Peripheral joint involvement in psoriatic arthritis patients

M.L. Acosta Felquer[1], O. FitzGerald[2]

[1]Rheumatology Section, Medical Services, Hospital Italiano de Buenos Aires, Instituto Universitario Escuela de Medicina, Hospital Italiano de Buenos Aires, CABA, Buenos Aires, Argentina.
[2]Department of Rheumatology, St Vincent's University Hospital, Dublin, Ireland.

Maria Laura Acosta Felquer, MD
Oliver FitzGerald, MD, FRCPI, FRCP(UK)

Please address correspondence to:
Prof. Oliver FitzGerald,
Department Rheumatology,
St. Vincent's University Hospital,
Elm Park,
Dublin 4, Ireland.
E-mail: oliver.fitzgerald@ucd.ie

ABSTRACT

Peripheral joint involvement is a common, potentially debilitating feature of psoriatic arthritis (PsA). Joint involvement is commonly symmetrical and polyarticular similar to rheumatoid arthritis (RA) but it can also be oligoarticular, asymmetrical or occasionally monoarticular. Involvement of the distal interphalangeal joints is a feature which distinguishes PsA from RA. Articular involvement in PsA can be severe with a mutilating arthropathy found in about 5%. These patients are characterised clinically by digital shortening and on radiographs by erosion on both sides of the joint and/or osteolysis. Treatments targeting joint disease frequently reduces symptoms and signs resulting in prevention of damage progression.

Introduction

Psoriatic arthritis (PsA) is a multifaceted disease that includes features of peripheral joint and axial involvement, enthesitis, dactylitis and extra-articular manifestations such as skin and nail disease. This manuscript focuses on peripheral joint involvement in PsA.

Epidemiology

The exact prevalence of PsA in patients with psoriasis (PsO) is unclear, and varies widely between 13.8% and 36% in the published literature depending on the classification criteria used (1, 3). Haroon *et al.*, found that 29% of psoriatic patients attending dermatology clinics had undiagnosed PsA (4), In other studies, the reported incidence of PsA has varied from 3.4 to 8 per 100.000 (5, 6).

Genetic studies have shown that PsO and PsA patients have a genetic predisposition. The primary genotype linked to PsO is HLA-Cw6. HLA-B27 was more associated with the early development of PsA and with specific disease features such as symmetrical sacroiliitis and enthesitis, whereas HLA-B08 and its component alleles were positively associated with features including joint fusion and deformities, asymmetrical sacroiliitis, and dactylitis (7, 8).

In the last few years much interest has focused on the development of new biological markers in rheumatic diseases. Biomarkers can be used in clinical practice in a number of ways including diagnosis and prognosis but they can also be used to predict response to treatment. Biomarkers have been described but not yet proven as predicting early psoriatic arthritis in PsO patients such as CD16 and dendritic cell specific transmembrane protein (DC-STAMP) (9). DC-STAMP is expressed on the surface of osteoclast precursors (OCPs) which stimulate the formation of bone resorbing osteoclasts (OCs) (10). The use of biomarkers and also ultrasound imaging could help identify PsA in patients with PsO, thus opening up the possibility of early intervention improving patient outcome.

Peripheral joint disease

Peripheral joint involvement in PsA can be quite variable. Patients can present with a mono-arthritis, an oligoarthritis when there are ≤4 joints involved, or they may present with polyarticular involvement (>4 joints). The joints involved may be symmetrically distributed as in rheumatoid arthritis (RA) or they may be asymmetrical. As described in the original description of PsA by Moll and Wright, 5 clinical patterns of joint involvement may be observed in PsA patients (see Table I) (11). Their first publication on the frequency of patterns identified asymmetric oligoarthritis as the most frequent clinical subgroup among PsA (12). However, during the past decades a number of publications, while confirming the varied clinical patterns in PsA, have reported that polyarthritis is the most frequent pattern observed with an estimated frequency of about 60% (13-18). Yet other publications suggest that the pattern of joint involvement changes over time.

Table I. Arthritis subgroups in PsA.

