Psoriatic Arthritis: What the Dermatologist Needs to Know, Part 1

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Abstract
Psoriatic arthritis is defined as inflammatory arthritis occurring in patients with psoriasis and is classified as a seronegative spondyloarthropathy associated with human leukocyte antigen B27. Between 25% and 35% of patients with psoriasis go on to develop psoriatic arthritis during the course of their disease. Given that the skin is affected before the joints in most cases, the dermatologist must be able to recognize the signs and symptoms in order to make a diagnosis and start the most appropriate treatment. This review aims to cover key aspects of the initial diagnostic workup and clinical evaluation. It examines the epidemiology, pathogenesis, and manifestations of psoriatic arthritis, as well as the complementary tests and diagnostic tools the dermatologist should be aware of in order to make the correct diagnosis.

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PALABRAS CLAVE
Psoriasis; Artritis psoriásica; Epidemiología; Patogenia

Artritis psoriásica: lo que el dermatólogo debe saber (Parte 1)

Resumen
La artritis psoriásica (APso) se define como la artritis inflamatoria asociada a la psoriasis y se clasifica dentro de las espondiloartropatias seronegativas asociadas a HLA-B27. Se estima que entre el 25 y el 35% de los pacientes con psoriasis pueden desarrollar una artritis psoriásica a largo de la enfermedad. Dado que en la mayoría de los casos la afectación cutánea precede a la articular, es de gran importancia que el dermatólogo sepa reconocer los signos y síntomas de esta para iniciar el proceso diagnóstico y establecer el tratamiento más adecuado para el paciente. En esta revisión se pretende abarcar los aspectos necesarios para abordar el diagnóstico y evaluación inicial de la artritis...
Introduction

Psoriatic arthritis is defined as inflammatory arthritis associated with psoriasis and is classified as a seronegative spondyloarthropathy associated with human leukocyte antigen (HLA) B27. Around 30% of patients with psoriasis are expected to develop joint disease, leading to functional disability and diminished quality of life.\textsuperscript{1,2} As the skin is affected before the joints in 80% of cases, patients are usually seen by a dermatologist, who must be able to recognize and take on the initial management of joint symptoms in order to provide optimal therapy and the opportunity for early referral to a rheumatologist for specialized assessment and treatment.\textsuperscript{3} Furthermore, joint involvement is a criterion for providing systemic treatment, irrespective of the extension or severity of the cutaneous manifestations at a given time; therefore, clinical knowledge of psoriatic arthritis enables the dermatologist to offer the most appropriate treatment available for each patient.

The present review aims to cover those aspects that must be addressed in the initial assessment and diagnosis of psoriatic arthritis in routine practice, by providing information on diagnostic tools and evaluation criteria at diagnosis and during treatment, additional tests the dermatologist should be aware of, and when to refer to a rheumatologist.

The review is divided into 2 parts. This first part examines the epidemiology, pathogenesis, symptoms, and diagnosis of psoriatic arthritis; the second will focus on methods of assessment, follow-up, and treatment.

Epidemiology

Although the prevalence of psoriatic arthritis is unknown, it is calculated to affect between 0.04\% (Faroe Islands) and 1.2\% (Sweden) of the general population.\textsuperscript{1} A study from the Mayo Clinic revealed the prevalence to be 0.1\%; however, the sample studied only included patients with psoriasis.\textsuperscript{1} In addition, a study performed in Holland showed how difficult it was for rheumatologists to make a diagnosis of psoriatic arthritis; a number of patients went undiagnosed because some of the participating rheumatologists did not question them about the presence of psoriasis, cutaneous signs of psoriasis were not looked for, and x-rays to identify erosive lesions were not performed.

