New Insights into the Concept of Psoriatic Disease

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ABSTRACT. The concept of psoriatic disease (PsD) derives from that of psoriatic arthritis (PsA), from which it evolved. The first step in this process was the concept of PsA; the second was the description of the wide clinical spectrum of PsA; and the third was the introduction of the new concept of PsD. This article describes this conceptual evolution and discusses emerging pathological implications deriving from it. (J Rheumatol 2012;39 Suppl 89:4–6; doi:10.3899/jrheum.120231)

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PSORIATIC DISEASE PSORIATIC ARTHRITIS PSORIASIS

FROM THE IDEA OF PSORIATIC ARTHRITIS TO THAT OF PSORIATIC DISEASE

In 1959, based on the results of an observational study of 154 patients with psoriasis and various rheumatic complaints, Verna Wright introduced the concept of psoriatic arthritis (PsA)[1]. He excluded from his analysis patients without erosive arthritis, to avoid possible interference from a chance association of skin and joint conditions. Patients with erosive arthritis and psoriasis were classified into 3 groups: (1) those with the typical distal interphalangeal joint involvement and onychopathy; (2) those with the severe type of deforming arthritis, including arthritis mutilans; and (3) those with an arthritis indistinguishable from rheumatoid arthritis (RA) in the absence of rheumatoid factor. This third group represented 75% of the cases. In patients with severe arthritis, psoriasis tended to be more extensive and recalcitrant to treatment. Although Wright found an increased incidence of sacroiliac joint involvement, his study failed to detect clear clinical spondylitis.

Fourteen years later, in 1973, we reach the second historical step. John Moll and Verna Wright recognized the wide clinical spectrum of the disease[2]. They described the classic 5 clinical subsets of arthritis, including also spondylitis. These observations directly contributed to the subsequent birth of the concept of seronegative spondyloarthropathies, which would be detailed further in 1974 by Moll, *et al*[3] and completed by Moll and Wright in *Seronegative Polyarthritis* (1976)[4].

Finally, in 2006 a group of Italian researchers introduced the new concept of psoriatic disease (PsD) in an editorial in the *Journal of Rheumatology*[5]. They described a situation in which tumor necrosis factor-α (TNF-α) plays the central role of a biological engine involved in the pathogenesis of all inflammatory changes that characterize the condition.

In that situation, the HLA profile is the predisposing factor, and the environment that of the inducing factor (including trauma, infections, diet, stress, etc).

Among the anatomical areas clinically involved, the gut appears for the first time as an established site of inflammation along with skin and joints. This hypothesis is based on the presence of microscopic colitis demonstrated in patients with PsA in the absence of signs and symptoms of bowel involvement[6]. This occult colitis has some structural aspects that show a marked difference from classic inflammatory bowel disease, and particularly from classic ulcerative colitis (increased cellularity in lamina propria with lymphoid aggregates in all cases; polymorph neutrophil infiltration in 60% of the cases; glandular atrophy only in 20% of the cases; mucosal surface changes and crypt abnormalities only in 1% of the cases).

The new concept of PsD extends the traditional idea of a disease confined to skin and joints. It represents an advance in the classification that focuses on molecular aspects, which are at the basis of the pathogenesis of psoriasis and of its related manifestations.

CONTRIBUTING FACTORS TO THE EVOLUTION FROM THE CONCEPT OF PsA TO THAT OF PsD

During these years, the diagnostic meaning of skin involvement has changed over time. When Moll and Wright proposed their diagnostic criteria for PsA, they emphasized the presence of a current psoriasis.

In 2003, Scarpa, *et al* had already described the clinical pattern of PsA without psoriasis, underlining the clinical value of familial history of psoriasis for the detection of this clinical subset[7].

The CASPAR (Classification for Psoriatic Arthritis) criteria, introduced in 2009[8], ratified the clinical value of familial psoriasis as a classification item in the absence of overt psoriasis or of a medical history of psoriasis.

A second element contributing to this evolution was the notion introduced by McGonagle, *et al* that, while RA is a synovial-related arthritis, PsA is an entheseal-related condition[9]. This hypothesis had actually already been anticipated in the works of Olivieri, *et al*[10] and Salvarani, *et al*[11], who

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had outlined the clinical value of isolated enthesitis in the early recognition of PsA and of other spondyloarthropathies.

Finally, there is the increasing evidence of bowel involvement in patients with PsA. Based on histologic evidence derived from our studies, we have recently been able to hypothesize the existence of a psoriatic colitis, different from classic inflammatory bowel diseases[12].

NEW INSIGHTS INTO THE CONCEPT OF PsD

Apart from a significant morbidity as a result of stable articular damage, it is well known that inflammatory rheumatic diseases such as RA or systemic lupus erythematosus are predisposing to an increased rate of cardiovascular disease and to premature mortality due to an accelerated atherosclerotic vascular disease[13,14]. Chronic inflammation acts directly or in association with traditional risk factors in the pathogenesis of accelerated atherosclerosis, which complicates the clinical spectrum of rheumatic diseases. Inflammation promotes insulin resistance, dyslipidemia, and lipid oxidation, and causes the development of endothelial dysfunction. By the enhanced expression of adhesion molecules such as intercellular adhesion molecule-1 and vascular cell adhesion molecule-1, some cytokines, in particular TNF-α, stimulate the adhesion of monocytes to the surface of endothelial cells and promote the infiltration of the vascular wall, favoring the conversion of monocytes into macrophages[15].

