Psoriatic Arthropathy: Where Now?

Gleb Slobodin MD¹, Itzhak Rosner MD², Michael Rozenbaum MD², Nina Boulman MD², Aharon Kessel MD³ and Elias Toubi MD³

Departments of ¹Internal Medicine A, ²Rheumatology and ³Immunology, Bnai Zion Medical Center, and Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel

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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].

PsA is a distinct inflammatory arthropathy, manifesting in a wide range of patterns, but no single clinical, radiological or laboratory sign pathognomonic for PsA has been reported

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 syndesmosmosphites and/or periostial reaction compared to ankylosing spondylitis or spondyloarthritides related to inflammatory bowel disease.

The evidence of features of spondyloarthritides (inflammatory enthesopathy, dactylitis, spinal involvement, periostial 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 majority of patients with PsA. Pitting is the most common psoriatic nail lesion, while onycholysis, nail bed discoloration, subungal 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 periostial 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 CASsification of Psooriatic ARthritis (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

DIP = distal interphalangeal
Anti-CCP = anti-cyclic citrullinated peptide
RA = rheumatoid arthritis
• 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 basisof data analysis of 588 patients with PsA and 534 patients withother arthropathies, have a specificity of almost 99% and sen-sitivity of 91.4%. In addition to their very high specificity, theCASPAR criteria are progressive by permitting the diagnosis ofPsA in the absence of psoriasis (PsA sine psoriasis) as well as inRF-positive patients. Relatively low sensitivity, particularly inthe early stage of disease, has been thought to limit the use-fulness of these criteria [11]. A recent study, however, reported anexcellent sensitivity and performance of the CASPAR criteriainearly psoriatic arthritis [23]. A detailed comparison of thehistorical and current diagnostic and classification criteria forPsA can be found in the literature [11,22].

PsA MECHANISMS
Both cellular interactions and molecular pathways of inflam-mation in PsA have not been elucidated sufficiently. In general,synovial histopathology of PsA, whether oligo- or polyar-ticular, is closer to that of other spondyloarthritides than toRA. Particularly, the increased synovial vascularity, triggeredby vascular growth factors, and massive neutrophil infiltrationare characteristic for PsA [24,25]. Of interest, both increasedangiogenesis and abundance of neutrophils are seen also inpsoriatic skin lesions.

Intracellular citrullinated peptides, frequently recognized inRA synovium, are not seen in PsA [24]. The synovial infiltratein PsA, besides neutrophils, is formed mainly by T lympho-cytes, with the presence of cells of B-lineage, macrophages anddendritic cells as well. Both CD4 and CD8 T cells, with thelatter predominating in the joint effusions in PsA, may showoligoclonal expansion, suggesting an antigen-driven response[26]. However, the T cell-activating antigens have not yet beenidentified. Of relevance, CD40L was recently reported to beover-expressed on stimulated T cells from patients with pso-riatic arthritis compared to RA patients and healthy volunteers[27]. Th17 lymphocytes, a recently reported lineage of pro-inflamatory 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 – includ-ing interleukins-2, 4 and 10, tumor necrosis factor-beta andinterferon-gamma – in the synovial fluid in PsA has beenfound 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 inflam-matory arthropathies [31].

Macrophages, which usually serve as a main source ofTNFα, may differ in the inflamed synovium of PsA from thatin 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 aggregatesin the synovium, which may point to antigen-driven B celldevelopment [33]. However, the precise organization andfunction of B cells in PsA are not clear.

Dendritic cells recently gained attention as a potential keyplayer in psoriasis [34]. Plasmacytoid CD123+ DCs serve as amajor interferon-α producer, while myeloid CD11c+ DCsproduce a variety of cytokines and chemokines, being abun-dant in psoriatic skin lesions [reviewed in 34]. DCs, whilerecognized in the synovium and joint fluid in PsA [35], have notbeen sufficiently studied.

Disturbed bone remodeling, as expressed by both exten-sive bone erosions and exaggerated bone formation in thesame patients, is another characteristic and poorly under-stood feature of PsA. The receptor activator of nuclear factor-kappa B ligand (RANKL), TNFα and IL-7 were recently sug-gested as critical molecules in the activation of osteoclastsand subsequent bone resorp-tion in PsA [36]. A reduction in the number of osteoclastprecursors in the peripheral blood after anti-TNF treatment in patients with PsA was also reported [37]. On the other hand, the mechanisms ofincreased bone formation and its potential relation to PsAosteitis have not yet been explored.

PROGRESS AND PROBLEMS IN PsA TREATMENT
Enhanced understanding of disease mechanisms led to theintroduction in the last decade of new, highly specific andeffective therapies in the arsenal of medicines for treating PsA[Table 1]. Experience with some of these therapies was gainedfrom RA and ankylosing spondylitis and applied to PsA, whileothers were used initially in patients with psoriasis. This newgeneration of “biologics” differs from traditional drugs usedin PsA, such as methotrexate, sulfasalasine, cyclosporine andother disease-modifying anti-rheumatic drugs, by their tar-geted action on a specific structure, leading to the neutraliza-tion of this structure (i.e., anti-TNF treatments) or interrup-tions that block TNFα action. Most of these biologics are ex-pressed in the synovium and joint fluid in PsA, leading toan increase in joint fluid in PsA patients [38].

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

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PSoriatic arthritis (PsA) is a chronic inflammatory condition that affects up to 0.3% of the world’s population. It is characterized by a painful and disabling joint inflammation, skin plaques, and extra-articular manifestations. PsA is similar to rheumatoid arthritis (RA) in many respects, such as joint pain, swelling, and stiffness, but it has unique clinical features, including dactylitis and enthesitis. The pathogenesis of PsA involves the interaction of genetic, environmental, and immune factors. The genetic component of PsA is complex and involves multiple susceptibility loci. Environmental triggers, such as infections and smoking, play a role in the development of PsA. The immune system in PsA is characterized by a Th17 cell-mediated inflammation, which is also present in psoriasis, a disease with a similar pathogenesis. The treatment of PsA is challenging due to the presence of extra-articular manifestations and the need for long-term management. The use of biologics, targeting TNFα, IL-12/23, IL-17, and IL-6, has revolutionized the management of PsA, providing effective and sustained response in many patients. However, the use of biologics is limited by the high cost, potential for adverse effects, and the need for regular monitoring. Alternative treatments, such as small-molecule drugs and small interfering RNA, are being explored to address the needs of PsA patients.
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.

Correspondence:
Dr. G. Slobodin
Dept. of Internal Medicine A, Bnai Zion Medical Center, Haifa 31048, Israel
Fax: (972-4) 835-9790
email: gslobodin@yahoo.com

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(review) and in a mouse model of multiple sclerosis. This selective inhibition was mediated by activation of the amino acid starvation response. Amino acid depletion mimicked the effects of halofuginone, whereas excess amino acids rescued TH17 differentiation. The results highlight the importance of amino acid metabolism in regulating inflammation.

Capsule

**Halofuginone and starvation regulate T cells differentiation and inflammation**

The TH17 lineage of CD4+ helper T cells, characterized by the ability to secrete interleukin-17, is an important mediator of inflammation and autoimmunity. DAMPening the responses of these cells or inhibiting their differentiation is of great therapeutic interest. Sundrud et al. show that the small molecule halofuginone inhibits the differentiation of TH17 cells but not other CD4+ T cell helper lineages both in vitro and in a mouse model of multiple sclerosis. This selective

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**“No protracted war can fail to endanger the freedom of a democratic country”**

Alexis de Tocqueville (1805-1859), French political thinker and historian