The prevalence of psoriasis ranges from 6\% according to the study by the Mayo Clinic to 42\% in a South African clinic.\textsuperscript{1} A population-based study calculated prevalence to be 11\%. In fact, the results of studies carried out in Italy and Sweden in which patients were followed by dermatologists and rheumatologists suggest that the real prevalence must lie between 25\% and 34\%. These figures show that psoriatic arthritis is much more prevalent in the general population than suggested by previous studies. Therefore, if psoriasis is present in 1\% to 3\% of the population and 30\% of these patients have psoriatic arthritis, then the prevalence of the latter in the general population is 0.3\% to 1\%, which is similar to the prevalence of rheumatoid arthritis.\textsuperscript{1}

Genetics and Pathogenesis

Both psoriasis and psoriatic arthritis are more common in patients with first-degree relatives who have the disease, thus indicating that common genetic factors play a pathogenic role. Psoriatic arthritis is associated with polymorphisms in the genes coded in the HLA region of chromosome 6, which codes for class 1 antigens (HLA-B13, B57, B39, Cw6, and Cw7); HLA Cw6 shows the closest association both with psoriasis and with psoriatic arthritis. In contrast, the alleles HLA-B27, B38, and B-39 correlate with specific joint patterns of psoriatic arthritis. Polymorphisms (238G>A and 857C>T) have also been detected in the tumor necrosis factor (TNF) \( \alpha \) gene on chromosome 6. These are associated with the presence of psoriatic arthritis but not with psoriasis and are independent of the PSORS1 allele. The genes \( IL12B \) (JL-12p40) and \( IL23R \) (IL-23 receptor) have also been identified as indicators of susceptibility to psoriatic arthritis.\textsuperscript{4}

In addition to the genes found in the major histocompatibility complex (MHC), there has been speculation about the involvement of other genes in the pathogenesis of psoriatic arthritis. Some of these genes are found on chromosome 16q ( locus PSORS8), chromosome 2q (IL-1 gene cluster), and chromosome 19q13.4 (killer cell immunoglobulinlike receptor genes).\textsuperscript{5} Identification of the genetic factors involved in susceptibility to psoriasis and psoriatic arthritis has been the subject of genome-wide association studies such as that by Liu et al,\textsuperscript{6} who found that the strongest associations were with polymorphisms in the class 1 region of the MHC and with polymorphisms in...
the regions coding for the IL-23 and IL-12B receptors. New associations have also been reported in the region coding for the lipoma HMGIC fusion partner gene (LHFP) and component 6 of the conserved oligomeric Golgi complex in chromosome 13q13, the late cornified envelope of the PSORS4 complex, and the LD region of chromosome 15q21. This region is of particular interest, because it harbors pseudogenes close to the HLA-C that code for ubiquitin-specific protease 8. It also contains SPL2A, which codes for a peptidase that activates TNF-α and triggers expression of IL12 in dendritic cells.

The authors who identified the above genes also identified a locus on chromosome 4q27 containing the genes IL2 and IL21 that has been involved with 4 autoimmune diseases: celiac disease, type 1 diabetes mellitus, Graves disease, and rheumatoid arthritis.

This information enables us to deduce that the genes involved in psoriasis and psoriatic arthritis are not the same, since, of the 8 clusters identified in psoriasis (PSORS1-8), only some genes in cluster PSORS1 are associated with the pathogenesis of psoriatic arthritis, thus adding support to the hypothesis proposed by some authors that the diseases are different.7

Although gene markers are useful for identifying patients affected by this disease, they currently serve no purpose in daily clinical practice or in the development of therapeutic strategies.

Some authors consider that, in addition to genetic factors, environmental factors may be involved in the pathogenesis of psoriasis and psoriatic arthritis; therefore, the presence of infectious agents would trigger the inflammatory response as a result of the molecular similarity between streptococcal antigens and epidermal self-antigens.1 The involvement of viruses such as the human immunodeficiency virus has also been postulated, as individuals with AIDS commonly experience exacerbations of psoriasis and of psoriatic arthritis. Other authors postulate that repeated injury can trigger psoriatic arthritis via a mechanism involving elevated levels of substance P, neuropeptide, and vasoactive intestinal peptide in the synovial fluid and skin of the injured joint. As for the nails, McGonagle et al8 proposed a model in which the nail is an anatomical and functional component of the musculoskeletal system. Thus, the nail is functionally linked to the distal phalanx and the distal interphalangeal joint structures including the extensor tendon fibers and collateral ligaments. Consequently, inflammation of the distal interphalangeal joint or enthesitis in this area could also play a secondary role in nail diseases affecting patients with psoriasis and psoriatic arthritis.8

