The joint in psoriatic arthritis

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ABSTRACT

Psoriatic arthritis (PsA), a chronic inflammatory joint disease associated with psoriasis, is notable for diversity in disease presentation, course and response to treatment. Equally varied are the types of musculoskeletal involvement which include peripheral and axial joint disease, dactylitis and enthesitis. In this review, we focus on the psoriatic joint and discuss pathways that underlie synovial, cartilage and bone inflammation and highlight key histopathologic features. The pivotal inflammatory mechanisms and pathobiology of PsA parallel findings in other forms of spondyloarthritis but are distinct from disease pathways described in rheumatoid synovitis and bone disease. The diagnosis of PsA from both a clinical and imaging perspective is also discussed.

Introduction

Psoriatic arthritis (PsA) is a chronic inflammatory arthropathy with distinctive clinical features that are generally divided into five domains (skin and nails, peripheral arthritis, axial disease, dactylitis and enthesitis). These domains are discussed in detail in accompanying manuscripts in this supplement. Skin manifestations presenting as plaque, guttate or palmar plantar lesions tend to precede musculoskeletal symptoms by about a decade and up to 25% of patients with skin psoriasis develop musculoskeletal inflammation (1). Features of PsA, which distinguish it clinically from rheumatoid arthritis are diffuse swelling of digits or dactylitis, leading to the classically described "sausage digits", and enthesitis or inflammation at ligament and tendon insertions on bone. PsA is also characterised by abnormal bone turnover that often leads to both pathologic bone resorption and abnormal bone deposition. Finally, synovial inflammation in peripheral joints is the most prevalent feature of the disease ranging in severity from mild joint inflammation to disabling peripheral arthritis. In addition, about 40% of patients develop axial involvement, often in combination with other domains, which can greatly impair quality of life and function. The sheer complexity of this disease presents great challenges for patients and clinicians. In this brief review, we will discuss clinical and diagnostic features, histopathology and briefly review key pathogenetic concepts related to joint involvement in PsA.

Patterns of joint involvement

The original Moll and Wright case series divided joint disease in PsA into five phenotypic categories: polyarticular symmetric/asymmetric, oligoarticular, predominant distal interphalangeal (DIP) disease (more likely to have nail involvement (2)), axial disease (about 40% of cases) and arthritis mutilans (3). Diagnosis of PsA is often a major challenge, owing to the wide diversity in disease manifestations coupled with the fact that some patients may transition from oligoarticular to the polyarticular form over time. To complicate matters, distinguishing seronegative rheumatoid arthritis (RA), inflammatory osteoarthritis, enteropathic arthritis or reactive arthritis from PsA may be difficult, particularly when the patient has coincident skin psoriasis.

One of the most interesting recent findings is that joint phenotypes in PsA are associated with specific Human Leukocyte Antigen (HLA) haplotypes. The most notable association, reported in ankylosing spondylitis, was between HLA B27 and axial disease (4). Following this initial report, HLAC6:02 (formerly called HLA-Cw6) was found to be strongly associated with psoriasis, with the gene present is in nearly 60% of patients with psoriasis (5). In regards to PsA, Chandran et al. reported associations between HLA-C12/B38, HLA-B27 and HLA-C06/B57 haplotypes and PsA (6).

Fitzgerald *et al*. examined HLA haplotypes and PsA phenotypes and found that specific genetic susceptibility genes correlated with different disease mechanisms in PsA, which could have implications for diagnosis and therapy. These authors reported several observations. First, the time between onset of psoriasis and arthritis was much shorter in the HLA-*B27:05:02* or *B39:01:01* subset than in the *HLA-C06:02* subset of PsA cases (7, 8). Second, the prevalence of the C0602 phenotype (associated with psoriasis) was observed in 58% of psoriasis compared to 28% of PsA patients in their cohort, a highly significant difference. Third, HLA-C6, B27, B8, B38 and B39 demonstrated increased susceptibility to synovial disease, whereas HLA-B44 had a protective effect (8). Fourth, symmetric sacroiliitis was associated with the HLA-B27:0502 genotype whereas asymmetric involvement was associated with B08:01-C07:01 genotype. These data suggest that the specific peptides bound by individual HLA molecules may influence both the type and location of cutaneous or musculoskeletal involvement.

