Psoriatic Arthropathy: Where Now?

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Psoriatic arthropathy is a common inflammatory arthritis that characteristically occurs in individuals with psoriasis [1]. PsA was classified as a distinct entity for the first time in 1964 [2], but the antiquity of this disease can be dated back tens of centuries [3]. The many faces of PsA have historically complicated the timely diagnosis on the one hand, while its aggressive and destructive behavior has been recently recognized in up to 20% of affected persons on the other [4]. As such, PsA has attracted much attention lately, resulting in tremendous progress in the understanding, classification and treatment of the disease in recent years. This review will summarize the current experience in PsA in light of the recent developments in the field.

EPIDEMIOLOGY AND SIGNIFICANCE

Since PsA occurs in about 30% of patients with psoriasis, its prevalence will be higher in populations prone to skin psoriasis and vice versa. Consequently, if the estimated prevalence of psoriasis in Europe and the United States is between 2% and 3%, the prevalence of PsA in these countries may come close to that of rheumatoid arthritis. PsA usually affects young persons (typically in their third or fourth decade), resulting in early joint damage and disability in many patients. About 20% of PsA patients may suffer from severe destructive disease [4]. Extra-articular manifestations of PsA, such as uveitis and aortitis, may be a significant cause of morbidity [5,6]. On the other hand, PsA, like rheumatoid arthritis and other chronic inflammatory arthropathies, may be accompanied by accelerated atherosclerotic vascular disease and a potentially higher rate of heart attack and stroke [7].

CLINICAL SPECTRUM AND DIFFERENTIAL DIAGNOSIS

Traditionally classified as belonging to the group of spondyloarthritides, PsA may manifest clinically in the whole gamut of patterns, which were first recognized by Moll and Wright in 1973 [8]. Since then many large series of patients with PsA were reported and new data were accumulated. We recognize today that PsA may be not only an oligoarticular or polyarticular disease, or affect peripheral or axial joints, or spine, but it may also evolve from one pattern to another with time [9]. These patterns may also overlap, particularly in patients with longstanding disease. In most patients PsA coexists with skin psoriasis, which may be extensive, limited, or even hidden with the patient unaware of its existence. On the other hand, in as many as 7–30% of patients, arthritis may precede the appearance of psoriatic skin lesions and is called "PsA *sine* psoriasis" [4]. In these patients, where a key trigger for its emergence is absent, the correct diagnosis of PsA will depend solely on the recognition of specific features of the articular disease. Nevertheless, no single clinical, radiological or laboratory sign, pathognomonic for PsA, has been reported, thus setting expert physician opinion as the gold standard in the diagnosis of PsA [10,11].

Of the five main patterns of PsA, both oligoarticular and spinal variants may be difficult to distinguish from the other members of the spondyloarthritides group [12]. In clinical presentation and radiological features these patterns of PsA are similar to those of reactive arthritis, while a wide spectrum of skin rashes and lesions in the course of the latter may merely complicate the differential diagnosis.

Enthesopathy, which is a characteristic feature of the entire group of spondyloarthritides, may be particularly prominent in PsA, affecting more frequently plantar fascia or Achilles tendons. Bone marrow edema adjacent to the entheseal insertion sites is characteristic of PsA and is thought to be a manifestation of underlying osteitis. The involvement of the entheses at the very earliest stage of PsA has been demonstrated by magnetic resonance imaging and led recently to an enthesis-based biomechanical hypothesis of disease pathogenesis [13].

Dactylitis, an inflammation affecting both the joints and tendons of the whole digit may be seen in 16–48% of patients with PsA, and is usually less common in other spondyloarthritides. PsA is also typified by the relative asymmetry of sacroiliac/spinal involvement and more extensive paramarginal syndesmosmophytes and/or periosteal reaction compared to ankylosing spondylitis or spondyloarthritides related to inflammatory bowel disease.