As for inflammatory mediators, the elevated levels of TNF-α that are associated with psoriasis are also responsible for joint disease, since elevated levels of TNF-α can be detected in both the synovial fluid and the synovial tissue of the affected joint.9 TNF-α acts by activating nuclear transcription factors such as nuclear factor κB (NFκB) and by promoting the expression of molecules such as cytokines, which play an important role in inflammation. Furthermore, in joints, TNF-α can damage bone and cartilage by activation of metalloproteinases produced by fibroblasts and by inducing the maturation and activation of osteoclasts. TNF-α induces expression of adhesion molecules on the surface of keratinocytes, endothelium, and dendritic cells that attract inflammatory cells to the site of inflammation in both skin and cartilage. Other important cytokines in the immunopathogenesis of psoriatic arthritis are interleukin (IL) 1, IL-6, IL-12, IL-15, and IL-18.9 Given their role in the pathogenesis of these diseases, the members of the IL-1 superfamily IL-18 and IL-33 have recently been proposed as possible molecular targets in the treatment of psoriatic arthritis and other rheumatoid conditions.9 IL-33 (or IL-1F11) has recently been identified as a ligand of the T1/ST2 receptor of the IL-1 family. The biological effects of IL-33 are produced after binding to the T1/ST2 receptor and activation of intracellular signaling pathways that are common to those triggered by IL-1, with subsequent activation of extracellular signal-regulated kinases, p38, Jun N-terminal kinases, and NFκB. Consequently, IL-33 could be a molecular target in future strategies to treat psoriatic arthritis. Other genes associated with the pathogenesis of psoriasis and psoriatic arthritis are those that act on the IL-23/T17 pathway, which are alleles of the IL-12p40 gene (IL12B) and the IL-23 receptor (IL-23R). Activation of this pathway leads to production of IL-22 and IL-17 by T17 cells, which are involved in adaptive immunity to pathogens. An aberrant T17 response can lead to immunologic abnormalities such as those found in psoriasis and psoriatic arthritis.4

The finding of elevated levels of vascular endothelial growth factor, transforming growth factor β, and angiotropins in the synovial tissue of patients with psoriatic arthritis supports the hypothesis that angiogenesis intervenes in the process of joint inflammation. This represents yet another potential target in the treatment of psoriatic arthritis.

Signs and Symptoms

Although there is no agreed definition of the disease, psoriatic arthritis is considered an inflammatory arthritis that is seronegative for rheumatoid factor and is associated with psoriasis.10 However, with regard to the new psoriatic arthritis classification criteria, a positive rheumatoid factor result does not rule out a diagnosis of psoriatic arthritis.

Men and women are affected by psoriatic arthritis in similar proportions, with a mean age at onset of 36 to 40 years. Clinically, both peripheral joints and the axial skeleton are involved.1 The initial symptoms involve inflammatory arthralgia and/or asymmetric arthritis of large and small joints—whether associated or not with inflammatory rachialgia—accompanied by morning stiffness in the affected areas.

The classic description of psoriatic arthritis includes 5 clinical patterns:10

1. Oligoarticular pattern
   - The first joints involved are usually the fingers and toes, which are affected by arthritis that is sometimes accompanied by inflammation of the flexor tendons
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5. Spondylitis with or without sacroiliitis
3. Distal interphalangeal joint involvement
2. Symmetric polyarthritis
4. Arthritis mutilans
5. Spondylitis with or without sacroiliitis

Spondylitis with or without sacroiliitis
- Usually affects <5 joints.