By contrast, susceptibility to RA is associated with Class II in contrast to Class I major histocompatibility locus (MHC) HLA antigens. Data support a strong interaction between smoking and the shared epitope (HLA-DRB1). RA has features of a classic autoimmune disease with the presence of citrullinated protein (anti-CCP) antibodies in circulation and in the RA synovium. A relationship between the shared epitope, present in the third hypervariable region of HLA-DR1 and 4 and anti-CCP antibodies has been repeatedly observed (9). The case for an autoimmune mechanism in PsA is not well established and recent emphasis has turned to innate immune triggers.

Imaging

Psoriatic arthritis has characteristic findings on all modes of imaging. Plain x-rays of hands and feet generally show asymmetric erosive changes, involving primarily the proximal interphalangeal and the distal intraphalangeal joints, the latter are not typically involved in RA. Patients may show complete destruction of one joint and a perfectly preserved joint on the adjacent digit. Erosive changes in the terminal phlanges lead to the classic "pencil-in-cup" deformity. The x-ray changes in PsA may sometimes be difficult to distinguish from severe erosive osteoarthtitis, which also targets the same joints. Plain films of the sacroiliac joint may assist in diagnosis, with characteristic unilateral or less common bilateral involvement of both the iliac and the sacral aspects of the joint. Ankylosis, a feature rarely seen in RA, may be found both in involved peripheral and axial joints. MRI is generally the gold standard mode of imaging of axial disease for both PsA and other spondyloarthropathies primarily because this instrument can detect the presence of bone marrow oedema (BME). MRI studies in ankylosing spondylitis demonstrated that BME is often a precursor of syndesmophyte formation, although whether this proves to be the case in PsA remains to be determined (10). MRI of the peripheral joints can help to distinguish synovitis from enthesitis or osteitis.

Another imaging modality, which has for the most part been used as a research instrument, is micro-CT, which detects bone lesions <0.5 mm in width or depth (11). Schett *et al*. applied this technology to study osteophytes and erosions in the metacarpophalangeal joints and reported that neither TNF inhibitors nor methotrexate blocked osteophyte formation in PsA (12), similar to axial findings reported in ankylosing spondylitis (13). Similarly, psoriasis patients PsA showed enthesophyte formation at mechanically exposed sites of the joint compared to healthy controls (14). These findings suggest a continuum of musculoskeletal involvement from psoriasis to PsA.

In recent years, musculoskeletal ultrasound has emerged as an important imaging modality, which allows the clinician to distinguish synovitis from tenosynovitis and enthesitis fairly quickly, without exposing the patients to radiation. The capacity of ultrasound to detect erosions is at least as good as micro-CT (15). Figure 1 is an ultrasound image of the hand, showing synovitis and tenosynovitis in a patient with PsA.

Joint pathology
Synovial tissue
Synovial biopsies of peripheral psoriatic joints demonstrated synovial tissue characterised by less pronounced intimal lining layer hyperplasia, marked vascularity, and a synovial infiltrate comprised of B cells, plasma cells, dendritic cells, CD163+ macrophages, more neutrophils and fewer synovial T cells compared with RA (16). In general, synovial biopsies from oligoarticular and polyarticular PsA resemble other spondyloarthropathies than RA (16). Surprisingly, ectopic lymphoid hyperplasia is seen in both RA and PsA (17). Synovial tissue from patients with RA shows synovial hyperplasia and often stains positive for intracellular citrullinated proteins and MHC-HC gp39 peptide complexes (16). Table I summarises the major differences between PsA and RA.

RA and PsA show divergent disease mechanisms. Analysis of blood and synovial fluid in the 2 disorders revealed that the expression of IL-17 is higher in the synovial fluid than peripheral blood in PsA but not RA, and a strong role for CD4- cells was demonstrated. Importantly, the PsA joint fluid is enriched for IL-17+CD8^{+} T cells and the levels of this T cell subset correlated significantly with disease activity and findings on musculoskeletal ultrasound (18). Another striking feature of PsA synovium is the abundant overexpression of proinflammatory cytokines, including tumour necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6, and IL-18 (19). Although Th17 cells have been found in the synovia of patients with both diseases, treatment with anti-Th17 monoclonal antibodies as a monotherapy has proven efficacious in PsA but not RA (20). Heterogeneous expression of IL-17 receptors between different RA, PsA and OA tissues was reported (21) but the mechanism for the differential response of RA and PsA to IL-23-IL-17 blockage remains unknown at this time.