Moll and Wright subgroups for PsA (11)	Veale subgroups (15)
Distal interphalangeal joint predominant arthritis (DIP) 5%	Asymmetrical oligoarthritis (35%)
Asymmetrical oligoarticular arthritis 70%	Symmetrical polyarthritis (60%)
Symmetrical polyarthritis 15%	Predominant spondylitis (5%)
Arthritis mutilans 5%	
Predominant spondylitis 5%	

Thus, some patients with oligoarticular-onset disease could develop polyarticular disease over time and other patients with polyarticular-onset disease may become oligoarticular with treatment (19). Most reported series of PsA are based on patients with established disease with very few studies addressing the clinical presentation and progression of in an inception cohort. Kane *et al.*, described the clinical presentation and radiological outcomes of 129 early PsA patients and they reported that 60% had polyarticular and 40% oligoarticular at presentation (16).

The subset classification and indeed the necessity to define some of these subsets remain controversial. It could be argued that with the pattern of joint involvement changing or evolving over time, that a simpler division into peripheral joint disease, predominant spondylitis and the classic arthritis mutilans phenotype may be more appropriate.

Symmetrical polyarthritis
This is defined by a cut-off of >4 involved joints, commonly affecting the small joints of hands and feet in addition to larger, weight-bearing joints. Symmetrical polyarthritis accounts for 60% of disease at presentation. This pattern is often difficult to distinguish from RA with the presence of skin psoriasis, nail dystrophic change and the presence of a negative rheumatoid factor helpful in diagnosis of PsA. Patients with this clinical pattern are predominantly female and 50% of joints (grouping together the small joints of hands and feet) are involved as matched pairs (*i.e.* symmetric) (20, 15, 21, 22).

Some patients with PsA may have low grade positive rheumatoid factor or indeed CCP antibody with the clinical phenotype, in particular, the presence of other disease features such as dactylitis, enthesitis or axial involvement,

helpful to distinguish PsA. It is also possible indeed that both RA and PsO may co-exist as both are common conditions. In this setting, the pattern of symmetrical small joint involvement, a strongly positive rheumatoid factor or CCP antibody and the absence of musculoskeletal features thought more typical of PsA should point towards the diagnosis of RA.

Asymmetrical oligoarthritis
This is characterised by asymmetric involvement and ≤4 joints involved. Distal Interphalangeal (DIP) joints, large joints and feet can all be involved. This pattern has male preponderance (15, 23) and a reported frequency of about 30–40% (18, 24).

DIP joint involvement
This may be symmetric or asymmetric, may affect a few joints or many, and commonly leads to progressive erosive bony lesions. Predominant DIP joint disease was considered a classic form of joint involvement in PsA but a few studies have suggested that DIP involvement is not a separate category but can occur across all of the PsA subgroups (15, 25).

Arthritis mutilans
This is recognised as the most severe destructive form of PsA and is characterised by digital shortening with severe osteolysis on imaging, leading to irreversible deformity and loss of function (26). The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) developed a consensus definition and suggested that *"involvement of just 1 joint with arthritis mutilans (AM) as being sufficient to be included in the AM group"* (27). The frequency ranges between 1 and 5% according the different publications (28, 18). A recent publication from Ja-

don *et al.*, found AM in 6% of 610 PsA patients. They also found that mutilans cases have earlier age of onset of PsA, poor function and more prevalent nail disease (28). Most patients with AM had psoriasis before the diagnosis of arthritis with mean age of psoriasis diagnosis at 25.6 years and of PsA diagnosis at 30.9 years (29). Based on data availability on 244 patients, 49% were males, with a mean (SD) age of 44.7±14.7 years (27). Osteolysis is the defining radiographic feature and according to a review of the literature, the most common radiographic changes were the presence of bone resorption (45%), pencil-in-cup change (17%), ankylosis (21%), total joint erosion (13%), and subluxation (9%).

Dactylitis or "sausage digit"
Dactylitis should be included in this section as synovitis or joint involvement is frequently a component of this feature. (*For Enthesitis, see Chapter on Enthesitis*) Dactylitis is considered a hallmark feature of PsA but it can also sometimes occur in other spondyloarthropathies, sarcoidosis, gout or infections (tuberculosis, syphilis). The reported prevalence among PsA patients is between 30–50% (30, 31, 32). Defined as the diffuse swelling of a digit (finger or toe), dactylitis relates to a combination of tenosynovitis, enthesitis and synovitis and can be acute or chronic. Acute dactylitis is defined as the presence of painful swelling of an entire digit (33, 34). and chronic dactylitis is defined as a persistent swelling in the absence of pain. Tender inflammatory dactylitis in PsA is associated with erosive disease and radiologic progression in the affected digits (35). Distribution is asymmetric and studies report that Dactylitis is found more commonly in the toes as compared to fingers (78% *vs.* 42%, respectively) (36).