Symmetric polyarthritis
- Has recently come to be considered the most common articular pattern.
- Affects hands, wrists, hips, and feet.
- Can be distinguished from rheumatoid arthritis by involvement of the distal interphalangeal joints with relative asymmetry, absence of cutaneous nodules, and negative rheumatoid factor test result, although the pattern may be indistinguishable from that of rheumatoid arthritis.

Distal interphalangeal joint involvement
- Although characteristic of psoriatic arthritis, distal interphalangeal involvement only appears in 5% to 10% of cases, mainly in men.
- Usually accompanied by involvement of the nails, often making it difficult to appreciate the presence of arthropathy.
- Usually affects <5 joints.

Arthritis mutilans
- Characterized by the presence of bone resorption in the affected joint and disappearance of part of the joint, thus leading to a pencil-in-cup radiologic pattern.
- More common in men and in early-onset forms.

Spondylitis with or without sacroiliitis
- Occurs in 5% of patients, mainly in men.
- Either or both can occur simultaneously with any of the previously mentioned subgroups.
- Can appear with no evidence of sacroiliitis. When present, sacroiliitis is usually asymmetric, or may appear in the radiograph without the classic symptoms of morning stiffness affecting the spinal column (Figure 1). Therefore, in sacroiliitis, there is little clinical correlation between symptoms and radiographic signs.
- Involvement of the vertebrae differs from that of ankylosing spondylitis, in which the atlantoaxial joint may be affected by erosion and dislocation of the odontoid process.

Atypical radiographic signs may be present, for example, syndesmophytes, paravertebral ossification, and, less commonly, vertebral fusions with calcification of discs.

The clinical patterns described above must be recognized in order to make a correct diagnosis of psoriatic arthritis. They could assist in the recognition of early-stage disease; however, as they do not include all the possible presentations of the disease and can undergo variations over time, they are not useful when trying to classify the disease.

Furthermore, enthesitis (also known as enthesopathy) —inflammation of the sites where the tendons or ligaments insert into the bone—is more common in psoriatic arthritis than in rheumatoid arthritis. The most commonly affected areas are the insertion site of the Achilles tendon and the plantar fascia in the calcaneum. Dactylitis, which is caused by interphalangeal involvement of the tendons and ligaments of the fingers, occurs in 35% of patients with psoriatic arthritis. It is accompanied by skin and nail disease, and extra-articular manifestations.

Consequently, psoriatic arthritis is currently understood as a disease comprising different clinical domains, which must sometimes be assessed and treated independently. These domains are defined as each of the clinical aspects comprising the disease—whether rheumatological, dermatological, or psychological—and should be used to guide history taking and physical examination (see below).

Peripheral arthritis manifests as pain and/or inflammation of the affected joints. In the interphalangeal joints, the distribution pattern is linear and involves all the joints of the finger, although not those of the other fingers. Another pattern of peripheral arthritis is distal interphalangeal disease with nail involvement. This pattern enables peripheral arthritis to be distinguished from other conditions, such as rheumatoid arthritis, in which mainly the proximal interphalangeal and metacarpophalangeal joints are involved. A characteristic finding of psoriatic arthritis is the presence of erythema or purple coloration of the skin around the affected joints. In the case of rheumatoid arthritis, the presence of erythema in a joint suggests septic arthritis. The morning stiffness that is characteristic of rheumatoid arthritis only affects 50% of patients with psoriatic arthritis, and this may help the dermatologist to distinguish between the 2 conditions. Therefore, the fact that patients with psoriatic arthritis present inflammatory characteristics less commonly than patients with rheumatoid arthritis has led to this condition being underdiagnosed and to the erroneous idea that it is a mild condition. Dactylitis is typical of psoriatic arthritis, occurs in 16% to 48% of patients, and is one of the Classification Criteria for Psoriatic Arthritis (CASPAR) (Table 1). It is considered an indicator of poor prognosis and is characterized by synovitis, tenosynovitis, and enthesitis, together with soft tissue edema, leading to sausage fingers and subsequent inflammation of the whole finger. Involvement of the flexor tendons of the fingers, Achilles tendon, and plantar fascia leads to tenosynovitis in patients with dactylitis (Figure 2).