Axial inflammation
The mechanisms that lead to axial inflammation in PsA are not well understood, although the central importance of TNF and the IL-23-IL-17 pathway in

axial spondyloarthritis supports a parallel disease model as that described for peripheral arthritis. Axial joint involvement in PsA and other spondyloarthropathies is for the most part detected as sclerosis and erosions on plain radiographs (most commonly unilateral), or presence of bone marrow oedema in the sacroiliac joints or spine on MRI imaging seen as enhancement. Cervical involvement is also common and may be caused by soft tissue inflammation or osteitis with syndesmophyte formation. Ankylosis is accompanied by marked impairment of neck motion. Biopsies from patients are scarce, and most of what is known about axial inflammation is derived from mouse models and studies in ankylosing spondylitis. One study in TNF transgenic mice with inflammatory arthritis, found using contrast-enhanced MRI and histologic evaluation of the knee joints, that bone marrow oedema represents an influx of mononuclear cells. BME signals in TNF-transgenic mice are characterised by yellow to red marrow conversion, with increased myelopoiesis and increased marrow permeability (22).

Disease mechanisms: contrasts with RA and animal models

RA is considered an autoimmune disorder given the strong association between shared epitopes in the DRβ region of the MHC and antibodies against citrullinated peptides as outlined above. A parallel autoimmune response is not present in PsA and the data point to an immune response that is largely innate in composition promoting differentiation of both type 1 and 17 T lymphocytes (23, 24).

Initial clues to the involvement of the IL23/IL17 axis in spondyloarthritis (SpA) arose from the observation that a polymorphism in the receptor for IL23 (IL-23R) was associated with altered susceptibility to ankylosing spondylitis and PsA (25, 26). Specifically R381Q IL23R carriers show decreased IL23-dependent IL17 and IL22 production and a lower percentage of circulating Th17 cells (27). These individuals also showed a decreased IL23-dependent signalling. Interestingly, IL23R R381Q gene carriers are protected against pso-
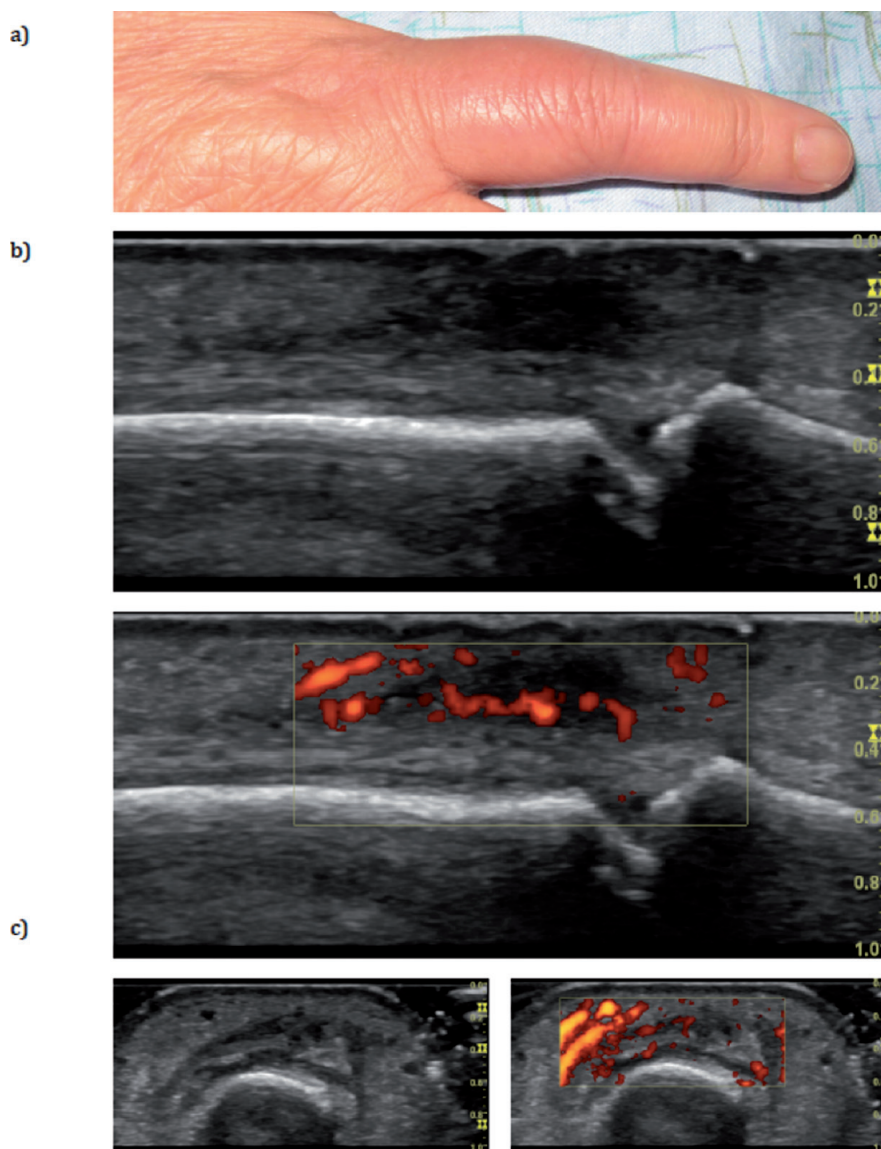