On clinical examination, dactylitis is commonly asymmetric compared to the contralateral digit. Diagnosis can be more challenging when symmetrically involved. The Leeds dactylometer instrument, measures the circumference of the digit compared to the contralateral digit and has been shown to be sensitive to change (37). Haroon *et al.*

reported a positive association of dactylitis in cross-sectional study of PsA patients with both HLA B 27 and HLA B 08. This important observation likely reflects the association of HLA-B27 with enthesitis on the one hand and HLA-B08 with synovitis on the other (8). Siegel *et al.* summarised new studies in an animal model highlighting the importance of the interleukin 23/Th17 pathway and mechanical stress in pathogenesis of dactylitis (38).

Differential diagnosis

There are currently no diagnostic criteria for PsA with the diagnosis usually considered when a patient with PsO presents with typical musculoskeletal features in the absence of rheumatoid factor. Classification criteria, such as the CASPAR criteria, are available but should not be used for diagnosis. Classification criteria are best used when trying to ensure patient uniformity when recruiting PsA patients to studies or clinical trials.

Because of the wide range of clinical presentations, the differential diagnosis of PsA is extensive and at times challenging. RA and undifferentiated spondyloarthropathy (USpA) are inflammatory conditions characterised by different clinical, laboratory and imaging hallmarks. In some patients, features can overlap and it may be difficult to be sure of the correct diagnosis. Furthermore, a patient may have more than one diagnosis for example seropositive RA and PsO or osteoarthritis (OA) with DIP involvement and PsO. We summarised clinical, laboratory and radiological findings PsA compared to RA, USpA and OA in Table II.

Synovial pathology

Synovial tissue in PsA is characterised by a sub-lining infiltrate with T cells and B cells, vascular proliferation and also by expression of pro-inflammatory cytokines, including IL-1, interferon-γ, tumour necrosis factor (TNF)-α, IL-6, IL-12, IL-15, IL-17 and IL-18. Other studies demonstrated that RANK ligand is overexpressed whereas osteoprotegerin (OPG) is down regulated. This upregulation of activated osteoclasts results in bone resorption (39-43).

Table II. Comparison of the clinical, laboratory and radiographic features in psoriatic arthritis (PsA) as compared to rheumatoid arthritis (RA), undifferentiated spondyloarthropathy (USpA) and osteoarthritis (OA).

	PsA	RA	USpA	OA
Psoriasis	+	–	–	–
Symmetrical	+	++	+	++
Asymmetrical	++	+	++	+
DIP involvement	+	–	+	+
Spinal disease	+	–	+	+
Enthesitis	+	–	+	–
Dactylitis	+	–	+	–
Nail dystrophy	+	–	–	–
HIV association	+	–	?	–
RF/CCP	–	+	–	–
Erosions	+	++	+	+
Periostitis	++	+	+	+
Sacroiliitis	+	–	+	–
HLA class	I	II	I	–

Table III. Differentiating immuno-histologic features in psoriatic arthritis (PsA), spondyloarthropathy (SpA) and rheumatoid arthritis (RA) (41, 44).

	SpA *vs.* RA	PsA *vs.* RA
Increased in SpA/PsA	Vascularity Neutrophils CD163+ macrophages	Vascularity Neutrophils
Increased in RA	Lining layer thicknessCD83+ dendritic cells CCP+ MHC/HC gp-39+	Lining layer thickness CCP+ CD68 macrophages MHC/HC gp-39+

A few studies have compared the immuno-histologic features of PsA with those of other spondyloarthropathies and with RA. Earlier studies have highlighted the thinner lining layer, with fewer macrophages trafficking into the tissue as compared with RA. Table III summarises the differences observed in studies which compared PsA with both RA and other forms of peripheral SpA (41, 44). Hyper-vascularity and an increase in neutrophils were associated with PsA.

Imaging

During the last decades, advances in imaging have been very helpful in the assessment and management of patients with PsA.

On plain radiography, there are both non-specific features, but there are also some more specific findings which are useful, and should prompt the rheumatologist to think about PsA. The features which are helpful in differentiating PsA from other inflammatory arthropathies include fewer erosions than in RA, new bone formation, bony resorption and pencil-in-cup type deformity which results from a combination of new bone formation and osteolysis (16). Radiographic examination should include AP views of hands and feet in patients with peripheral joint involvement.

Ultrasonography (US) and MRI are more sensitive than radiographs to detect inflammatory and destructive joint changes in patients with PsA and they are also useful for entheseal or tenosynovial involvement (45).