In the case of severe psoriasis, several studies, particularly Gelfand, *et al*, have shown a significant increase in the risk of myocardial infarction[16] and of cardiovascular mortality[17]. In particular, the increased risk of cardiovascular mortality is not associated with the presence of traditional cardiac risk factors. This suggests that severe psoriasis may play the role of an independent risk factor for cardiovascular death. In addition, more recently Abuabara, *et al* demonstrated that patients with severe psoriasis are also at increased risk of death from a variety of causes other than cardiovascular events. Infections, kidney diseases, and dementia seem to be important, a finding not previously suspected[18]. Finally, patients with psoriasis show an increased prevalence of the metabolic syndrome[19], suggesting the need for early recognition and for rapid therapeutic intervention in clinical practice.

Our group has recently contributed to this emerging field, outlining the involvement of the vascular system in patients with PsA.

When compared to controls matched for age, weight, height, and cardiometabolic profile, patients with PsA show increased arterial stiffness (measured with aortic pulse wave velocity), even in the absence of traditional cardiovascular risk factors[20].

In addition, we have observed the possible usefulness of TNF-α blockers in countering the evolution of atherosclero-

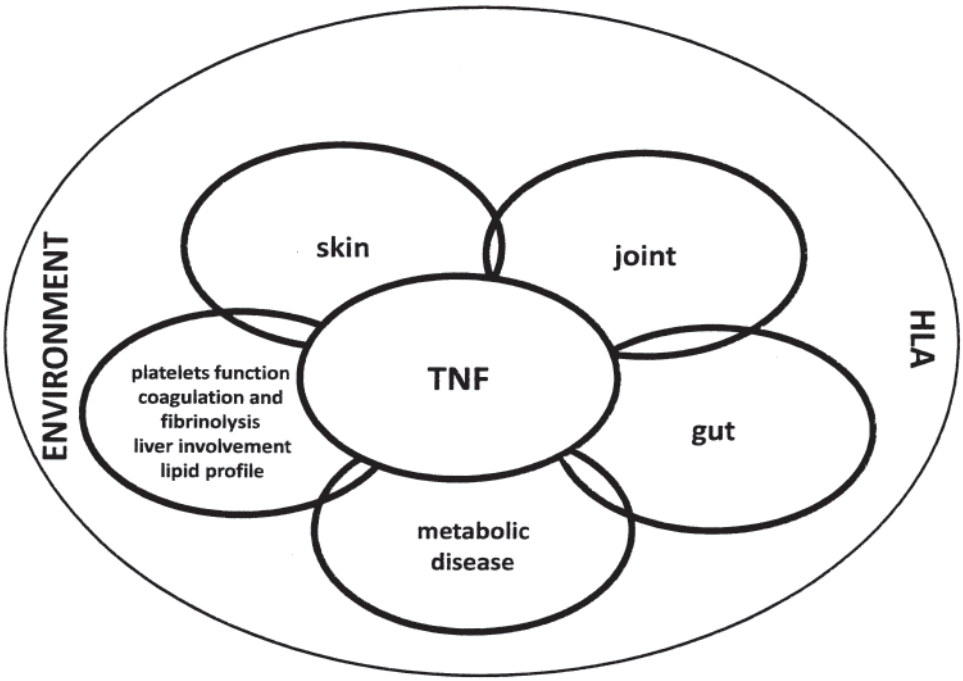

Figure 1. Tumor necrosis factor (TNF)-α plays a central role in the clinical spectrum of psoriatic disease. TNF-α causes skin, joint, and gut inflammation. In addition, through the involvement of cytokines and inflammatory cells, induces phenomena leading to metabolic disease and atherosclerosis. New factors to be evaluated in future research are the role of platelets, the balance between phenomena related to coagulation and fibrinolysis, and involvement of the liver and lipid profile. HLA antigens remain in their predisposing role, while the environment influences the expression of the clinical aspects characterizing the multisystemic involvement of psoriatic disease.

sis in PsA. In fact, patients with PsA treated with TNF-α blockers have shown a marked improvement of carotid intima-media thickness (measured by bilateral ultrasonography at the level of common artery and bulb) when compared to those on traditional disease-modifying antirheumatic drugs[21].

These studies point to the role of TNF-α, related cytokines, and inflammatory cells in the induction of phenomena leading to development of atherosclerosis.

Increasingly, PsD is considered to be a systemic condition (Figure 1) with a complex pathogenetic pattern. What was designated in 1959 as a form of arthritis distinct from the rheumatoid condition has become an intricate clinical puzzle with many gray areas (such as platelet function, the balance between coagulation and fibrinolysis, involvement of the liver, and lipid profile). These areas still need clarification through future research.

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