Fig. 1. a) Right hand in a patient with psoriatic arthritis showing apparent second PIP swelling. **b**) Grey-scale ultrasound of the right second PIP long view (*top*) and with power Doppler (*bottom*) showing evidence of peritendinitis, a finding that is characteristic of psoriatic arthritis. Note that the extensor tendon sheath does not cover the dorsum of the fingers, therefore this finding is not consistent with tenosynovitis. **c**) Grey-scale ultrasound of the same right second PIP transverse view (*left*) and with power Doppler (*right*) showing evidence of peritendinitis. Please note also that the joint itself is spared.

riasis, Crohn's disease and ankylosing spondylitis (28).

The Th17 cell subpopulations release a variety of cytokines including IL-17, IL-21, IL-22, IL-23 and TNF-α which trigger inflammatory cascades in several cell lineages, resulting in altered tissue phenotypes, presenting clinically as psoriasis and PsA. Indeed the importance of the IL17/IL23 pathway was highlighted by the impressive efficacy of ustekinumab in treatment of patients with psoriatic arthritis and the observation that blockade of these pathways slowed radiographic progression of

PsA total (29-31). Recently, blockade of IL17 alone has proven to be efficacious in treatment of psoriasis and psoriatic arthritis (20).

Sherlock and colleagues work reported that in a mouse model of enthesitis, musculoskeletal inflammation was linked to the presence of a subset of T-cells (IL-23R+, CD3+CD4−CD8−). They showed that administration of IL23 lead to proliferation of a special T-cell population resident to the enthesis that expressed the IL-23 receptor (30). They also reported that development of enthesitis was associated with

Table I. Comparison of rheumatoid arthritis with psoriatic arthritis.

	Rheumatoid arthritis	Psoriatic arthritis
Peripheral disease	Symmetric	Asymmetric
Sacroilitis	No	Asymmetric
Female: Male	3:1	1:1
Enthesitis	No	Yes
Nail Lesions	No	Yes
Psoriasis	Uncommon	Yes
Genetics	MHC II HLA-DRB1 also known as the "shared epitope"	MHC I HLA C6, B27, B8, B38 and B39 increase the risk HLA B44 protective
Immune mechanism	Acquired/autoimmune: Th1 cells producing autoantibodies against citrullinated peptides	Innate and acquired: Th1 and Th17 cells the major players
Synovium	Intimal layer hyperplasia Low in neutrophils Often stains positive for intracellular citrullinated proteins	Intimal layer hyperplasia less marked High neutrophils Increased vascularity CD163 + macrophages,
Bone phenotype	Impaired bone repair leading to osteoporosis	Abnormal bone formation and osteoporosis
Associated symptoms	Secondary Sjögren's, scleritis, episcleritis, vasculitis, cytopenias, Felty's syndrome	Psoriasis, inflammatory bowel disease, anterior/posterior uveitis, metabolic syndrome

increased levels of IL-6, IL-17 and IL-22. These cytokines were not released when mice were pre-treated with anti-IL23 antibody. They concluded that IL23 alone, in the absence of any other inflammatory signal, was sufficient to reproduce the classical enthesitis feature of PsA (26, 30).

Other murine studies have also demonstrated that IL23 promotes Th17 cells to secrete IL22, and that IL22 plays an important role in joint destruction and abnormal bone deposition (32, 33) Whether similar findings are present in human PsA remains to be determined.

