sites can be assessed quickly and more economically than with MRI. Interestingly, ultrasound screening of musculoskeletal asymptomatic patients with psoriasis demonstrates the presence of ultrasound abnormalities consistent with inflammatory enthesial and joint changes, suggesting presence of subclinical disease, the significance of which is unclear. Could this represent preclinical PsA? A recent study using the MASES index has somewhat disappointingly not shown a close correlation between ultrasound and physical examination findings at enthesal sites, with examination potentially underestimating the presence of inflammation. However, another study in early PsA showed much closer correlation. As use of more sensitive imaging techniques increases, it is possible that we will discover that many of the aches and pains that patients experience outside of the joint line in their limbs or around the pelvis or thorax, which may resolve with

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Table 2. Enthesial sites assessed in outcome measures for enthesitis from Gladman, et al. J Rheumatol 2007;34:1740–50.14

<table>
<thead>
<tr>
<th>Enthesal Site</th>
<th>MASES (Maastricht)</th>
<th>Major (Berlin)</th>
<th>SPARCC (Canada)</th>
<th>San Francisco</th>
<th>LEI (Leeds)</th>
<th>4-Point</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1/C2</td>
<td></td>
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<td>C7/T1</td>
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<td>T12/L1</td>
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<tr>
<td>1st costochondral</td>
<td>R,L</td>
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<tr>
<td>7th costochondral</td>
<td>R,L</td>
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<tr>
<td>Lateral epicondyle humerus</td>
<td></td>
<td></td>
<td>R,L</td>
<td>R,L</td>
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<tr>
<td>Medial epicondyle humerus</td>
<td></td>
<td></td>
<td>R,L</td>
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<tr>
<td>Posterior superior iliac spine</td>
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<tr>
<td>Anterior superior iliac spine</td>
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<tr>
<td>Iliac crest</td>
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<td>R,L</td>
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<tr>
<td>5th lumbar spinous process</td>
<td>X</td>
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<tr>
<td>Ischial tuberosity</td>
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<tr>
<td>Medial condyle femur</td>
<td>R,L</td>
<td>R,L</td>
<td>R,L</td>
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<tr>
<td>Lateral condyle femur</td>
<td>R,L</td>
<td>R,L</td>
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<tr>
<td>Insertion plantar fascia</td>
<td>R,L</td>
<td>R,L</td>
<td>R,L</td>
<td>R,L</td>
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<tr>
<td>Supraspinatus insertion</td>
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<tr>
<td>Quadriceps insertion patella</td>
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<td>R,L</td>
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<tr>
<td>Inferior pole patella</td>
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<td>R,L</td>
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<tr>
<td>Tibial tubercle</td>
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<td>R,L</td>
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L: left; R: right; X: single site present, not bilateral; LEI: Leeds Enthesitis Instrument; Major: Major Enthesitis Index; MASES: Maastricht Ankylosing Spondylitis Enthesitis Score; SPARC: Spondyloarthritis Research Consortium of Canada.
use of effective therapy, are actually due to enthesitis. There is evidence of effectiveness of anti-tumor necrosis factor (TNF) agents for the treatment of enthesitis, but we do not have systematic evidence of effectiveness of other agents because it has not yet been studied24,25.

Dactylitis represents a combination of synovitis and enthesitis involving a whole digit, rendering the digit swollen and “sausage-like.” This finding, like enthesitis, is a hallmark finding in the spondyloarthropathies, and of these, is most commonly seen in PsA, typically being reported in 30%–50% of patients8,20. Dactylitis is one of the clinical features that helps identify PsA per the CASPAR criteria1. In the IMPART study, dactylitis was reliably assessed by rheumatologists but not by dermatologists21. Gladman and others have noted the importance of distinguishing “cold” dactylitis, i.e., a digit that has had prior inflammation and remains enlarged, presumably with fibrotic tissue, from digits with active inflammation, which may be more amenable to treatment. The digit with active inflammation should be more tender with palpation of the joints of the fingers as well as palpation between joints along the shaft of the digit; however, one study showed only quantitative rather than qualitative differences between tender and nontender dactylitis22. Historically, dactylitis has been assessed by simply visually identifying a swollen digit and palpating tenderness. Some clinical trials use a 0–3 severity scoring system. The most quantitative approach has been introduced by Helliwell, et al via use of a “dactylometer”23. Using a loop tape and centimeter rule, this instrument documents digit circumference, and a scoring system for clinical trials has been developed. As with enthesitis, imaging assessment is best achieved with ultrasound or MRI. Also as with enthesitis, treatment effectiveness has been demonstrated with anti-TNF therapies but has not been assessed with other therapies24.