The evidence of features of spondyloarthritides (inflammatory enthesopathy, dactylitis, spinal involvement, periosteal proliferation) in all patterns of PsA is of primary importance and may serve as a clue to the correct diagnosis in many patients.

A distal pattern affecting the distal interphalangeal joints must be differentiated from osteoarthritis, particularly inflammatory erosive osteoarthritis. The joint involvement in these two disorders may be very similar both clinically and radiologically. A clue to the correct diagnosis lies in the concomitant psoriatic nail involvement in the

PsA = psoriatic arthropathy

majority of patients with PsA. Pitting is the most common psoriatic nail lesion, while onycholysis, nail bed discoloration, subungual hyperkeratosis, transverse grooves or longitudinal ridging may be seen as well [14]. Of interest, nail changes were reported to occur in about 90% of patients with PsA (all patterns), compared with 45% of psoriatic patients without arthritis [15]. Recent MRI studies demonstrated that involvement of the distal phalanges in the inflammatory process accompanies both the distal interphalangeal joints and psoriatic nail lesions in patients with PsA, being a potential connective link between the two phenomena [16,17].

Laboratory parameters of inflammation (erythrocyte sedimentation rate and C-reactive protein) are frequently normal or minimally elevated in PsA, contributing little to the differential diagnosis in this setting. However, the fine interpretation of X-rays may help to differentiate between PsA and osteoarthritis in some patients. The lack of apposition of adjacent bony margins would be characteristic of PsA, while in osteoarthritis undulating osseous surfaces are usually closely applied. Pencil-in-cup appearance of the joints, irregular periosteal bone proliferation, or resorption of the distal tuft, if present, may be diagnostic for PsA [18].

A polyarticular pattern must be distinguished from that of rheumatoid arthritis. In this setting, PsA may be recognized by its tendency to asymmetry and involvement of the joints in the 'ray' pattern rather than the 'raw' pattern typical for rheumatoid arthritis. The presence of erythema over the inflamed joint is unusual in rheumatoid arthritis but may be seen frequently in PsA, probably reflecting exaggerated angiogenesis characteristic of psoriatic disease. Concomitant involvement of DIP joints, spine, or psoriatic nail lesions in PsA patients should not be sought. Positive serology (both rheumatoid factor and anti-cyclic citrullinated peptide antibodies) may sometimes be deceptive, occurring in PsA (mainly polyarticular) in up to 10–15% of patients [19,20]. Intriguingly, an association of a positive test for anti-CCP antibodies and HLA-DRB1-shared epitope in patients with PsA was reported [21]. Radiologically, both PsA and RA are characterized by osseous erosions; however, irregular excrescences of bony proliferation and the lack of juxtaarticular osteoporosis would strongly favor the diagnosis of PsA.

Arthritis mutilans is the most destructive form of PsA, which may lead to extensive and irreversible joint damage with appearance of the "telescoping" phenomenon and shortening of the digits within a short time. All the aforementioned clinical and radiological features of PsA may contribute to the diagnosis, which necessitates an aggressive therapeutic approach.

CLASSIFICATION CRITERIA

At least six different criteria sets have been proposed since the first diagnostic criteria of Moll and Wright, which included three main points: the existence of an inflammatory arthritis, the presence of psoriasis, and seronegativity [8,22]. The many patterns of PsA necessitated, however, more specific classification criteria to distinguish PsA from other members of the spondyloarthritides group – osteoarthritis, rheumatoid arthritis, or gout (the latter may be a frequent phenomenon in extensive skin psoriasis). A high prevalence of both psoriasis and the aforementioned rheumatic diseases further complicates the diagnosis, leading to a statistically plausible non-causal association of skin psoriasis and other arthropathies.

Recently, an international group of experts on PsA, the **C**l**AS**sification of **P**soriatic **AR**thritis (CASPAR) study group, compiled a new set of simple and highly specific classification criteria [11]. These criteria allow the classification of an inflammatory articular disease as PsA with at least three points from the following (two points for current psoriasis, every other criterion one point):

- current psoriasis (2 points) or personal or family history of psoriasis
- typical psoriatic nail dystrophy
- dactylitis
- negative test for rheumatoid factor
- juxtaarticular new bone formation (excluding osteophytes) on plain radiographs of the hand or foot.