Enthesitis consists of inflammation of the site where the tendon inserts into the bone (eg, the Achilles tendon...
or plantar fascia with the calcaneum, leading to pain and inflammation and formation of heel spurs). Areas affected by enthesitis should be palpated to rule out inflammation. In some cases, the areas palpated could coincide with those examined in fibromyalgia; therefore, examination should be meticulous.

Involvement of the axial skeleton leads to spondylitis, which includes inflammation of the sacroiliac joints and apophyseal joints. Clinically, spondylitis manifests as lumbar pain that usually appears at rest and with periods of immobility. It improves with exercise and activity, although in some patients it is asymptomatic. It is often associated with morning stiffness. This form of psoriatic arthritis is characterized mainly by unilateral disease and alternating inflammation of the sacroiliac joints (which help distinguish it from other forms of spondyloarthropathy). The spondylarthritis observed in psoriatic arthritis usually has a less severe prognosis in radiographic and structural terms than that presented by patients with ankylosing spondylitis.

Juvenile psoriatic arthritis accounts for 8% to 20% of all cases of childhood arthritis. The initial manifestations are usually monoarticular. Mean age of onset is 9 to 10 years, with a predominance in girls. It is usually mild, although in some cases severe destructive forms may appear and progress in adult life. Arthritis is monoarticular in 50% of children. Tenosynovitis affects 30% of children, with nail involvement in 71%; pitting is the most common clinical characteristic but also the least specific. Involvement of the epiphysis resulting from inflammation of the joint can lead to shortening of the affected limb in 47% of cases. Sacroiliitis occurs in 28% of children and is usually associated with the presence of HLA-B27. Simultaneous onset of cutaneous and joint symptoms is more common in children, and in 52% of cases, arthritis precedes psoriasis.

### Cutaneous Manifestations

Psoriasis is the most important extra-articular manifestation of psoriatic arthritis. In most cases (80%), joint involvement begins on average 10 years after the onset of cutaneous symptoms, although in some cases, joint symptoms occur simultaneously or even before the cutaneous symptoms (10%). They can sometimes precede the cutaneous symptoms by 20 years or more. The form of psoriasis most commonly associated with psoriatic arthritis is psoriasis vulgaris, although other forms can also be observed.

### Nail Lesions

Nail lesions more commonly appear in patients with psoriatic arthritis, and this is probably associated with pathogenesis (see above). Although the nail is an adnexal cutaneous structure, some authors consider that it is

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**Table 1** Comparison of Screening Questionnaires for Psoriatic Arthritis Proposed by the Group for Research in Psoriasis and Psoriatic Arthritis (Modified by Qureshi et al)

<table>
<thead>
<tr>
<th></th>
<th>ToPAS</th>
<th>PEST</th>
<th>PASE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening center</td>
<td>Rheumatology clinic/Dermatology clinic/Family doctor</td>
<td>Any hospital</td>
<td>Dermatology clinic/Rheumatology clinic</td>
</tr>
<tr>
<td>Nail examination</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>89-95%</td>
<td>97%</td>
<td>88%</td>
</tr>
<tr>
<td>Specificity</td>
<td>85-95%</td>
<td>79%</td>
<td>83%</td>
</tr>
<tr>
<td>Active disease</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Remission</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Response to treatment</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Involvement of the axial skeleton</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Specific characteristics</td>
<td>Photographs of cutaneous involvement/ nail disease</td>
<td>Photograph of symptom and nail disease mannequin indicating function subscales</td>
<td>Photograph of symptom and function subscales</td>
</tr>
</tbody>
</table>

Abbreviations: PASE, Psoriatic Arthritis Screening and Evaluation; PEST, Psoriasis Epidemiology Project; ToPAS, Toronto Psoriatic Arthritis Screen.
affected because of the close anatomical relationship between the musculoskeletal system and the nail matrix and propose that enthesitis at the insertion sites of the extensor muscles of the fingers and the flexor retinaculum affects the nail bed and leads to pitting and onycholysis.  