As PsA is a member of the spondyloarthritides family of rheumatic diseases, patients by definition may experience inflammatory spine disease. However, unlike AS, where spine involvement is an essential part of the condition, spine disease, including sacroiliitis, occurs clinically in at least one-third of patients with PsA2,8. Facet arthritis and enthesitis involving intervertebral ligament inflammation and calcific synovymode formation occur. It is important to ask patients about pain and stiffness present in the upper buttock area (implying sacroiliac involvement), lumbar, thoracic, and cervical spine. Characteristic features that distinguish inflammatory spine pain from degenerative or mechanical spine pain, as established by the Assessments in Ankylosing Spondylitis working group (ASAS), include age at onset < 40 years, insidious onset, improvement with exercise, no improvement with rest, and pain at night (with improvement upon arising)24. It has been determined that measures of spine disease developed by ASAS, the BASDAI (Bath AS Disease Activity Index), BASFI (Bath AS Function Index), and BASMI (Bath AS Metrology Index) do work well in patients with axial PsA27. Radiographs of the pelvis, to assess the sacroiliac joints and spine, to assess facet disease, vertebral squaring, and syndesmophyosis, are helpful but may significantly temporally lag behind the onset of clinical symptoms. MRI with T2 STIR or gadolinium enhancement is much more sensitive to identify inflammatory changes early in the disease course. Ultrasound is not useful in the spine. As noted above, CRP and ESR are only occasionally elevated in PsA and thus are not reliable markers of inflammation. The gene marker HLA-B*27 is also present in less than half of patients with axial PsA, so also is not a reliable biomarker for presence of inflammatory spine disease. However, when present, it may be used as an element in the new classification criteria for axial spondyloarthritis that have been developed by ASAS25,26.

Because axial disease does not occur in all patients and is variable in severity, the effectiveness of therapies has not been assessed in controlled clinical trials. To conduct proper study of a treatment, costly axial MRI imaging would need to be performed, in addition to measures such as the BASDAI, BASFI, and BASMI, which have not been done. Instead, researchers have used data from AS trials as a “surrogate” for determining effectiveness of therapies to treat PsA spondylitis27,28,29. As a result, there has been an assumption that oral DMARD therapy is not adequately effective in treating the symptoms of axial disease and that one should move directly from NSAID to anti-TNF therapy in patients not responding to NSAID. Also, although it has been convincingly demonstrated that anti-TNF therapies improve spine symptoms and improve function in AS, no therapy has been shown to definitively halt the development of ankylosis and syndesmophyosis in AS, and this has not been studied in PsA7.

Significant work has taken place to put together several of the above-mentioned outcome measures of individual clinical domains, with appropriate weighting, so that a composite score of disease activity and response to therapy can be used in clinical trials30.

In summary, determination of inflammatory disease of joints, entheses, and spine in PsA can readily be accomplished by a combination of clinical history, physical examination, and imaging, looking for patterns that tend to be unique for PsA. Although a skilled dermatologist or primary care physician may be able to confidently diagnose and monitor inflammation in patients with obvious patterns in these clinical domains, some patients, particularly those with modest symptoms, or predominantly oligoarticular, enthesal, or axial disease, may be more difficult to distinguish from patients with conditions such as OA, tendonitis, or mechanical back pain; in this case working as a team with a rheumatologist and using advanced imaging techniques may be necessary for accurate diagnosis and optimal management. Groups such as GRAPPA and ASAS are working

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to develop improved outcome measures and composite indices of disease activity and response to therapy for clinical trials and simplified measures practical to use in clinical practice.

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REFERENCES