Gutierrez *et al.* demonstrated that grey-scale US and power Doppler (PD) allow a detailed assessment of the structural changes and were sensitive in detecting abnormal blood flow at multiple sites in patients with PsA. US also is useful for detection of joint effusions, synovial proliferation, erosions and hyperaemia. In patients with dactylitis, US can detect a combination of tenosynovitis, synovitis and soft tissue oedema (46, 4).

Magnetic resonance imaging (MRI) allows visualisation of soft tissue, articular and entheseal lesions and

therefore, can be helpful in the detection of enthesitis, dactylitis, synovitis, bony changes (such as erosions or bone oedema) and for detection of subclinical arthritis. In a study by McQueen and colleagues, MRI could not distinguish between peripheral PsA and RA when synovitis and erosions were evaluated (47).

In another comparative study of 10 PsA and 10 RA conventional and dynamic contrast-enhanced MRI of swollen MCPs was not able to differentiate between RA and PsA on the basis of entheseal-related disease but a subgroup of PsA patients had diffuse extra-capsular enhancement (30%) or diffuse bone oedema (20%). The RA patient group had a greater degree of MCP synovitis and tenosynovitis than PsA patients There were no significant differences in either the total number of erosions or the presence of peri-articular bone oedema between the groups (48). Micro CT is a high-resolution imaging technique designed to visualise the bone architecture. Micro CT also can be helpful in differentiating the structural changes of peri-articular bone in patients with PsA and RA. Finzel *et al.*, found that the number of erosions in MCP joints in both groups was similar but they were less severe and smaller in size and depth in PsA. The shape of the erosions was different in PsA compared to RA, being Omega shaped in PsA and more tubular shaped in RA. Osteophytes were increased in number, extent and size in PsA as compared with RA and could in some cases affect the entire circumference of bone to form a bony "corona" (49). Whether any of these changes are sufficiently sensitive or specific to be useful in diagnosis or management is yet to be proven.

Treatment

PsA is a progressive disease with 47% developing erosive disease within 2 years of diagnosis (16). Clinical features associated with radiographic progression include polyarticular disease, dactylitis and an elevated erythrocyte sedimentation rate (50, 51, 1).

Published guidelines recommend traditional non-biologic disease-modifying anti-rheumatic drug (nb-DMARDs) including methotrexate, leflunomide, or sulfasalazine for 3 or 6 months, as the first step for the treatment of peripheral arthritis. These drugs have demonstrated efficacy for peripheral arthritis but not for axial disease, enthesitis or dactylitis

In 2014, the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) published a literature review for treatment of peripheral arthritis in PsA. There are limited data for efficacy of nb-DMARDs, specifically methotrexate (MTX), where results from 2 randomised controlled trials (RCTs) suggested its potential efficacy. On the other hand, the use of anti-tumour necrosis factor (TNF) blockers in peripheral arthritis is supported with much higher levels of evidence from RCTs and from observational studies. Etanercept, adalimumab, infliximab, golimumab, and certolizumab pegol have demonstrated significant improvements in peripheral joint scores and in composite, largely joint-related scores (ACR20, DAS28CRP, PsARC) compared with placebo. Other biological DMARDs, specifically ustekinumab, abatacept, brodalumab (development programme recently on-hold), and secukinumab, have also demonstrated statistically significant improvements compared to placebo. To date, only ustekinumab has been licensed for approval to treat PsA. Apremilast, a small molecule that specifically inhibits phosphodiesterase 4, was superior to placebo in a series of 4 Phase III studies and has been approved by both FDA and EMEA (52). *(for details, see chapter on treatment)*.

Early intervention in psoriatic arthritis, as well as the treating-to-target (T2T) have received particular attention in the past few years. T2T is defined as a strategy in which the treatment is gradually escalated in order to reach or maintain a therapeutic target such as remission or low disease activity (53). The TIght COntrol of PsA (TICOPA) study was the first study using a T2T strategy in early PsA (disease duration <24 month). Patients were DMARD-naive and divided in two groups, the first receiving an intensive treatment strategy and the second received standard care.

The Minimal Disease Activity (MDA) measure was used as the therapeutic target. At 48 weeks, ACR20 was achieved by 62% of tight control treated patients as compared to 45% of those receiving standard care. More biologic and combination therapy was used in the tight control arm (54). *(For more details see Treat-to-target chapter)*

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