**Extra-articular Manifestations**

Extra-articular manifestations are more common in patients with rheumatoid arthritis than in patients with psoriatic arthritis. In the latter, mainly the flexor tendons are involved and the extensor tendons are spared, whereas in the former, both tendons are usually involved. The subcutaneous nodules that usually appear in rheumatoid arthritis are not common in patients with psoriatic arthritis. A patient with subcutaneous nodules, psoriasis, and arthritis with rheumatoid factor should lead us to suspect co-occurrence of psoriasis and rheumatoid arthritis more than psoriatic arthritis.

The eyes are involved in 30% of patients with psoriatic arthritis (20% conjunctivitis and 7% acute anterior uveitis). Of those patients with uveitis, 43% have sacroiliitis and 40% are positive for HLA-B27.

Inflammation of the root of the aortic valve can lead to heart failure. This phenomenon has been reported in 6 patients with psoriatic arthritis and is similar to that which frequently occurs in patients with ankylosing spondylitis or Reiter syndrome.

In some cases, the patient can develop secondary amyloidosis.

**Diagnostic Tools (PASE, ToPAS, and PES)**

Psoriatic arthritis has an indolent and progressive course; consequently, any delay in diagnosis and treatment can lead to erosive arthropathy. Therefore, the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis has developed 3 screening tools that have been validated for the detection of psoriatic arthritis during its early stages. 

The questionnaires can be self-administered.

The Psoriatic Arthritis Screening and Evaluation (PASE) tool was prepared to help dermatologists detect those patients with psoriasis who could benefit from referral to a rheumatologist; however, it is not a diagnostic tool. It consists of a 15-item questionnaire divided into 2 subscales, one to assess symptoms and the other to assess function. PASE also makes it possible to identify those individuals with more mutilating forms.

The Toronto Psoriatic Arthritis Screen (ToPAS) is a screening tool that is useful for patients with psoriasis, although it has also been validated for detection of psoriatic arthritis in the general population.

The Psoriasis Epidemiology Project (PEST) tool was designed using questions from the Psoriatic Arthritis Questionnaire (PAQ) and the modified PAQ of Alenius et al.; it contains additional questions and a picture of a mannequin so that patients could locate the areas affected by the disease. The questions on joint pain and morning stiffness have proven to be more sensitive—though less specific—than those referring to nail disorders.

All the tools mentioned above (Table 1) can be applied in the dermatologist’s office, although they are no substitute for a subsequent examination by the rheumatologist. Nevertheless, they make it possible to improve the criteria for referral between specialists.

**Classification Criteria (CASPAR)**

The classification criteria of psoriatic arthritis proposed by the Classification of Psoriatic Arthritis group (CASPAR) grades the disease based on an exhaustive analysis of 588 patients with psoriatic arthritis and 536 patients with other forms of inflammatory arthritis at 30 international centers. The CASPAR classification replaces the classic criteria proposed by Wright and Moll in 1973.

For the criteria to be applied, the patient must suffer from an inflammatory musculoskeletal disease with peripheral arthritis, spondylitis, or arthritis. Once this condition has been established, there is a 90% likelihood that the patient has psoriatic arthritis if he/she presents 3 or more of the conditions reflected in the criteria (Table 2). The CASPAR criteria have a specificity of 98.7% and a sensitivity of 91.4% for the diagnosis of psoriatic arthritis.

Although the CASPAR criteria were based on individuals with advanced psoriatic arthritis, their efficacy has been proven for use during the initial stages of the disease, both in clinics specialized in treating psoriatic arthritis and in primary care centers. The sensitivity and specificity of these criteria are high, suggesting that they can be used as diagnostic criteria.

**Conflict of Interest**

The authors declare that they have no conflicts of interest.
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