The CASPAR criteria, which were developed on the basis of data analysis of 588 patients with PsA and 534 patients with other arthropathies, have a specificity of almost 99% and sensitivity of 91.4%. In addition to their very high specificity, the CASPAR criteria are progressive by permitting the diagnosis of PsA in the absence of psoriasis (PsA *sine* psoriasis) as well as in RF -positive patients. Relatively low sensitivity, particularly in the early stage of disease, has been thought to limit the usefulness of these criteria [11]. A recent study, however, reported an excellent sensitivity and performance of the CASPAR criteria in early psoriatic arthritis [23]. A detailed comparison of the historical and current diagnostic and classification criteria for PsA can be found in the literature [11,22].

PsA MECHANISMS

Both cellular interactions and molecular pathways of inflammation in PsA have not been elucidated sufficiently. In general, synovial histopathology of PsA, whether oligo- or polyarticular, is closer to that of other spondyloarthritides than to RA. Particularly, the increased synovial vascularity, triggered by vascular growth factors, and massive neutrophil infiltration are characteristic for PsA [24,25]. Of interest, both increased angiogenesis and abundance of neutrophils are seen also in psoriatic skin lesions.

Intracellular citrullinated peptides, frequently recognized in RA synovium, are not seen in PsA [24]. The synovial infiltrate in PsA, besides neutrophils, is formed mainly by T lymphocytes, with the presence of cells of B-lineage, macrophages and dendritic cells as

DIP = distal interphalangeal
Anit-CCP = anti-cyclic citrullinated peptide
RA = rheumatoid arthritis

RF = rheumatoid factor

Table 1. Available data on the efficacy of disease-modifying and biologic medicines in psoriatic arthritis and psoriasis

Treatment	Target	Peripheral PsA	Axial PsA or AS	Enthesitis	Dactylitis	Skin psoriasis
SSZ	?	Y	N	N	N	Y
MTX	Adenosine receptor?	Y	N	NA	NA	Y
LEF	Pyrimidine	Y	N	NA	N	Y
CS	Calcineurin	Y	NA	NA	NA	Y
AZA	Inosinic acid	Y	N	NA	NA	NA
Infliximab	TNFα	Y	Y	Y	Y	Y
Etanercept	TNFα	Y	Y	Y	NA	Y
Adalimumab	TNFα	Y	Y	NA	NA	Y
Alefacept	CD2	Y	NA	NA	NA	Y
Efalizumab	LFA-1	N	NA	NA	NA	Y
Abatacept	CD80/86	NA	NA	NA	NA	Y
Pamidronate	Osteoclasts	NA	Y	NA	NA	NA

AS = ankylosing spondylitis, SSZ = sulfasalazine, MTX = methotrexate, LEF = leflunomide, CS = cyclosporine, AZA = azathioprine.
Efficacy: Y = efficient, N = non-efficient, NA = data unavailable.

well. Both CD4 and CD8 T cells, with the latter predominating in the joint effusions in PsA, may show oligoclonal expansion, suggesting an antigen-driven response [26]. However, the T cell-activating antigens have not yet been identified. Of relevance, CD40L was recently reported to be over-expressed on stimulated T cells from patients with psoriatic arthritis compared to RA patients and healthy volunteers [27]. Th17 lymphocytes, a recently reported lineage of pro-inflammatory T helper cells essential in both psoriasis and RA, have not yet been investigated in PsA [28,29].

The general pattern of T cell-derived cytokines – including interleukins-2, 4 and 10, tumor necrosis factor-beta and interferon-gamma – in the synovial fluid in PsA has been found similar to that of RA but in lower concentrations [30]. Of other inflammatory cytokines, TNFα is abundant in PsA synovium, as well as in both psoriatic skin lesions and inflammatory arthropathies [31].