The exact role of Th17 cells in PsA is not clear, but the Th17-related cytokines IL-17 and IL-23 are expressed in the joints of PsA and RA patients. Treatment with monoclonal antibodies that target these cytokines are effective for treatment of psoriasis and PsA (34). A recent study found not only an abundance of Th17 T cells in the synovial fluid, but reported that most of these cells were memory T-cells. They also identified a Th17 receptor in the synovial fibroblasts of patients with PsA (35).

RA had been considered a Th1-cell-mediated disorder, and thought to be triggered by a population of T cells producing inflammatory cytokines such as IL-2, TNF and interferon-γ (36). It has been suggested that early RA and RA flare may be driven by a Th17 response but this concept is currently under in-

vestigation (35). Certainly TNF is important in both RA and PsA, although IL-6 may be more important in RA. A hierarchy of cytokines in disease pathogenesis was proposed, with TNF and IL-17 pivotal in PsA and TNF and IL-6 critical cytokines in RA (36).

Bone and cartilage involvement
The long-term consequences of joint inflammation in PsA are development of both bony erosions and new bone formation leading to syndesmophytes, enthesophytes or frank ankylosis. Therefore, the pathobiology of PsA is characterised by dysfunction of both osteoblasts and osteoclasts. Although a detailed discussion of the biochemical pathways involved in bone turnover are beyond the scope of this short review, Wingless (Wnt), transforming growth factor (TGF)-β/bone morphogenetic protein (BMP), and the prostaglandin E2 pathway are potentially involved (37).

In one study, McQueen *et al.* reported that treatment of PsA patients with a bisphosphonate (zolendronic acid) did not lead to reduced bone resorption, but did reduce joint inflammation. This result suggest that osteoclastogenesis occurs via a different pathway in these patients than in osteoporosis (38). Murine studies have indicated that both IL17 and TNF are important in driving abnormal bone resorption (39), whereas IL 22 is thought to be a potential promoter of

abnormal bone formation (34). Studies in bone from the axial skeleton of patients with ankylosing spondylitis demonstrated expression of IL-17 by monocytes and neutrophils not observed in osteoarthritis samples. It is not known of this mechanism is also operative in psoriatic spondylitis (40). The contribution of innate immune cells, innate lymphocyte populations and NK cells also remains to be determined.

A central paradigm for understanding cartilage involvement in PsA at present is the "synovio-entheseal complex." This concept is discussed in detail by McGonagle and Tan in this Supplement. The original conceptual link between enthesitis and synovitis was that liberation of proinflammatory mediators in response to stress from the local bony attachment sites triggers inflammation. While this concept remains generally accepted, the relationship between the two sites of inflammation has proven to more complex than initially envisioned. Entheseal inflammation detected by musculoskeletal ultrasound and histopathology was also present in RA joints early in disease course, although the prevalence and significance of this finding is unknown (41).

Practical considerations
The major challenge to the clinician is early diagnosis of PsA, given its diverse array of clinical presentations.

Availability of better imaging modalities such as ultrasound, MRI and CT should allow us to detect joint involvement at an earlier stage, and initiate treatment before patients suffer debilitating joint deformities. Greater awareness of musculoskeletal involvement among dermatologists has also aided in earlier disease detection.

There is a great need for a validated scoring system to help compare disease activity between patients and track patients over time. Disease activity score (DAS)-28 has generally been validated for RA but its use in PsA is problematic due to exclusion of feet and DIP joints, which are major targets in PsA. Ideally, recording 66/68 joint counts provides the most complete picture of active joint involvement but feasibility in clinical practice remains a major barrier. A lower number of assessed joints (32, 36, 44) have been studied in small patient series but have not been taken up in clinical trials or outpatient settings (42).

The diversity of musculoskeletal structures involved in PsA coupled with the absence of a diagnostic marker often result in delayed diagnosis and treatment. For most PsA patients, who manifest active peripheral arthritis, involvement of synovial tissues, cartilage and bone contributes to bony erosion and pathologic new bone formation along with enhanced cartilage resorption. Despite the potential for irreversible joint damage, greater awareness of PsA coupled with improved imaging techniques and expanded therapeutic options are exciting advances that should improve treatment responses, and dramatically lower joint damage, leading to better patient outcome.

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