Macrophages, which usually serve as a main source of TNFα, may differ in the inflamed synovium of PsA from that in RA by their numbers and subtypes, with more CD163+ macrophages found in PsA [24,32]. B cells, present in the PsA synovium, participate in the building of lymphoid aggregates in the synovium, which may point to antigen-driven B cell development [33]. However, the precise organization and function of B cells in PsA are not clear.

Dendritic cells recently gained attention as a potential key player in psoriasis [34]. Plasmacytoid $CD123^+$ DCs serve as a major interferon-α producer, while myeloid $CD11c^+$ DCs produce a variety of cytokines and chemokines, being abundant in psoriatic skin lesions [reviewed in 34]. DCs, while recognized in the synovium and joint fluid in PsA [35], have not been sufficiently studied.

Disturbed bone remodeling, as expressed by both extensive bone erosions and exaggerated bone formation in the same patients, is another characteristic and poorly understood feature of PsA. The receptor activator of nuclear factor-kappa B ligand (RANKL), TNFα and IL-7 were recently suggested as critical molecules in the activation of osteoclasts and subsequent bone resorption in PsA [36]. A reduction in the number of osteoclast precursors in the peripheral blood after anti-TNF treatment in patients with PsA was also reported [37]. On the other hand, the mechanisms of increased bone formation and its potential relation to PsA osteitis have not yet been explored.

PROGRESS AND PROBLEMS IN PsA TREATMENT

Enhanced understanding of disease mechanisms led to the introduction in the last decade of new, highly specific and effective therapies in the arsenal of medicines for treating PsA [Table 1]. Experience with some of these therapies was gained from RA and ankylosing spondylitis and applied to PsA, while others were used initially in patients with psoriasis. This new generation of "biologics" differs from traditional drugs used in PsA, such as methotrexate, sulfasalasine, cyclosporine and other disease-modifying anti-rheumatic drugs, by their targeted action on a specific structure, leading to the neutralization of this structure (i.e., anti-TNF treatments) or interruption of immunological signal transduction and modulation of T lymphocyte function (i.e., alefacept) [38].

While the efficacy of biologics in PsA has been repeatedly demonstrated in clinical trials and confirmed by evidence-based studies [reviewed in 38,39], the precise impact of these therapies on the disease course is unknown, primarily because of the absence of accepted outcome measures in PsA [40]. The widely used ACR (American College of Rheumatology) and DAS (Disease Activity Score) criteria, primarily developed for RA, as well as the Psoriatic Arthritis Response Criteria (PsARC), are based mainly on the affected joints count, and as such may be acceptable in polyarticular PsA, which shares some clinical similarities with RA. The widely agreed-upon measures of improvement in oligoarticular,

TNFα = tumor necrosis factor-alpha
DC = dentritic cell
IL = interleukin

spinal or predominant DIP patterns of PsA, as well as measures of enthesitis and dactylitis in PsA are still unavailable [40]. This lag between the appearance of new effective treatment modalities and the difficulties in assessment of some variants of PsA may lead to underestimation of the severity of PsA and inappropriately chosen treatment in some patients. It should be mentioned that the blind translation of RA therapies (both traditional DMARDs and biologics) for patients with PsA may be unwise, regarding the potential differences in the efficacy and toxicity of medicines in two different conditions. In addition, coordinated therapy, directed at both psoriatic skin lesions and affected joints, may be preferred in PsA patients. Finally, combination therapy of two or more non-biologic DMARDs or biologic and non-biologic DMARDs (methotrexate being the most frequently used) has repeatedly been shown to be superior to monotherapy in PsA.

In summary, significant progress has been achieved in the diagnosis and treatment of PsA during the last decade. However, additional studies elucidating the mechanisms of PsA are needed to explain the variability of its forms and severity to provide an improved, individualized approach to any single patient with PsA.

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DMARDs = disease-modifying anti-rheumatic drugs